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Volumen 82 | 1
Enero-Febrero-Marzo 2021

Índice

Summary

Pandemia por COVID-19: entre la esperanza y la incertidumbre

COVID-19 pandemic: between hope and uncertainty

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La pandemia por SARS-CoV-2 originada hace poco más de un año en Wuhan causó una emergencia de salud pública mundial y un impacto sanitario, social y económico, cuya magnitud está todavía por determinar. En este corto periodo de tiempo, a nivel mundial, se ha declarado más de 100 millones de casos y más de 2 millones de muertos. En España, se han diagnosticado más de 3 millones de pacientes infectados y se han registrado alrededor de 70.000 muertes por SARS-CoV-2 [1].

En la fase inicial, la falta de un adecuado sistema de vigilancia epidemiológica frente a infecciones emergentes y la toma de decisiones políticas erróneas condicionó el retraso en la adopción de medidas de contención, una trasmisión descontrolada en la comunidad y un rápido aumento exponencial del número de casos. La inmensa oleada de pacientes infectados provocó una situación inédita en el sistema sanitario español, considerado hasta entonces modélico: colapso de los servicios de Urgencias y las Unidades de Críticos en muchos hospitales de las áreas más afectadas (Madrid, Castilla-León, Aragón, País Vasco, Barcelona). En esta fase, el desconocimiento acerca del tratamiento de la infección y el desbordamiento de la capacidad asistencial condicionaron una elevada letalidad. La edad avanzada, se identificó como el principal predictor de neumonía grave y muerte[2].

La situación crítica, obligó al gobierno del estado a declarar el estado de alarma sanitaria (Real Decreto 463/2020, de 14 de marzo) soporte jurídico para la implantación de medidas drásticas de mitigación: confinamiento domiciliario masivo y reducción de todas la actividades sociales y económicas, con excepción de aquellas consideradas esenciales.

En relación con la importancia del retraso en la toma de decisiones, Steinegger B et al[3] analizan de forma retrospectiva los datos de la primera ola y, mediante modelado matemático, estiman que el inicio del confinamiento una semana antes del 14 de marzo hubiese reducido de 28.000 a 5000 en número de pacientes fallecidos. Además, observan que la velocidad de propagación de la infección (Rt) empezó a disminuir antes del confinamiento domiciliario, lo que sugiere un cambio en el comportamiento social inducido por la información relacionada con el dramático avance de la pandemia en el norte de Italia. En esta línea, Mayo-Yáñez y col[4], en el presente número de Galicia Clínica, analizan el comportamiento de búsqueda en internet de información relacionada con la pandemia por COVID-19 en Galicia, mediante un herramienta de búsqueda, Google Trends. Los autores encuentran una relación directa entre el aumento del número de casos y el volumen de búsqueda en Internet relacionado con el término coranavirus; sugieren que la inclusión de la información proporcionada por estos motores de búsqueda de información por los ciudadanos y profesionales sanitarios en los modelos de predicción de la evolución de la infección puede para útil para el diseño de estrategias de control de los brotes epidémicos.

En Galicia, el confinamiento se produjo en una situación de transmisión comunitaria inferior a la del epicentro de la pandemia y el impacto de la primera ola fue menor a la media del estado. No obstante, la incertidumbre inicial respecto al alcance del incremento de la demanda produjo un cambio drástico en la estructura de asistencial y la focalización de recursos humanos para hacer frente a la pandemia.

En este número de Galicia Clínica, Conde-Freire J y col[5] estudian, utilizando como fuente de información el conjunto mínimo básico de datos del centro, las repercusiones sobre la hospitalización, y las características de los pacientes atendidos entre el 1 de marzo y 30 de abril, en el hospital Lucus Augusti, con un número máximo 69 pacientes hospitalizados en camas convencionales y 21 en la UCI, durante el pico de la pandemia. Como hallazgos más relevantes, observan una disminución en el número de hospitalizaciones en los principales servicios médicos y quirúrgicos de adultos, entre el 3,5% y el 55,9%, con respecto a la media observada durante el mismo periodo en los 3 años previos. Se produjo asimismo una reducción en la estancia media y un aumento en el porcentaje de exitus ocurridos en primeras 24 horas de ingreso hospitalario (29,1% vs. 17,1%; P< 0.0001), por ra-

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Desde una perspectiva histórica, en comparación con plagas pretéritas, la pandemia por SARS-CoV-2 ha puesto de manifiesto la extraordinaria importancia que tiene el desarrollo científico y tecnológico para afrontar el colosal problema de salud publica y el brutal impacto social y económico

zones no aclaradas. En otro estudio, publicado en este número de la revista, Conde-Freire J y col[6], analizan la demanda en los servicios de urgencias y los ingresos hospitalarios subsiguientes en el área médica del mismo centro, en el periodo pre e inmediatamente posterior al estado de alarma. Observan que tras la declaración del estado de alarma la asistencia a Urgencias disminuyó un 65,1%, con un aumento del porcentaje de ingresos del 93,8%. Aunque el promedio de ingresos por día se redujo globalmente un 33%, Medicina Interna, por la mayor implicación en la atención a pacientes con Covid-19, tuvo un promedio diario de 10,5 pacientes, ligeramente superior al registrado en los 3 años previos.

La drásticas medidas del estado de alarma, consiguieron controlar inicialmente la transmisión de la infección, lo que permitió el levantamiento paulatino de las medidas de restricción. El 28 de abril de 2020 el Consejo de Ministros adoptó el "Plan para la transición hacia una nueva normalidad", cuyo objetivo fundamental era la recuperación paulatina de la actividad económica y social minimizando el riesgo que representa a la epidemia para la salud de la población. No obstante, el relajamiento de las medidas restricitvas, fue seguida de nuevos rebrotes de la infección, obligando a la adopción de nuevas medidas restrictivas dirigidas a disminuir la movilidad y los contactos sociales.

En Galicia, aunque el aumento de demanda asistencia estuvo bastante por debajo de la media española, en los periodos de mayor incidencia se puso al límite la capacidad asistencial en algunas áreas sanitarias lo que obligó al traslado de pacientes entre hospitales y se alteró de forma significativa la actividad asistencial: el retraso en los procedimientos quirúrgicos o la sustancial reducción en la accesibilidad de los pacientes a la atención primaria, son ejemplos evidentes. En este contexto, se hizo necesario establecer un marco jurídico que permitiese adoptar medidas de control para hacer frente a la dinámica variable de la pandemia, adaptadas a la situación epidemiológica y proporcionales a los niveles de riesgo de cada área sanitaria y de cada municipio. La flexibilidad en la implementación de las medidas de control, fruto del trabajo coordinado entre Saúde Pública, Consellería de Sanidade y un comité clínico externo asesor, asociadas al aumento exponencial de la técnicas de diagnóstico microbiológico, la consolidación de una estructura asistencial orientada al aislamiento precoz de los casos y trazabilidad de contactos, contribuyen a explicar que Galicia se haya mantenido durante toda la pandemia entre las comunidades con unas tasas de incidencia y mortalidad más bajas de todo el estado. Sin obviar por ello que el impacto de la pandemia en Galicia no ha sido menor. Hasta el 1 de Marzo de 2021, se diagnosticaron más de 112.000 casos y se registraron 2252 muertes con una tasa de letalidad del 2 %.

Desde una perspectiva histórica, en comparación con plagas pretéritas, la pandemia por SARS-CoV-2 ha puesto de manifiesto la extraordinaria importancia que tiene el desarrollo científico y tecnológico para afrontar el colosal problema de salud publica y el brutal impacto social y económico causado por las pandemias. Dos semanas después de que se diagnosticasen los primeros casos de neumonía atípica en Wuhan a finales de diciembre 2019 se consiguió aislar el virus y secuenciar el genoma, publicado inmediatamente en Internet. El trabajo incesante de la comunidad científica y la industria ha permitido conseguir en tiempo record métodos de diagnóstico rápido que permiten realizar campañas de cribado masivo, conocer las vías de propagación del virus y las medidas de prevención eficaces para frenar la propagación, y desarrollar sistema informáticos que nos permiten conocer el avance al epidemia y la trazabilidad de los casos y contactos. Otro gran hito en la historia de la ciencia ha sido la rapidez con que se han desarrollado y fabricado a gran escala vacunas seguras y con una eficacia muy elevada frente a SARS-CoV-2, aprovechando plataformas pre-existentes de ARNm (Moderna/NIAID y BioNTech/FosunPharma/Pfizer) y virus recombinante no replicativo (AstraZeneca/University of Oxford) y la puesta de marcha de campañas de vacunaciónen menos de 1 año.

Otro aspecto remarcable ha sido la cooperación entre los investigadores para realizar ensayos clínicos de calidad en red, con el soporte de organismos multinacionales como la OMS, que ha permitido obtener de forma rápida información valiosa respecto al tratamiento óptimo de la infección, rápidamente puesta al servicio de la comunidad.

Gracias a estos estudios, se demostró la falta de eficacia, y en algunos casos la potencial toxicidad, de los fármacos reposicionados al principio de la pandemia, como la hidroxicloroquina, el interferón o el lopinavir[7] para el tratamiento de los paciente con neumonía. Por el contrario, el estudio Recovery[8], demostró que la dexametasona a dosis de 6 mg/día x 10 días disminuía la mortalidad en un tercio de los pacientes con ventilación mecánica (29.3% vs 41.4%) y un 20% en los pacientes que necesitan O2 suplementario (23.3% vs. 26.2%). El uso de los corticoides y la optimización de las técnicas de ventilación han contribuido a disminuir la mortalidad en los pacientes más graves. La utilización de la heparina para la prevención de las complicaciones tromboembólicas, frecuentes en estos pacientes, y de otros fármacos antiinflamatorios, como el tocilizumab, en casos seleccionados, con enfermedad muy grave, han sido otros avances en terapéutica. La limitación de las opciones terapéuticas frente a SARS-CoV-2 ha sido uno de los factores que ha condicionado la necesidad de mantener una exigencia estricta del cumplimiento de las medidas preventivas como estrategia fundamental para evitar la progresión de la infección. Actualmente, solo disponemos de remdesivir, con una eficacia modesta en la reducción de la estancia hospitalaria[9] y, aunque los ensayos realizados con anticuerpos monoclonales ofrecen resultados esperanzadores parece lejana la posibilidad de disponer de un fármaco antiviral oral que administrado en la fase inicial de la infección, se capaz de evitar progresión de la infección y de frenar las cadena de transmisión.

La evolución epidemiológica favorable en las últimas semanas, condicionada por la adopción de medidas de restricción severas, y la esperanza de alcanzar en pocos meses, gracias a las campañas de vacunación masiva, una inmunidad de grupo suficiente para evitar la propagación de la infección, dibujan un panorama esperanzador. No obstante, todavía no hemos conseguido eliminar la amenaza pandémica y nos encontramos, probablemente, en una nueva fase evolutiva, con áreas de gran incertidumbre. Uno de los principales motivos de preocupación es la aparición de variantes virales con mayor capacidad de transmisión y/o mayor letalidad. En este sentido, la variante británica B.1.1.7, con una capacidad de trasmisión 30-50% más elevada y aparentemente con una mayor letalidad[10] que la variante europea, hasta ahora predominante, se ha convertido en la variante mayoritaria en muchas áreas, se estima que ya es la responsable de más del 80% de las infecciones que ocurren actualmente en Galicia, y ha sido uno de los factores que han contribuido a aumentar intensidad del brote vivido en la tercera ola, durante el pasado mes de enero. Preocupa también la potencial aparición de variantes menos susceptibles o con capacidad de eludir la inmunidad adquirida con la infección o mediante vacunación.

La duración de la inmunidad y la necesidad o no de implementar campañas de vacunación anuales frente a SARS-CoV-2, similares a la gripe, son preguntas todavía sin respuesta.

En adelante, la dinámica de la pandemia,y la recuperación de la actividad social y económica perdidas, van a estar condicionadas por el cumplimiento de una serie de medidas, que debieran aplicarse simultáneamente:

1) Coordinación entre gobiernos y agencias nacionales e internacionales que permita abordar el problema de la pandemia con una visión global.
2) Refuerzo de los mecanismos de vigilancia epidemiológica, con especial atención a la evolución viral, y de las medidas de contención y restricción necesarias para continuar disminuyendo el riesgo de transmisión comunitaria.
3) Rapidez en ejecución de las campañas de vacunación poblacional que permita alcanzar lo antes posible la inmunidad de grupo.
4) Compromiso de los ciudadanos con el cumplimiento de las medidas de prevención de transmisión de la infección.

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Pandemia por Covid19: otras consecuencias

Covid 19 pandemic: other consequences

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RESUMEN

Objetivo: Describir la evolución de la demanda en los servicios de urgencias, y los ingresos hospitalarios subsiguientes, en el área médica de un hospital general durante las fases iniciales de la pandemia por COVID19 y tras la declaración del estadio de alarma.

Métodos: Estudio observacional de todas las visitas al Servicio de Urgencias de adultos, y de todos los ingresos en los servicios médicos que se generaron, entre los días 1 y 31 de marzo de los años 2017, 2018, 2019 y 2020 en un hospital general. Consideramos las 00.00 horas del día 14 de marzo como el inicio del estado de alarma, y punto de corte entre dos periodos: pre-estado de alarma (días 1 a 13 de marzo) y estado de alarma (días 14 a 31 de marzo).

Resultados: Tras la declaración del estado de alarma la asistencia a Urgencias disminuyó un 65,1% y, entre estos pacientes, el porcentaje de ingresos se incrementó un 93,8%. A pesar de ello, el promedio de ingresos por día se redujo un 33%. Sin embargo Medicina Interna (incluyendo área COVID19) tuvo un promedio diario de 10,5 (SD 6,3) pacientes, levemente superior al registrado en años previos.

Conclusiones: En las primeras semanas tras la instauración del estado de alarma por la pandemia por COVID19 disminuyó en casi dos tercios la frecuentación a las urgencias hospitalarias y en un tercio los ingresos en todas las áreas de un hospital general. Por el contrario, Medicina Interna (que incluyó ingresos por COVID19) mantuvo los mismos promedios.

Palabras clave: Pandemia COVID-19, Gestión servicio Urgencias, Gestión distribución hospitalaria

ABSTRACT

Objective: Describe the evolution of the Emergency Department and the hospital admissions in the medical area of a general hospital during the initial phases of the COVID19 pandemic and after the state of alarm established in Spain.

Methodology: Observational study of the patients who were admitted in the Emergency Department and the admissions in medical services from 1st to 31th of March in 2017, 2018, 2019 and 2020 in a general hospital. The beginning of the state of alarm was considered at 00.00 on March 14th of 2020 and a cut-off point is also taken into account between two periods: before the state of alert (March 1st-13th) and the state of alert (March 14th-31th).

Results: After the state of alarm, the admission of patients decrease in the Emergency Department by 65.1% and the income in medical areas was increased in 93.8%. Despite this, the average of incomes per day decreased by 33%. However, Internal Medicine (including COVID19 area) had a daily average of 10.5 (SD 6.3) patients, slightly higher than the one registered in previous years.

Conclusions: In the first weeks after the state of alarm due to COVID19 pandemic, the attendance in the Emergency Department decreased about two thirds and the incomes in medical areas decreased a third in all areas of a general hospital. On the other hand, Internal Medicine (included COVID-19 area) maintained the same averages.

Keywords: COVID-19 pandemic; emergency department management, hospital distribution management.

INTRODUCCIÓN

La pandemia causada por el coronavirus SARS-CoV-2, causante de la enfermedad COVID19, ha provocado una emergencia mundial de salud pública con una evolución rápida y trágica[1-3]. La lucha contra esta enfermedad, en crecimiento exponencial en sus primeras semanas de desarrollo[4], ha obligado a tomar medidas en múltiples sentidos. Por una parte ha sido preciso dedicar grandes recursos médicos, estructurales y económicos a la asistencia de estos pacientes, especialmente los que cursan con enfermedad crítica. Por otra se han decretado medidas de confinamiento muy estrictas. Todo ello ha provocado grandes cambios en nuestros hospitales que alcanzan a todas sus áreas asistenciales[5-7].

Uno de los puntos de mayor impacto es el área de hospitalización médica. La necesidad de disponer de áreas de ingreso y de clasificación en exclusiva para pacientes con diagnóstico establecido, o sospecha fundada, sin duda modifica la atención de los pacientes con otros problemas médicos[5]. De hecho, en muchos hospitales del país, los ingresos por COVID19 han creado problemas de sobre-aforo y ha sido preciso utilizar todos los recursos existentes, e incluso abrir hospitales de emergencia[8]. Por otra parte, puesto que en España los ingresos en áreas médicas no son programados, y provienen fundamentalmente de Urgencias[9], podrían producirse tensiones en este Servicio, tanto en la atención inicial como en el proceso de ingreso[9]. Sin embargo esta es una situación completamente nueva y poco se conoce sobre las visitas a urgencias durante una pandemia, las necesidades de hospitalización que se generan o las repercusiones sobre los distintos servicios. De hecho la mayor parte de la investigación disponible aborda áreas asistenciales muy concretas, tanto médicas[10-12] como quirúrgicas[13-16] y es menos conocido el impacto sobre Urgencias, hospitalización médica o los servicios de Medicina Interna.

Por ello en este estudio describimos cómo evoluciona la demanda en los servicios de urgencias y los ingresos hospitalarios subsiguientes en el área médica durante las fases iniciales de la pandemia por COVID19 y tras la declaración del estadio de alarma.

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PACIENTES Y MÉTODOS

Estudio observacional de todas las visitas al Servicio de Urgencias de adultos, y de todos los ingresos en los servicios médicos que generaron entre los días 1 y 31 de marzo de los años 2017, 2018, 2019 y 2020 en el Hospital Universitario *Lucus Augusti* de Lugo. Este centro cubre la asistencia sanitaria de 240.000 habitantes y dispone de 879 camas.

La fuente de información fue el conjunto mínimo básico de datos del centro. Las variables analizadas, para cada día del periodo en estudio, fueron: fecha de visita a Urgencias, número de adultos evaluados en Urgencias por día, número de ingresos totales en el hospital por día, así como en Medicina Interna General y en Medicina Interna Enfermedades Infecciosas por día. En este último grupo se incluyeron los pacientes por COVID, atendidos por un grupo de facultativos pertenecientes a Neumología y Medicina Interna (General y Enfermedades Infecciosas). En todos los casos la información recogida fue agrupada y sin acceso a ninguna historia clínica concreta, respetando la normativa vigente sobre la confidencialidad de los datos. Se decidió considerar las 00.00 horas del día 14 de marzo como el inicio del estado de alarma puesto que se anunció horas antes de su entrada en vigor y entendimos que ese era el momento en que comenzó a tener relevancia a los efectos de este estudio. Este momento es el punto de corte entre dos periodos: pre-estado de alarma (días 1 a 13 de marzo) y estado de alarma (días 14 a 31 de marzo).

En el análisis estadístico se utilizaron las técnicas descriptivas habituales. Se usó el test X2 para la comparación de variables cualitativas, con la corrección de Yates cuando fue preciso. Para la comparación de 2 medias se utilizó, previa comprobación de la homocedasticidad, el test t de Student. En la comparación múltiple de medias se utilizó el análisis de la varianza y el test de Duncan. El nivel de significación estadística se estableció en $p < 0,05$. Se utilizó el paquete estadístico SPSS versión 17.0.

RESULTADOS

Entre el 1 y el 31 de marzo se atendieron un total de 8186 pacientes en 2017, 8729 en 2018, 8434 en 2019 y 4831 en 2020. La porcentaje medio de pacientes ingresados por día se situó en 16,09%, 16,18%, 15,22% y 21,32% respectivamente.

En la Tabla 1 se muestra la distribución diaria del número de pacientes que acudieron al Servicio de Urgencias y los porcentajes de ingreso. Se comparan las medias de los años 2017,2018,2019 con el 2020. Con respecto al número de atenciones en Urgencias se aprecia que, desde el día 11 o 12 de marzo, existe una franca disminución del número de pacientes que acuden a Urgencias, que se agudiza tras el señalamiento del estado de alarma y se mantiene hasta el día 31. De la misma forma se observa que si bien la disminución es muy importante todos los días, lo es más los fines de semana. De la misma forma se constata que, en paralelo se incrementa el porcentaje de ingresos. Este incremento es muy notable y muchos días supera el 30%, e incluso el 40%, de los pacientes evaluados en Urgencias.

En la Tabla 2 se comparan los datos agregados de los dos periodos de tiempo, antes y después del señalamiento del estado de alarma, para los diferentes años en estudio. Desde el día 14 la asistencia a Urgencias ha disminuido un 65,1% y el porcentaje de ingresos se ha incrementado un 93,8%. De la misma forma, el promedio de ingresos por día se ha reducido un 33%, si bien no a expensas de Medicina Interna (incluyendo el área COVID19) que ha mantenido aproximadamente el mismo promedio diario, e incluso levemente superior en relación con los años previos.

DISCUSIÓN

Este estudio muestra que en las primeras semanas de pandemia por COVID19, y tras la declaración del estado de alarma, se redujo de manera muy importante tanto el número de pacientes que acudieron al Servicio de Urgencias como el de ingresados en un Hospital General de este origen. Sin embargo, en el mismo periodo, los ingresos en Medicina Interna (que incluyen los enfermos con COVID-19) se mantuvieron e, incluso, aumentaron.

Las pandemias afectan profundamente a los sistemas de salud por las dificultades de atender a un gran número de pacientes con enfermedad severa, por la ausencia vacunas o por la dificultades para obtener los insumos precisos[17]. En los últimos años se ha analizado exhaustivamente las necesidades y los costes que requirieron otras pandemias, como influenza[18]. Estas investigaciones han evaluaron áreas tan diversas como las camas hospitalarias precisas[18], las unidades de críticos[19] o los requerimientos en otras zonas hospitalarias (por ejemplo, las quirúrgicas)[20]. Sin embargo existen otros aspectos menos analizados. Uno es cómo se comporta la población cuando percibe que el hospital es una zona de riesgo de contagio de una enfermedad grave. Nuestro estudio ha constatado una disminución de la afluencia a urgencias de un 65,1% en los primeros días del desarrollo de la pandemia y tras la declaración del estado de alarma. Las causas de este desplome no son claras. Sin duda el temor al contagio ha de jugar un papel relevante en este comportamiento. Esto podría explicar la reducción de la patología más banal que, a su vez, justificaría la mayor proporción de pacientes ingresados. Por otra parte, si bien parece claro que la patología traumática puede disminuir por la reducción de la movilidad y de tareas laborales de riesgo durante el estado de alarma, no existe una razón evidente para otras patologías de notable gravedad.

La reducción de ingresos es muy evidente: hasta un tercio menos si los comparamos con los años previos (Tabla 2). Esta reducción es incluso mayor puesto que en análisis hemos incluido a los pacientes con COVID19. Este hecho es inquietante por diferentes motivos. Por una parte puede significar que pacientes con patologías graves retrasan su solicitud de asistencia por miedo al contagio. Por otra que la presunción de COVID19 compite con otros diagnósticos y puede retrasar el diagnóstico y/o el tratamiento correcto[20]. No siempre es sencillo determinar en un primer momento si un paciente concreto tiene o no COVID19, sola o asociada a otra enfermedad. Clasificar rápida y correctamente a los enfermos potenciales es clave para un mejor control de la pandemia y para evitar

Tabla1. Asistencia al servicio de urgencias de adultos e ingresos subsiguientes entre los días 1 y 31 de marzo

Mes Marzo	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Nº Urgencias																															
Media 2017–18–19	261.6	275	284	266.6	306.3	285.3	269.6	276.6	274.3	282.3	271.3	275.3	278	260.3	272	267.6	269	260.6	283	292.6	268.6	264.3	259.6	275	278.3	277	269.3	276	269.3	262.3	252
Nº 2020	255	256	248	284	244	228	255	257	267	277	207	194	166	86	106	90	104	127	93	95	80	82	100	100	107	89	86	82	83	85	98
% Ingreso																															
Media 2017–18–19	17.19	17.16	17.15	15.38	14.99	17.40	16.23	16.22	16.85	17.43	14.35	13.18	16.96	15.73	16.44	14.89	15.88	14.89	14.1	16.39	16.77	14.96	14.37	15.2	14.92	17.59	17.19	15.38	12.54	15.52	16.11
2020	15.29	18.36	14.52	15.49	16.39	19.30	14.90	11.67	19.10	17.33	23.19	17.01	27.11	23.26	23.58	25.56	28.85	22.05	22.58	29.47	21.25	26.83	30	34	30.84	41.57	29.07	35.37	32.53	32.94	30.51

graves errores diagnósticos. Para ello es preciso disponer que de su atención se encarguen grupos con un amplio abanico de competencias y habilidades, ya que son más eficaces para enfrentarse a este tipo de crisis. Todo ello justifica la tasa de ingresos en Medicina Interna a cargo de un grupo mixto compuesto por diferentes especialidades médicas.

El papel del hospital ante una pandemia de las dimensiones del COVID19 es esencial. Discriminar correctamente entre COVID19 y otras patologías o dar una respuesta a los casos moderados y severos, son dos de los aspectos más relevantes. Conocer la demanda asistencial en esta situación es clave para preparar acciones de respuesta sólidas y adecuadas a la realidad. Nuestros datos ayudan a entender el impacto social de esta pandemia y a preparar al sistema de salud para posibles episodios futuros por este u otros virus.

Este estudio debe analizarse a la luz de varias limitaciones. En primer lugar son datos de un único hospital y quizá no representen de forma adecuada lo sucedido en toda Galicia. Si bien esto es cierto, nuestro estudio alerta sobre las peculiaridades de la atención en estas situaciones y puede ser útil para diseñar la asistencia en crisis futuras. Por otra parte, si bien no debieran existir diferencias en Galicia, donde existe una asistencia hospitalaria muy homogénea, es preciso realizar nuevos estudios que confirmen estos datos. Una segunda cuestión es que nuestro estudio se diseñó para analizar aspectos asistenciales al inicio de la pandemia y no fases más tardías. Por lo tanto no es útil más allá de las dos primeras semanas de la crisis. En tercer lugar utilizamos fechas de referencia que se corresponden con un mes natural pero que no se relacionan con el curso natural de la enfermedad. La razón es que el objetivo del estudio era conocer situación en los primeros días tras la declaración del estado de alarma. Esta elección permite disponer una referencia, clara, y sencilla (antes y después de la declaración) lo que le permite ser fácilmente comparable con los resultados de futuros estudios. Por último, en nuestra área la influencia de la pandemia fue moderada (292 contagiados por cada 100.000 habitantes)[21] por lo que nuestras cifras pudiesen no ser totalmente extrapolables a lugares con tasas de incidencia extremadamente altas o bajas.

En resumen, en las primeras semanas tras la instauración del estado de alarma por la pandemia por COVID19 disminuyó en casi dos tercios la frecuentación a las urgencias hospitalarias y en un tercio los ingresos en todas las áreas del hospital.

Tabla 2. Asistencia a urgencias e ingresos antes y después de la declaración del estado de alarma.

	MARZO- DÍAS			
	1 – 13		14 - 31	
N.º URGENCIAS		P		P
Media 2017-2018-2019 (DS) Media 2020 (DS)	277,36 (84.1) 241,38 (76,9)	NS	269,2 (83,6) 94,1 (18,4)	<0.001
RANGO N.º URGENCIAS				
2017-2018-2019 2020	233-350 166-277		213-349 80-127	
% INGRESOS DE URGENCIAS				
Media % 2017-2018-2019 Media % 2020	16,2% 17,5%	NS	15,5% 29,1%	<0.001
INGRESOS TOTALES DESDE URGENCIAS EN EL HOSPITAL				
Media 2017-2018-2019 (DS) Media 2020 (DS)	45,5 personas/día (4.6) 41,3 personas/día (4.1)	0,02	42 personas /día (5,8) 28 personas/día (3,6)	<0.001
INGRESOS EN MEDICINA INTERNA (CON INFECCIOSAS)				
Media 2017-2018-2019 (DS) Media 2020 (DS)	11,7 personas/día (7,8) 13,4 personas/día (6,4)	0,03	9,1 personas/día (6,9) 10,5 personas/día (6,3)	<0,001

Solamente los servicios a cargo de los pacientes con COVID19 mantuvieron tasas de ingreso similares a las previas. Son precisos nuevos estudios que confirmen estos resultados en otras áreas geográficas y que evalúen su evolución en plazos temporales más amplios.

Conflicto de intereses: Los autores declaran no tener ningún conflicto de intereses.

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El hospital en los tiempos del Covid-19: capacidad de reacción y adaptación

Hospital in times of Covid-19: reaction and adaptation

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RESUMEN

Objetivo: Describir las repercusiones sobre la hospitalización y las características de los pacientes atendidos en las primeras semanas tras la declaración del estado de alarma durante la pandemia por COVID-19 en un hospital general.

Métodos: Estudio observacional de todos los ingresos, en todos servicios hospitalarios, entre los días 1 de marzo y 30 de abril de los años 2017, 2018, 2019 y 2020 en un hospital general. La fuente de información fue el conjunto mínimo básico de datos del centro. Consideramos las 00.00 horas del día 14 de marzo como el inicio del estado de alarma y punto de corte entre dos periodos: previo al estado de alarma (días 1 a 13 de marzo) y estado de alarma (días 14 a 30 de abril).

Resultados: Tras la declaración del estado de alarma disminuyó el número de hospitalizaciones (p<0.0001), en un rango entre el 3,5% y el 55,9% con respecto al promedio de los 3 años previos en los diez principales servicios médicos y quirúrgicos de adultos y por todas las modalidades de ingreso (p<0.001). En paralelo se redujo la estancia media (p<0.001) y se incrementó el porcentaje de ingresados de procedencia urbana (p< 0.01). Si bien la mortalidad global no mostró cambios, si aumentaron los fallecidos en las primeras 24 horas de ingreso hospitalario (p<0.008).

Conclusiones: Este estudio describe los mecanismos de reacción y adaptación de un hospital durante el estado de alarma por la pandemia por COVID-19. Nuestros resultados podrían ayudar a otros centros a diseñar y dimensionar sus preparativos.

Palabras clave: COVID-19 Pandemia, Capacidad de reacción, gestión hospitalaria.

ABSTRACT

Aim: Describe the patient's features and the hospital changes during the first weeks of the COVID-19 pandemic alarm in a General Hospital.

Method: Observational study that asses all the admissions in the hospital departments between March 1st and April 30th of 2017, 2018, 2019 and 2020 in a General Hospital. The information was obtained from the basic data set of the Center. We consider 00.00 on March 14th of 2020 as the beginning of the alarm state and as cut-off point between two periods: before the state of alert (March 1st-13th) and the state of alert (March 14th- April 30th)

Results: After the state of alarm the number of admissions decreased (p< 0,0001) in all kind of admissions (p<0,001) and in the ten medical and surgical services of adults between 3,5% and 55,9% comparing with the main of 3 previous years. At the same time main stay decreased (p<0,001) and rate of admitted from urban areas increased (p<0,01). Although total mortality did not change, deaths during the first 24 hours after admissions were increased (p<0,008).

Conclusions: This study describes surge and adaptation mechanisms of a hospital during state of alert by COVID-19 pandemic. Our results could help other Centers with designing and measuring their preparations.

Keywords: COVID-19 pandemic, Reaction capacity, Hospital Management

INTRODUCCIÓN

La pandemia causada por el coronavirus 2019 (COVID-19) ha impactado sobre los sistemas de salud, el bienestar social y la economía a nivel mundial en una proporción que no tiene parangón en la historia moderna[1,2]. Además, el crecimiento exponencial de la enfermedad[3] ha obligado a adoptar medidas asistenciales y sociales no habituales, tanto en España como en otros países europeos. Por una parte, ha sido preciso focalizar múltiples recursos sanitarios en la asistencia de estos pacientes, especialmente a aquellos con enfermedad crítica. Por otra, el decreto de estado de alarma ha modificado la vida cotidiana de todos los ciudadanos, como no había sucedido en las últimas décadas, y provocado profundos cambios sociales y económicos[4-6].

A nivel hospitalario, además de los efectos de la enfermedad por si misma, se generan nuevos problemas colaterales. Entre ellos se incluyen el sobre aforo[7,8] o el retraso, cuando no la cancelación, de múltiples consultas, pruebas o intervenciones[9,10]. Si bien se han estudiado las necesidades y los costes que requirieron otras pandemias como influenza[11,12], los efectos y daños, secundarios o adicionales, provocados por el COVID-19 son aún poco conocidos[13]. Por ejemplo, poco se sabe sobre cual es la demanda asistencial en una situación de estado de alarma o la repercusión que tiene sobre la asistencia hospitalaria general[14]. Este conocimiento ha de ser clave para establecer las medidas que permitan resolver esta situación con eficacia y equidad.

Por ello, analizamos las repercusiones sobre la hospitalización y las características de los pacientes atendidos en las primeras semanas de la declaración del estado de alarma en un hospital general que da servicio a una población con una tasa de incidencia media por COVID19[15].

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PACIENTES Y MÉTODOS

Estudio observacional de todos los ingresos en todos servicios hospitalarios entre los días 1 de marzo y 30 de abril de los años 2017,2018,2019 y 2020 en el Hospital Universitario *Lucus Augusti* de Lugo. Este centro cubre la asistencia sanitaria de 240.000 habitantes y dispone de 879 camas.

La fuente de información fue el conjunto mínimo básico de datos del centro. Las variables analizadas fueron: sexo, edad, servicio de ingreso, tipo de ingreso, destino al alta, estancia hospitalaria, código postal y municipio de residencia. Todos los pacientes fueron seguidos hasta su alta o fallecimiento durante el mismo ingreso hospitalario. Se decidió considerar las 00.00 horas del día 14 de marzo como el inicio del estado de alarma puesto que se anunció horas antes de su entrada en vigor y se entendió que ese era el momento en que comenzó a tener relevancia a los efectos de este estudio. Este momento es el punto de corte entre dos periodos: pre-estado de alarma (días 1 a 13 de marzo) y estado de alarma (días 14 a 30 de abril). La variable tipo de ingreso se distribuyó en las siguientes categorías: Urgente procedente de Urgencias, urgente procedente de Consultas Externas, programado, traslado desde otro Centro y otros. Se catalogó como zona urbana el área centro del municipio de Lugo y como zona rural el resto de la provincia. Los datos se incluyen en un registro aprobado por el Comité Ético de Investigación del Centro y en todos los casos la información recogida fue anonimizada. No se accedió a ninguna historia clínica concreta, respetando la normativa vigente sobre la confidencialidad de los datos.

En el análisis estadístico se utilizaron las técnicas descriptivas habituales. En los cálculos de porcentajes se utilizó como referencia el número de ingresos en todos los casos. Se usó el test ji al cuadrado para la comparación de variables cualitativas, con la corrección de Yates cuando fue preciso. Para la comparación de 2 medias se utilizó, previa comprobación de la homocedasticidad, el test t de Student. En la comparación múltiple de medias se utilizó el análisis de la varianza y el test de Duncan. El nivel de significación estadística se estableció en $p < 0,05$. Se utilizó el paquete estadístico SPSS versión 17.0.

RESULTADOS

Entre el 1 de marzo y el 30 abril de los años 2017, 2018, 2019 y 2020 ingresaron un total de 13481 pacientes, 13237 de ellos de 14 o más años. Entre estos últimos 7007 (52.9%) fueron varones. La edad media fue 69.74 (DS 18,28) años, sin que se apreciasen diferencias por sexos. Las características generales de las hospitalizaciones de estos pacientes se muestran en la Tabla 1. En este periodo de tiempo de 2020, comparado con el mismo periodo de 2017, 2018 y 2019, el número de hospitalizaciones se redujo de manera muy evidente ($p < 0.0001$). Simultáneamente algunas de las características de los pacientes, como el incremento de casos de procedencia urbana ($p < 0.01$), se modificaron en 2020 con respecto a años previos. Por otra parte, también cambiaron algunas características de los ingresos, como la menor estancia media ($p< 0.0001$) o la mayor mortalidad en las primeras 24 horas del ingreso ($p<0.0001$).

Tabla 1. Características generales de los pacientes ingresados en el hospital de Lugo entre el 1 de marzo y el 30 de abril de 2017, 2018, 2019 y 2020

	TOTAL INGRESOS (n= 13237)	p
Sexo; varón (nº; %)	7007 (52,9%)	
Edad (media; DS) Global Varones Mujeres	 69,74 (18,28) 69,51 (16,89) 69,99 (16,67)	ns
Ingresos por año (nº; %) 2017 2018 2019 2020	 3377 (25,5) 3645 (27,5) 3601 (27,2) 2614 (19,7)	< 0,0001
Tipo de ingreso Urgente desde Urgencias Programado Urgente/ Consultas Traslado a otro centro Otros	 8330 (62,9) 2759 (20,8) 1115 (8,4) 211 (1,6) 822 (6,3)	
Lugar de residencia (urbano/ total/%) 2017 2018 2019 2020	 1193/2183/35,3 1189/2380/33,3 1212/2349/24,0 906/1542/37,1	< 0,01
Fallecidos totales (nº/ total) 2017 2018 2019 2020	 258/ 3119 307/3338 282/3319 237/2377	ns
Fallecidos en las 1º 24h (fallecidos 1º 24h/ total) 2017 2018 2019 2020	 49/258 45/307 51/282 69/237	0,0001

En las Tabla 2 se muestran diferentes aspectos de los pacientes y sus hospitalizaciones en dos periodos de tiempo: pre-estado de alarma (días 1 a 13 de marzo) y estado de alarma (14 de marzo a 30 de abril). Para cada variable en estudio se muestran los datos de los 4 años consecutivos en estudio. Destaca que, coincidiendo con el periodo de alarma de 2020, se incrementan el porcentaje de ingresados de procedencia urbana ($p< 0.01$), disminuyen de manera homogénea todos las modalidades de ingreso ($p<0.0001$), se redujo la estancia media ($p<0.001$) y se incrementan los fallecidos en las primeras 24 horas de ingreso hospitalario ($p<0.008$). Por el contrario no se apreciaron diferencias ni en la distribución por sexos, en la edad de los ingresados ni en la mortalidad global.

Durante el estado de alarma se redujo, en los diez servicios médicos y quirúrgicos con mayor tasa de hospitalizaciones,

Tabla 2. Características de los pacientes ingresados en el hospital de Lugo en los periodos de tiempo coincidentes con el pre-estado y estado de alarma de 2017,2018,2019 y 2020

	Pre- estado 1-13 marzo	Estado de alarma 14 marzo - 30 abril	p
Sexo (hombre/ mujer) 2017 2018 2019 2020	 411/352 423/395 397/402 440/388	 1421/1303 1498/1377 1482/1418 935/839	ns
Edad media (DS) 2017 2018 2019 2020	 69,98 (18,34) 70,55 (17,93) 70,97 (17,68) 70,40 (18)	 69,22 (18,40) 69,60 (18,86) 69,15 (18,55) 70,43 (17,18)	ns
Procedencia urbana 2017 2018 2019 2020	 263 (34,5) 259 (31,7) 255 (31,9) 278 (33,6)	 956 (35,1) 969 (33,7) 991 (34,2) 683 (38,5)	0,04
Tipo ingreso (nº urg–urg/ urg–consulta/ programado 2017 2018 2019 2020	 471/59/154 538/43/160 493/77/143 477/55/199	 1639/225/592 1770/194/641 1757/290/600 1185/152/240	0,001
Estancia media (DS) 2017 2018 2019 2020	 8,47 (8,03) 8,51 (8,50) 8,63 (8,78) 7,06 (8,02)	 8,38 (8,53) 8,51 (8,58) 8,11 (8,27) 7,32 (6,87)	0,001
Fallecidos en las 1º 48 horas/total 2017 2018 2019 2020	 9/43 8/51 13/49 9/63	 40/199 37/188 38/192 59/174	0,008

Tabla 3. Diferencias en la ocupación durante en los años 2017,2018 y 2019 en el mismo periodo del estado de alarma de 2020 para diferentes servicios.

INGRESOS ESTADO ALARMA (13/03-30/04)					
	2017	2018	2019	2020	Variación %
MEDICINA INTERNA + NEUMOLOGÍA	724	735	761	636	-6,8%
CIRUGÍA	302	284	313	139	-53,6%
TRAUMATOLOGÍA	218	224	219	105	-52,3%
GERIATRÍA	170	209	213	87	-55,9%
DIGESTIVO	119	154	147	75	-46,2%
UROLOGÍA	127	140	162	89	-37,7%
CARDIOLOGÍA	141	145	156	72	-51,1%
HOSPITALIZACIÓN A DOMICILIO	122	97	120	109	-3,5%
UNIDAD CUIDADOS INTENSIVOS	94	130	121	77	-33%
GINECOLOGÍA	125	111	100	70	-37,5%

el número de ingresos de manera muy llamativa (Tabla 3). Sin embargo la disminución fue muy distinta según los servicios. La asociación de los Servicios de Neumología y Medicina Interna (con enfermedades infecciosas), que se encargó conjuntamente de los enfermos con COVID-19 durante este periodo, atendió un número de pacientes levemente inferior al de años precedentes. De la misma manera el número de pacientes atendidos por Hospitalización a Domicilio se redujo un 3,8%. Sin embargo los restantes Servicios disminuyeron su actividad en hospitalización entre el 33% de UCI y el 55,9% de Geriatría.

En el periodo de tiempo que abarca nuestro artículo en el área de referencia del Centro se diagnosticaron, con PCR positiva, un total de 746 pacientes. En el pico de la pandemia el número máximo de ingresados simultáneos fue de 69 pacientes en hospitalización y 21 en la Unidad de Cuidados Intensivos. Fallecieron 18 pacientes.

DISCUSIÓN

Este estudio muestra como en el hospital de un área con una influencia media por COVID-19 durante el estado de alarma se redujeron las hospitalizaciones en todos los servicios y el tiempo de estancia, ingresó un mayor porcentaje de pacientes de procedencia urbana y, aunque no se incrementó la mortalidad global, si lo hicieron los fallecidos en las primeras 24 horas.

Los hospitales han de estar, en todo momento, totalmente operativos para dar una respuesta adecuada a todo tipo de desastres, como una pandemia. Capacidad de reacción (surge capacity) es el término usado para describir la competencia de un hospital para asumir una sobrecarga repentina de pacientes por un motivo concreto y sin dejar de atender otras patologías urgentes[16]. Para ello las acciones estratégicas más habituales son cancelar intervenciones, reducir los ingresos programados no urgentes y acelerar, en lo posible, las altas. Se considera que con todo ello es posible reducir la ocupación en un 34% en el plazo de una semana[14]. En nuestro caso esta estrategia permitió reducir todos los tipos de ingreso y la ocupación disminuyo en más de un 50% en 4 de los 10 servicios principales (Tablas 1,2 y 3). Entendemos que este efecto fue muy superior a lo esperado y que se justifica por la suma de varios factores: una tasa de incidencia media por COVID-19 en nuestra área, un manejo intra-hospitalario adecuado de los

pacientes que permitió que la ocupación máxima no superase el 10% de las camas del hospital[17], una preparación previa muy exitosa y una baja afluencia de pacientes durante el estado de alarma. Una de las características de las pandemias víricas es que actúan de manera repentina y con un impacto variable en distintas zonas, hasta el punto de que no es posible predecir cuales serán las más afectadas. Por ello la preparación ha de efectuarse en todos los hospitales y diseñada para que no sean desbordados, incluso en las circunstancias más adversas[18]. Sin embargo, la baja ocupación que registramos no puede atribuirse solamente a una tasa de incidencia media o a una preparación adecuada. Un factor determinante en nuestro caso ha sido la baja afluencia de pacientes durante el estado de alarma; un fenómeno que todavía ha de ser estudiado en su justa medida[13]. En todo caso no siempre es posible descifrar o explicar numéricamente los sentimientos que están detrás de las decisiones que toman las personas.

Y no sólo ha de valorarse la capacidad de reacción hospitalaria. Nuestros datos sugieren que tanto pacientes como personal sanitario intentan adaptase a la nueva situación. Por parte de los pacientes, acudir al hospital durante una crisis como la del COVID-19 podría generar inseguridad o que minimizasen sus síntomas. Esto podría explicar la menor afluencia a Urgencias y la reducción de los ingresos en todos los servicios, independientemente de su relación con el COVID-19 (Tabla 3). Además, el incremento leve de la edad y del porcentaje con residencia más cercana al hospital pueden interpretarse como formas de autoselección. Es decir, los pacientes intentan adaptarse a la situación y evitan, en la medida de los posible, el ingreso hospitalario. Por parte de los profesiones es llamativa la reducción de hasta un día de la estancia media en este periodo. Entendemos que es una adaptación, probablemente inconsciente, que pretende bajar la presión sobre el hospital ante el temor de un incremento de los ingresos. Más difícil es explicar el leve, pero significativo, aumento de la mortalidad en las primeras 24 horas de ingreso sin que se modifique la mortalidad total. Este deslizamiento temporal puede tener interpretaciones muy diversas. Una opción sería que los casos de mayor gravedad acudan al hospital en etapas más evolucionadas de su enfermedad. Otra opción, no descartable, es que en esta situación de alarma un mayor número de pacientes y familias decidan que un fallecimiento se produzca en el hospital[18].

Este estudio debe valorarse teniendo en cuenta sus limitaciones. En primer lugar son datos de un único hospital y no necesariamente similares a otros Centros de nuestro entorno. Si bien esto es cierto, nuestro estudio puede ser útil para diseñar nuevos y más amplios estudios que ayuden a preparar el control de crisis futuras. Una segunda cuestión es que este estudio analiza la capacidad de respuesta de un hospital al inicio de la pandemia y no es útil más allá de los dos primeros meses de crisis. En tercer lugar, en nuestra área sanitaria, las tasas de incidencia de la pandemia fueron intermedias entre las registradas en las distintas Comunidades Autónomas. Por tanto nuestras cifras pudiesen no ser extrapolables a lugares con tasas de incidencia mucho más altas o bajas.

En resumen, este estudio contribuye al análisis de los mecanismos de reacción y adaptación de un hospital durante el estado de alarma por la pandemia por COVID-19. Nuestros resultados podrían ayudar a otros centros a diseñar y dimensionar sus preparativos. Sin embargo, son necesarios nuevos estudios que confirmen y amplíen estos resultados en otras áreas geográficas.

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Estudio de la búsqueda de información sobre la pandemia SARS-CoV-2 en Galicia

Study of the information search behaviour on the SARS-CoV-2 pandemic in Galicia

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ABSTRACT

Introduction: This manuscript analyses the use and evolution, through Google Trends as a source of information, of internet-based information-seeking behaviour related to the SARS-CoV-2 pandemic using the terms: Coronavirus, COVID-19, SARS-CoV-2 from January 1, 2020 to April 15, 2020.

Methods: A generalized linear model was used to analyse the relation between SARS-CoV-2 data epidemiology and the Search Volume Index of the terms obtained from the Google Trends query. Significant trend changes were assessed by Joinpoint methodology.

Results: A total of 7,873 SARS-CoV-2 confirmed cases were collected with an increase of 4.7% in the selected period. A relation was found between the confirmed cases (dependent variable) and the Search Volume Index of the *Coronavirus* term, with a correlation rho = 0.79 (p <0.000).

Conclusion: The analysis of search engine query data in order to create mathematical models that forecast disease spread could be useful and helpful to activate and improve strategic plan to control an outbreak.

Keywords: SARS-CoV-2; Google Trends; Correlation Data; Data Analysis; Infodemiology.

INTRODUCTION

To date, SARS-CoV-2 (COVID-19) has spread rapidly in 185 countries, with approximately 3,000,000 confirmed cases and over 200,000 deaths as of April 27, 2020.[1] Considering the global threat, the outbreak was declared a Public Health Emergency of International Concern on 30 January 2020 by the World Health Organization (WHO).[2] In the last few weeks, several scientific reports have been published on the epidemiology of the infection, the clinical course, laboratory testing and treating support.[3,4] However, there are no vaccines against SARS-CoV-2 or specific therapeutic drugs for this communicable disease.

The use of internet data has become an integral part of health informatics over the past decade. Big Data is associated with the massive computational resources needed to cope with the increasing volume and complexity of data from many sources. It has shown great potential in forecasting and better decision making, being continuously integrated into research with novel approaches and methods.[5–8] In this sense, studies have demonstrated that many people seek health information from internet sources.[9] Data from Google Trends have been shown to be valuable to monitor health information-seeking behaviour trends, epidemiology, aetiology and management of specific health conditions, predictions or detection of outbreaks.[10,11] Scrutinising such information now constitutes a new research discipline termed "Infodemiology", which is defined as "the science of distribution and determinants of information in an electronic medium, specifically the Internet, or in a population, with the ultimate aim to inform public health and public policy".[12]

It seems clear that we need urgently to develop further public health activities in order to better understand the epidemiology of the novel virus and characterize its potential impact on public health. Given the actual situation, and taking advantage of these new technologies of "Infodemiology",[12] the main objective of this study is to analyze the use and evolution, through Google Trends as a source of information, of internet-based information-seeking behaviour related to the COVID-19 pandemic in the territory of the autonomous community of Galicia (Spain). The secondary objective is to evaluate the relationship between COVID-19 searches and related mass media stories.

METHODS

Google Trends Tool

Google Trends provides access to Internet search patterns by analyzing a portion of all web queries on the Google Search website and other affiliated Google sites.[10] It analyses a sample of the billions of daily search results and provides information on geospatial and temporal patterns in search volumes for user-specified terms.

Google Trends creates a "Search Volume Index" (SVI), which represents the relative search volume for a search term indexed against the overall search volume. Search volume index values are adjusted to a normalised data scale of 0–100 based on a topic's proportion to all searches on all topics in order to reduce data redundancy and improve data integrity.[13] Different regions that show the same search interest for a term don't always have the same total search volumes.

Users are able to download the output of their searches to conduct further analyses. The value 0 does not necessarily indicate no searches, but rather indicates very low search

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volumes that are not included in the results. The adjustment process also excludes queries that are made over a short time frame from the same internet protocol address and queries that contain special characters.

Data collection

Data were collected using a Windows®10 (Microsoft®, Washington, USA) laptop computer. All cookies from Google Chrome 81.0.4044.113 (Google LLC, California, USA) browser were removed before data collection was started. Based in previous studies,[14] on April 27, 2020, we queried Google Trends and downloaded the data for the following search input using the keywords individually and in combination for comparison: *Coronavirus*, *COVID-19*, *SARS-CoV-2*. Restricting the search to the geographical region of Galicia. Category filters were not included. The selected date range was from January 1, 2020 to April 15, 2020.

Once the points of each term with a greater SVI or that meant a significant change in the trend have been identified, a search on the Google Search Engine website applying the filters for the dates corresponding to those points and using the "news" query category was performed. Likewise, Galicia epidemiological data for the established date range, provided by the Ministerio de Sanidad (Gobierno de España),[15] of the SARS-CoV-2 pandemic were obtained in order to make a comparison with the search volume of the most used term.

Statistical analysis

Following the recommendations on big data analysis with Google Trends of specialized literature,[7,8,12,16] genomic and proteomic a statistical analysis was performed with the statistical package Stata® 14.2 (StataCorp LLC, Texas, USA). Statistical tests were two-tailed with a 95% confidence interval. The Spearman's correlation coefficient was used to examine the associations between search terms. A generalized linear model selecting the model according to the Akaike information criterion (AIC) and the analysis of the residuals was performed to assess the correlation between terms.[17]

The Joinpoint Regression Program, Version 4.8.0.1 (Statistical Research and Applications Branch, National Cancer Institute, USA) was used to identify significant trends changes over time for each search.[18] The Joinpoint methodology, based on Traditional Bayesian Information Criteria, is ideally suited to examine trends over time and to test whether an apparent change in trend is statistically significant.[19] The selected parameters were: A minimum of 1 week between two joinpoints were required, and a maximum of three joinpoints were allowed for describing the data. The trend was expressed by an annual percent change, a summary measure of the trend over a pre-specified fixed interval.[20]

RESULTS

Confirmed Cases (WHO data)

A total of 7,873 SARS-CoV-2 confirmed cases in Galicia were collected by the Ministerio de Sanidad between January 1 and April 15. The trend model (figure 1) indicates an increase of 4.7% (p <0.000) during that period, with four well-differentiated segments found in Table 1.

Coronavirus term

The *Coronavirus* term is the most searched, and it has suffered a progressive increase in the last 3.5 months, marking its highest peak in search volume on March 12 (figure 1). The statistical trend analysis of the *Coronavirus* term shows an increasing evolution, with a global APC of 3.6% (p <0.000). Three joinpoints with their 4 corresponding segments were found in the term search volume trend (table 1). The start of the ascent begins on January 21, until February 25 (SVI = 22). Analyzing the news during that period, they are general information about the "new Wuhan coronavirus", which compared it to previous epidemics such as the flu or talked about its symptoms and the possibility that it could spread outside China. Another noteworthy news in that period is the appearance of the first case in the USA.

After a period of relative stability regarding the SVI, on March 7 (SVI = 18) there is a sharp rise until March 12 (SVI = 100). In this period, reports of the first cases and deaths in Spain, Italy, Iran, Mexico, etc. begin to appear in the news. It also matches with the WHO declaration of a pandemic and the first confinement measures in some countries. After this last peak it seems that the tendency is to decrease significantly.

COVID-19 term

The term *COVID-19* also presented an increase (Global APC = 3.7%; p <0.000), but with a later onset (7 days) than the term *Coronavirus* according to trend analysis (figure 1 and table 1).

Search volume begins to climb slowly from February 21 until March 8 (from SVI = 0 to SVI = 7), at which point it undergoes a much steeper fluctuating increase to its peak on March 19 (SVI = 89) and April 3 (SVI = 100). Analyzing the news of those dates, the beginning of the increase in searches coincides with the date on which the WHO released the name of the disease. The steepest rise coincides with the beginning of the containment measures and the increase in cases in various countries.

Figure 1. Trend lines of the search volume index of the terms described and the confirmed cases.

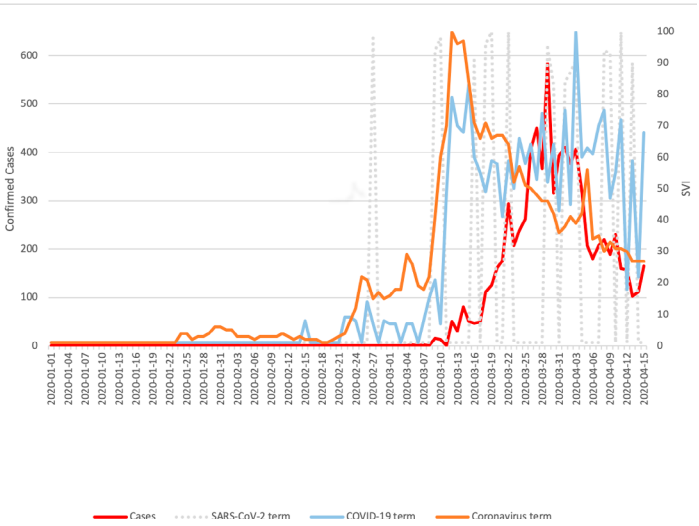

Table 1. Trend and jointpoints of each of the search terms, as well as the number of confirmed cases of SARS-CoV-2 from January 1 to April 15, 2020.

	Segment	Lower Endpoint (Days)	Upper Endpoint (Days)	APC	Lower 95%CI	Upper 95%CI	Test Statistic (t)	Prob > |t|
Confirmed Cases	1	1	66	0.3	-0.2	0.8	1.3	0.2
	2	66	74	60.4	40.3	83.5	7.0	0.0
	3	74	88	17.9	11.9	24.3	6.2	0.0
	4	88	106	-7.7	-10.6	-4.6	-4.9	0.0
	Global	1	106	4.7	3.3	6.2	6.6	0.0
Coronavirus term SVI	1	1	33	5.5	4	7	7.6	0.0
	2	33	48	-3.3	-7.9	1.5	-1.4	0.2
	3	48	73	16	13.5	18.5	13.6	0.0
	4	73	106	-3.7	-4.9	-2.4	-5.5	0.0
	Global	1	106	3.6	2.5	4.7	6.6	0.0
COVID-19 term SVI	1	1	40	-0.0	-1.4	1.4	-0.0	1.0
	2	40	66	6.9	4.0	9.9	4.8	0.0
	3	66	74	37.1	13.4	65.7	3.3	0.0
	4	74	106	-1.3	-3.1	0.7	-1.3	0.2
	Global	1	106	3.7	1.9	5.6	4.1	0.0
SARS-CoV-2 term SVI	Global	1	106	2.4	1.5	3.3	5.1	0.0

APC, Annual Percent Change; CI95%, Confidence Interval 95%; WHO, World Health Organization; SVI, Search Volume Index.

The trend analysis showed 3 changes in trend coinciding with those previously described (table 1).

SARS-CoV-2 term

The term *SARS-CoV-2* it was the least sought after, with an APC of 2.4% (p <0.000) during this period, and only one segment, without jointpoints (table 1). It is the one that later begins to increase the volume of searches, doing it in a very fluctuating way (figure 1), and not clearly associating itself with news in the media.

Correlation and generalized linear model

A linear correlation was found between the confirmed cases (dependent variable) and the de SVI of the *Coronavirus* term (rho = 0.79; p <0.000), the rest of independent variables (*COVID-19* and *SARS-CoV-2* terms) did not show a statistically significant relationship (table 2). A linear correlation between *Coronavirus* term and *COVID-19* term (rho = 0.85; p <0.000), and *Coronavirus* term and *SARS-CoV-2* term (rho = 0.41; p <0.000) was also found.

DISCUSSION

The study of Internet search patterns has facilitated opportunities for evaluating public interest encompassing a variety of health-related topics.[12,16] Further, behavioural measures are needed in the healthcare environment and in public health planning, where national indices of progress on behaviour measures could guide policy and conveyance planning.[12] Using internet big data analysis in healthcare research holds promise, extrapolating data from a portion of 3 billion searches daily, Google Trends represents a powerful tool for gauging public interest and has demonstrated its unique value in numerous analyses.[16]

On 31 December, at the end of 2019, some cases of pneumonia of unknown etiology were notified to the WHO Country Office in China, regarding Wuhan, a city in the province of Hubei.[21] The 3 months since the emergence of COVID-19 have demonstrated the rapid pace at which a virus can spread and at which science can develop. Every outbreak provides an opportunity to gain important information, some of which is associated with a limited window of opportunity.[22] In this case, the strategy against the pandemic seeks to detect the needs for the prevention, diagnosis and treatment of this pathology, as well as to establish work objectives and agreed-upon care recommendations and application of these to as many people as possible.

Since its launch in 2006, Google Trends has proven to be a valuable and accessible tool. It has mostly been used for monitoring and surveillance of communicable diseases and epidemics.[16,23] Despite concerns regarding the adequacy of available patient education materials,[24,25] with an increasing number of users turn to the Internet for health related background information. Our data analysis suggests that the

Table 2. Generalized linear model results.

Variable	Coefficient	Standard Error	P>|z|
Coronavirus term SVI	0.52	0.14	0.000
COVID-19 term SVI	0.02	0.03	0.523
SARS-CoV-2 term SVI	-0.01	0.02	0.703

Coronavirus term follows a linear correlation with the number of confirmed cases of SARS-CoV-2 in a statistically significant way. It can be seen that the trend lines are similar, with the *Coronavirus* term trend changes occurring a minimum of 15-30 days before the increase in cases (table 1). It could be possible that the search engine query data serves as an epidemiological model for future pandemics, or as a method of monitoring peak cases with the intention of anticipating and preparing for them. This has already been tested in other countries with this same methodology.[26]

Likewise, any news stories, new interventions or aetiology related to SARS-CoV-2 can manifest as an increase in information-seeking behaviours for any of the proposed search terms. This is consistent with the results obtained in previous studies.[14] This strengthens the idea that information-seeking behaviour is influenced by the level of awareness exposure,[23,27] and therefore, it may be possible that the mass media campaigns, in a direct and indirect way, can produce positive changes or prevent negative changes in health-related behaviours across large populations.[28]

It should be mentioned that there seems to be a correlation between *Coronavirus* and *COVID-19* or *SARS-CoV-2*. Both combinations were linked to the same influencing factors and happened during the same period of time. It seems that people use them indifferently, but possibly the term *Coronavirus* is the most used because it is more generic. Therefore, Google Trends could also be a powerful tool to understand the terminology used by patients in different regions.[14]

The Internet is unique as it serves as both a primary source of medical information and as a tool to study health information seeking behaviours. The mass media can hugely affect it. Therefore, understanding healthcare information seeking behaviour is essential in order to control and plan the quality of knowledge provided by health organisations, advocacy groups and health professionals regarding SARS-CoV-2 pandemic. A combination of the existing source containment strategy, contact investigation, infection control at health care facilities, as well as in community settings along with this new kind of search engine query data-based approach in order to create mathematical models to forecast disease spread, could be useful and helpful to activate and improve strategic plan to control an outbreak.[4] Further research is needed to understand how healthcare providers can use Google Trends to understand health information-seeking behaviours and its effect on public knowledge, awareness, disease-related anxiety and the interaction between patients and healthcare information providers. Despite this, the results are promising for future applications.

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Enfermedad Neuroinvasiva por Virus del Nilo Occidental: por qué debería considerarse en la Península Ibérica

West Nile Virus Neuroinvasive Disease: why it should be considered in the Iberian Peninsula

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ABSTRACT

Introduction: West Nile virus has caught attention given the spike of European cases in the season of 2018. The number of infected humans exceeded the total cases of the past seven years and the virus expanded to area previous disease-free, causing significant morbimortality.

Objectives: To highlight from a clinical standpoint West Nile virus as a possible aetiology in neuroinvasive disease on humans in the Iberian Peninsula.

Materials and Methods: Data was obtained from Centres for Disease Control and Prevention and the European Centre for Disease Prevention and Control and it was conducted a review of the literature in PubMed electronic database.

Results and Discussion: West Nile virus can be transmitted by mosquitoes' bites, blood transfusion, and organ transplant. Although most infections are asymptomatic, <1% of patients develop neuroinvasive disease presenting as meningitis, encephalitis or acute flaccid paralysis. West Nile virus should be considered as a differential diagnosis in the face of neurological symptoms of unknown aetiology in the appropriate epidemiological circumstances. Diagnosis in the clinical setting is based in serological analysis. As available treatment is only supportive, preventive measures are key to diminish this virus' impact. The future of West Nile virus is difficult to predict, even though ongoing global changes could be factors influencing its course.

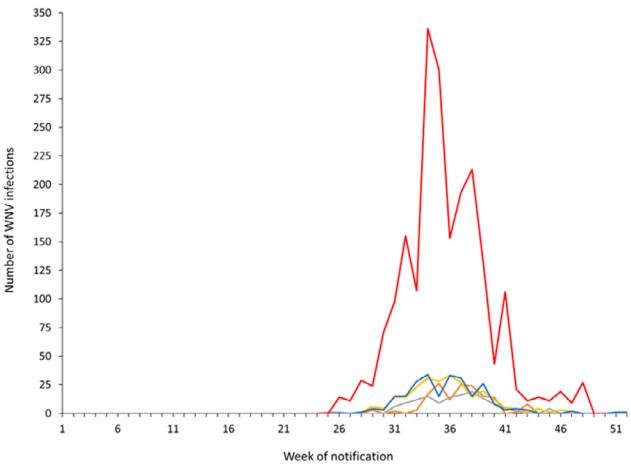
Conclusion: West Nile virus depicts the unpredictability around zoonotic diseases, hence, justifying the need of further surveillance and information in the Iberian Peninsula, considering the existence of the vector and the already recorded human/animal cases.

Keywords: West Nile virus, Meningitis, Encephalitis, Acute Flaccid Paralysis, Iberian Peninsula.

INTRODUCTION

The year of 2018 was unprecedented as the number of human cases of West Nile virus (WNV), 2083 autochthonous cases reported in Central and Southern Europe (Fig.1), surpassed the previous seven years all together (2010-2017), affecting new areas, and being a factor of severe morbimortality (181 deaths reported).

Figure 1. Number of WNV infections in European Union/ European Economic Area Member States and European Union neighbouring countries by epidemiological week of notification (to national authorities or if missing, week of notification to European Centre for Disease Prevention and Control - ECDC), 2014-2018. Graphic and data from the ECDC. WNV- West Nile virus



WNV is considered as a good example of how an apparently stable zoonosis can emerge with unpredictable consequences. Most infected individuals are asymptomatic, however, it is important to be recalled as a differential diagnosis in the case of WNV's neuroinvasive manifestations, to prevent iatrogenic complications from misdiagnoses and subsequent therapies [1].

The virus has been known to cause occasional outbreaks especially in countries of Central and Southern Europe. In those European countries, WNV raises more awareness than in Iberian Peninsula, even though human cases have been described and the virus is known to be in circulation[2,3]. Hence, there is a growing concern over the future of WNV in whether global changes will increase the human and animal impact of this disease.

The WNV is a neurotropic arthropod-borne flavivirus genetically related to the Japanese encephalitis virus. It has a transmission cycle which comprises several species of wild migratory and/or resident birds (reservoir host) and mainly the *Culex* mosquitoes species (vector); humans and mammals like horses may be infected by these mosquitoes' bites, however they do not play a part on further transmission because their short-timed low level viremia does not allow it, being described as "dead-end hosts"[4].

WNV was first isolated from a human patient in 1937 in the West Nile district of Uganda, and from that point onwards it has been detected in several regions of the World even in the American continent in 1999 [1]. In the past, the virus was mostly

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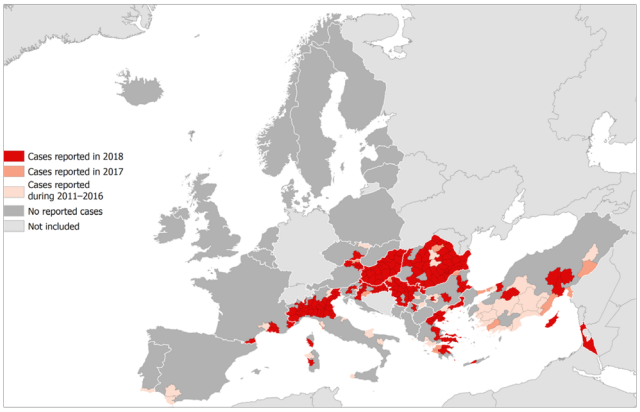
spread via migratory birds that overwinter in Africa which contributed to the usual WNV season of activity in Europe, ranging from mid-June to mid-November which matches with the birds' return and also with the vectors peak of activity[5,6]. Nowadays, the virus is endemic to the Old Continent (Fig.2)[4].

Figure 2. Distribution of West Nile virus infections in humans by affected areas in the European Union/ European Economic Area Member States and European Union neighbouring countries in the transmission season of 2018 and previous ones (with overlap); latest data update 13 December 2018. Map and data from the ECDC.



This manuscript intends to highlight from a clinical standpoint WNV infection as a differential diagnosis in the case of meningitis, encephalitis or acute flaccid paralysis, given the recent spike of cases in Europe, that might propel a greater spread of the virus in the Iberian Peninsula, considering the disseminated vector presence in the region.

METHODS

To fulfil this objective, data related to WNV epidemics and current recommendations were obtained on the websites of the Centres for Disease Control and Prevention and the European Centre for Disease Prevention and Control (ECDC) and it was conducted a review of the literature in PubMed electronic database using the terms: *West Nile virus, West Nile fever, neuroinvasive disease, meningitis, encephalitis and acute flaccid paralysis*. Articles written in English and Portuguese were analysed with publication date till February 2019. There were no restrictions on the type of study. Additional studies found in the references of the selected ones and pertinent book chapters were also included.

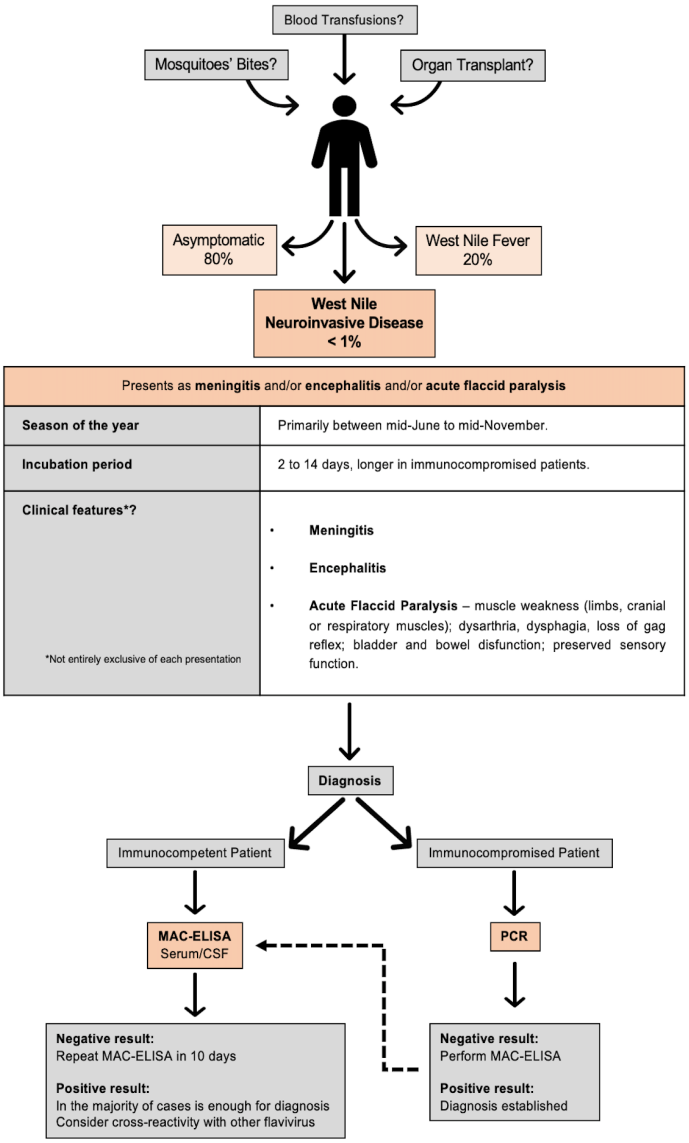
RESULTS AND DISCUSSION

Epidemiology Matters

Anamnesis is key to consider WNV as a differential diagnosis. Location of patient's residence and travel history is of utmost importance in order to verify his presence in an area with active transmission - this factor may make or break the diagnostic hypothesis[7]. Therefore, in the Iberian Peninsula, local cases as much as imported ones must be considered.

In order to identify a WNV infection it is important to recognize and comprehend its clinical presentations, however, it could be difficult to discriminate each one since overlap is common[8].

Figure 3. Resume of the characteristics of WNV infection, focusing on neuroinvasive disease and a short scheme of diagnostic work-up.



The Virus and Transmission Routes

The virus is generally introduced in humans by a mosquito bite and the infection can be characterized in three phases: early phase – it infects skin cells in the point of entry; visceral dissemination phase – the virus spreads to the nearest lymphatic node from which it cause viremia followed by organs invasion such as the central nervous system (CNS), in which it presents as neuroinvasive disease – the CNS phase[9]. This last phase is the most important because of its clinical repercussion.

While mosquito bites are the most common route of infection (Fig.3), WNV can be spread by transfusions of diverse products obtained from blood of infected donors[10]. Countering this risk, a European directive (2004/33/EC) states that travellers who return from an area with ongoing transmission of WNV should be deferred from donating blood for 28 days. Bearing in mind a blood donations shortage, nucleic acid amplification techniques (such as polymerase chain reaction – PCR) to detect WNV RNA can be implemented in WNV affected

countries and in countries without active transmission but with a considerable number of travellers returning from those areas, as the WNV peak of activity coincides with the high travel season in Europe.

Two other ways of transmission, although rare, should be kept in mind. One is through solid organ transplant from an infected individual, which could be particularly dangerous as patients are deeply immunocompromised[11]. Infection has been reported through organs from a donor with no traceable WNV RNA but detectable immunoglobulin (Ig) M/IgG anti-WNV which highlight the complexity involving transplantation and WNV control, as the virus may reside hidden in organs after viremia was cleared or by long-term persistence of WNV characterized by a sporadic viremia[12]. Therefore, implementing a screening test to donors is difficult and probably not cost-effective[13]. The other is vertical transmission, an even rarer possibility, with very few possible intrauterine and breastfeeding infections which could neither be excluded or confirmed, requiring more reports and investigation[14].

Clinical Manifestations

Symptoms and signs are only detectable after an incubation period which can vary from 2 to 14 days, but it can go up to 21 days in immunocompromised patients[10]. Most infected patients will remain asymptomatic (around 80%) so it is only possible to verify its infection by a blood screening mostly performed in situations concerning blood donations[8].

The most common presentation is West Nile fever (WNF) in about 20% of infected patients, characterized as a flu-like syndrome with a sudden onset of fever (which may be of low grade), fatigue, headache, and myalgia[15]. Other symptoms include nausea, vomiting, and a morbilliform or maculopapular rash that affects 25 to 50% of patients[16,17]. The rash tends to be non-pruritic, more prevalent in the head, neck, torso and extremities sparing palms and soles [16]. WNF ranges from a mild condition lasting only a few days to an incapacitating state persisting weeks to months[18]. However, the majority of patients should have a full recovery[19].

Neuroinvasive Disease

WNV is able to penetrate the blood-brain barrier affecting the meninges and causing neural parenchymal damage. This is more common in older and immunocompromised individuals[20,21]. WNV neuroinvasive disease may present as meningitis, encephalitis, and acute flaccid paralysis (AFP) or as a combination of these different presentations (Fig. 3). Despite affecting 1% or less of infected patients, these conditions are the more damaging clinical outcomes[18].

Meningitis

Meningitis caused by WNV is similar to a typical viral meningitis, being impossible to distinguish by clinical manifestations. It is characterized by fever and retroorbital or frontal headache, meningeal signs, photophobia, and phonophobia[22,23]. The characteristic rash is less observed comparing to WNF [16]. Constitutional signs may also be present such as abdominal pain, anorexia, myalgia, nausea, and vomits[22,24].

Encephalitis

In WNV encephalitis, mental status changes are very common and can range from mild confusional state to severe encephalopathy and coma[8]. Behavioural differences such as disorientation, confusion and irritability[23] are also present. Diffuse and focal neurological manifestations, such as extrapyramidal symptoms with the appropriate epidemiologic context is a very characteristic feature[8,23]. Chronologically, changes in the consciousness level usually presents first and they are followed by movement disorders[8,20]. Bilateral tremor and myoclonus may be present, both more common in the upper extremities and the latter also in facial muscles[18,23]. Patients may develop cerebellar ataxia with gait imbalance and parkinsonism characteristics such as bradykinesia, rigidity, and postural instability which can lead to falls[23]. Seizures, increased intracranial pressure or cerebral oedema are rare[8].

Acute Flaccid Paralysis

Muscle weakness in the form of paresis or paralysis can be observed as an outcome of WNV infection and represents damage dealt to the lower motor neurons of the spinal cord[25-27]. On physical examination, this AFP syndrome is typically characterized by hyporeflexia or areflexia of the affected muscles[23,25]. Muscle weakness related to AFP develops in the acute phase of infection, 24 to 48 hours after symptoms onset. It is frequently asymmetric affecting only one limb but might present as quadriplegia[18]. In some particular cases, bilateral cranial muscle weakness may be observed, affecting particularly the muscles innervated by the seventh cranial nerve[27]. Persistent loss of muscular strength leads to muscular atrophy in late stages[28]. However, the most dangerous situation is when respiratory muscles are affected as it propels respiratory failure[25,26]. Invasive mechanical ventilation might be required for prolonged periods or even permanently, increasing mortality and morbidity[26]. It is important to access patients with risk of developing respiratory failure, especially those that concomitantly have dysarthria, dysphagia or loss of gag reflex[21]. Bladder and bowel disfunction are common; pain is reported by some patients; however, modification in sensory sensations are absent for most cases[21,23,25].

Differential Diagnosis

Summing up, in this stage with the details from patient's history and the presentation of neuroinvasive disease, hypothetical diagnoses can be formulated. At this moment, more attention must be drawn towards WNV.

However, affirming the diagnosis of WNV infection based solely on the clinical manifestations is very challenging: apart from symptoms' lack of specificity, in areas with co-circulation of other flavivirus (dengue, yellow fever, Zika, Japanese encephalitis, St. Louis encephalitis viruses), due to similar clinical outcomes is hard to distinguish between them[4,28]. Many other infectious conditions (such as herpes simplex 1, enterovirus, varicella zoster and human immunodeficiency viruses or bacteria as meningococcus or pneumococcus) present as meningitis or encephalitis[29]. AFP might also be described as a poliomyelitis-like syndrome for its resemblance with clinical manifestations of poliovirus infection[22]. Patients infected with WNV presenting with AFP can be misdiagnosed

with Guillain-Barré syndrome (GBS) especially its acute motor axonal neuropathy subtype[28]. However, sensory impairment of GBS is uncommon in AFP, and can be confirmed with physical examination or nerve conduction studies. Myopathies and neuromuscular junction disorders might too be listed as differential diagnoses. This clinical presentation can also be observed in other infectious diseases such as Lyme disease, syphilis, and botulism[30].

Diagnostic Considerations

Taking into account the clinical information gathered, the suspicion of WNV infection is confirmed by detection of IgM antibodies anti-WNV in serum or cerebrospinal fluid (CSF) by an IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) which is sufficient in the majority of cases [28,31]. IgM is highly suggestive of acute infection, rising as early as 4 days to 10 days after symptoms onset; consequently, it is possible to have a negative MAC-ELISA result if the test is performed before the rise of IgM level; in this situation, the test should be repeated days later[15,28]. IgM titres usually decline from the 21st day onwards being undetectable 1 to 2 months after clinical resolution[28].

An important factor to consider is the possibility of cross-reactivity in MAC-ELISA test with other flaviviruses, depicting the importance of patient's travel history and residence area and/or in the event of recent vaccination for Japanese encephalitis/yellow fever virus[15,28,31]. Therefore, a confirmatory test should be requested in order to verify if MAC-ELISA is falsely positive for WNV. Plaque reduction neutralization test (PRNT) indicates the highest dilution of serum able to neutralize WNV among other flaviviruses using cell cultures: the higher the titre, the higher the antibody' serum concentration and the test is considered positive and the diagnosis is confirmed when is documented a difference 4 times greater for WNV than for other flaviviruses tested[28,31]. The problem of PRNT lies with its complexity, demanding a biosafety level 3 laboratory to be performed, limiting its utility[31,32].

Ultimately, the viremia level can be detected by PCR to prove an acute infection, but humans develop a frail viremia with low concentration of WNV genome material for a short amount of time, so it is considered unpractical in a clinical setting, although being a very specific test[31,32]. Exception could be made when testing an immunocompromised patient, since the development of antibodies is delayed or absent and viremia is sustained for longer periods[33].

Lumbar punctures can be performed, unless contraindicated: testing for IgM anti-WNV is important, since IgM is unable to cross the blood-brain barrier, it's detection in the CSF is a hallmark sign of WNV neuroinvasive disease; CSF is typically characterized by an increase of white blood cells (generally less than 500 cells/mm^3, but some patients have normal cell count, especially those with an immunocompromised status that are unable to mount a significant inflammatory response against WNV infection) – and increased protein levels, the latter being of greater magnitude in the case of WNV encephalitis; glucose levels are normal most of the time[8,22,28,34].

Neuroimaging studies should be performed in order to help exclude differential diagnosis. In fact, imaging examinations (in particular magnetic resonance imaging - MRI) do not correlate exactly with active severe infection as they can remain without relevant findings during several weeks after onset of the disease[8]. Concerning WNV encephalitis, the most characteristic MRI finding is bilateral signal abnormalities in the basal ganglia and the thalami[35]. In an AFP setting, signal abnormalities are usually found especially in the anterior spinal cord, representing damage in the anterior corticospinal tract[21].

Electroencephalography in WNV encephalitis may present nonspecific abnormalities as generalized irregular slow waves, triphasic sharp waves, or it can even document seizures[8,23].

When muscle weakness is observed and AFP is suspected, electrodiagnostic studies of the peripheral nervous system such as an electromyography or a nerve conduction study can be requested. Typically, motor axonopathy is shown, normally without any demyelinating abnormalities, with intact sensory function[20,23].

Treatment

There is no specific treatment for WNV and usually only supportive measures are deployed to assist patients[28]. Pain and emesis management are the most commonly used, likewise ventilatory support in respiratory failure, prevention of superinfection and pressure sores or even seizures and intracranial pressure control[30,33]. Some agents as interferon alpha-2b, ribavirin, and intravenous immunoglobulin have been advanced as potential therapies but no studies showed a clear benefit in humans and most evidence for their proposed advantage comes from animal models or in vitro results[15,36-38].

Prognosis

The general prognosis of a WNV infection is excellent taking into account the very low percentage of infected individuals that develop neuroinvasive disease, which is far more debilitating and life-threatening than other presentations[15,28,38]. Older age seems to be the most relevant prognostic factor[39]. Some medical conditions were showed to have an association with the development of WNV neuroinvasive disease[40].

Follow-up of patients with neuroinvasive disease show that the majority of patients become functionally independent within several months to years, however a significant number might require long-term rehabilitation[23,41]. Mental status might remain persistently changed[23]. Neuroimaging studies might help predict prognosis[35].

WNV meningitis is mostly associated with a positive outcome with a smaller chance of developing long-lasting neurological symptoms[23]. WNV encephalitis' fatality rate is around 10% which can go up to 30% in older and/or immunocompromised patients[36,40]. Persistent physical complains are the most common findings[24,41]. Parkinsonism features and myoclonus are also reported[23,38]. Depression, apathy, and anxiety can be seen in the process of recovery from WNV encephalitis[24,41]. Cognitive deficits are also described, such as loss of memory and of thought[23,24,41]. The severity of the initial presentation is a debatable indicator of final outcome as patients with severe

WNV encephalitis can recover without significant long-term functional losses[21,38].

In the beginning of AFP's convalescence phase quality of the life could be compromised as the majority of patients still report muscle weakness which may require therapy to improve their physical impairment[21,41]. In the months post-infection, usually after 6 to 8 months, most patients recover from muscle weakness, varying with the extension of the disease[21]. Severe situations such as respiratory muscles involvement (responsible of 50% of deaths related with AFP) or quadriplegia are more difficult to overcome, in fact, previous health state before the WNV infection may never be reached[21,38,41]. But some patients recover successfully from dare clinical presentations[21]. The severity of the initial setting of APF is not the most reliable prognostic factor likewise WNV encephalitis, whereas electrodiagnostic studies might be more worthwhile, revelling the evolution of motor denervation when compared to initial tests[21,42].

Prevention

Prevention is key to reduce the impact of WNV. Adopting individual precautions should follow the four D's rule: N,N-diethyl-m-toluamide (DEET), an insect repellent; dress, clothes with long sleeves and long pants; drain standing water near one's residence; avoid being outdoors from dusk till dawn[43,44]. Community-based mosquitoes control policies take an important part in reducing the WNV's vector population by the means of insecticide spraying[43,44].

Although being a demanding process, surveillance is always crucial to an effective and rapid response to an outbreak as it helps to predict an epidemic's magnitude improving the overall health system's preparedness[4]. A collaboration of several public institutions regarding human, animal and environmental health may improve the cost-effectiveness of WNV's infection control and prevention as the One Health approach[45,46]. Blood screening protocols significantly helped reducing the risk of transmission through transfusion[46]. Animal surveillance is also recommended: horses can be studied to determine the existence of WNV in a certain area – however, with the availability of an equine vaccine against WNV, the utility of this parameter is limited; searching for WNV infection in birds is useful in order to early warn public health services of WNV circulation, but due to logistical and economic costs this type of study is reserved to countries which experience large epidemics[46].

Future Perspectives

WNV is subject to the constant changes the World has been facing the past decades, successfully adapting to the challenges presented by an ever-mutating society. Its geographic expansion is proof of the previous statement. What does the future hold for WNV, especially in the Iberian Peninsula? It is a difficult question to answer, however some predictions can be made regarding the current course of human development and its impact on the environment.

Higher density urban populations enable zoonotic diseases to flourish because transmission to humans becomes more frequent and mosquitoes have better breeding conditions specially in less sanitary conditions[1,47]. The population boom in certain parts of the globe will push for a greater land usage which if not planned and regulated will put in further contact humans and vectors[48]. Another consequence will be the increased movement of people for work purposes, tourism, or migration and the accompanying international traffic of goods which may play a part in expanding WNV and/or its vector to new areas[1,47]. Earth biosphere will be even more connected, and the smallest disturbance of balance might have a great impact on the general environment.

The increase in median temperatures and modifications of precipitation patterns across the globe will facilitate the spread of mosquitoes as they would be able to survive and thrive in areas that previously could not support their existence and will also alter birds' migration routes[1,48,49]. These factors would work together to globally extend the WNV period of activity and its geographic distribution.

Another future development regarding WNV infection prevention is related to the creation of a vaccine for human beings and some studies have been conducted[50]. However, the cost of designing a vaccine, the wide geographic area in which WNV is endemic, and the benign course in the large majority of the infected individuals are disadvantages towards such goal. [50].

It is also important to remember that WNV is capable of intrinsic change as well, by the means of genetic mutation. A new strain might develop sustained viremia in humans ending the status of "dead-end host" or the percentage of patients with neuroinvasive disease might increase if a more aggressive strain appears, for example[1].

CONCLUSION

WNV was discovered 82 years ago and it has taught the scientific community that they should be prepared for the unexpected. In the presence of neurological symptoms and epidemiological links, WNV should be considered as a differential diagnosis, also in the Iberian Peninsula, as the vector *Culex* is widely distributed in the temperate regions. A serological analysis can make a difference between misdiagnosing and overtreating a patient. In conclusion, the dynamics of WNV have to be better understood in order to more effective measures can be implemented, whether in development of a vaccine, finding appropriate specific treatment or investing further on prevention. Each season of WNV is unique and provides a chance to gather more information, and one can only wonder how the future of WNV might play out.

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Colangiocarcinoma en un paciente con enfermedad de Wilson

Cholangiocarcinoma in a patient with Wilson´s disease

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ABSTRACT

The incidence of hepatobiliary malignancies, and especially intrahepatic cholangiocarcinoma (ICC), for patients with Wilson's disease (WD), is very low, even for cirrhotic patients. It has been suggested that hepatobiliary carcinomas are less frequent in Wilson's disease (WD) than in liver diseases of other etiology. However, the protective role of copper against malignancies is debated. Only a few cases of cholangiocarcinoma (CCC) in WD have been published. Here we report a case of a 39-year-old female, WD diagnosed at 19-year-old based on low ceruloplasmin level, low serum copper, and increased urinary copper. She was followed up and treated with chelating agents throughout nineteen years, after this asymptomatic period she reported abdominal pain. MRI showed hepatic lesions not suggestive of hemangiomas and a nodular lesion of 15mm in the right lobe. Liver biopsy was made, with non-specific fibrosis; negative for malignancy. Few months later she was admitted in the hospital because of rapidly development of epigastric/right hypochondrium abdominal pain with four days of evolution, anorexia and asthenia. Biopsy revealed cholangiocarcinoma as the primary tumor confirmed by strong CK7 and CK20 positivity. The curiosity of the presented case is the very rapid development of CCC despite continuous chelating agent therapy.

Palabras clave: Enfermedad de Wilson; Cobre; Colangiocarcioma.

Keywords: Wilson´s disease; Copper; Cholangiocarcinoma.

INTRODUCTION

Wilson´s Disease (WD) was first described in 1912 when doctor Kinnier Wilson published the article "Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver" in the "BRAIN" medical journal[1]. Since then, there were various studies that had in common the difficulty in gathering a significant and representative sample of patients, to allow a good quality and powerful evaluation, and/or randomization to study therapies and strategies.

WD is a rare genetic condition known to be caused by a mutation in the *ATP7B* gene (the also known as "Wilson gene"), that is hereditary in a recessive form, and results in a defective biliary elimination of Copper with the consequent toxic accumulation in different organs. This gene encodes a protein (ATPase) with the main function in the transmembrane transport of cooper in the liver (from out of the hepatocytes to the bile). When this shift is compromised by the genetic defect, the cellular accumulation leads to inflammation, and subsequent passage to blood stream, with the deposition in other organs (such as brain and kidneys), leading to its correspondent toxicity. The loss of this protein function is also responsible for the ceruloplasmine failure to uptake cooper. There are more de 500 mutations described in the Wilson gene, and the incidence of this condition is 1:30000[2]. Although it could appear at any age, it is more usual to be diagnosed between 5 and 35 years. Its diagnosis is greatly dependent on medical suspicion and direct testing. In cases of neurologic symptoms (ataxia, rigid-akinetic syndromes, cognitive deterioration, or psychiatric symptoms), the diagnosis seems to be quicker and straightforward. The clinical manifestations are very heterogeneous, depending on the organ/organs affected, and the degree of the lesion. Ideally, patients should be identified and diagnosed before they achieved advanced liver damage with neurological symptons and Kayser-Fleischer rings. The liver damage might precede neurological symptoms in years, but typically, most of the neurological patients will have hepatic changes by the time of diagnosis. Signs related to liver damage are variable, since asymptomatic analytic findings (typically the augmented bilirubin with normal or abnormally low alkaline phosphatase and slightly elevated aminotransferases), to the other edge of the spectrum, with established cirrhosis accompanied by portal hypertension, or an acute liver failure. It is important to point out that the Wilson gene can give origin to any type of liver disease and/or neurological- psychiatric symptoms or Coombs negative hemolytic anemia[3]. One of the most typical and famous findings are already mentioned Kayser-Fleischer rings, found in the cornea, but they're neither specific nor a sensible finding of WD.

One growingly question relates to the oncologic complications of WD. Being a cause of chronic liver disease and cirrhosis, it is a known risk for Hepatocellular carcinoma (HCC), it has fallen under the usual cirrhotic lesion screening program. It has been suggested that HCC seems to be less frequent in WD than in liver diseases of other origin[4,5]. Actually, some studies have shown that the cases of malignancy in WD are rare, even when cirrhosis is established[6], when compared to cirrhosis from other causes. In this sense, some authors defend a protective role of copper against malignancies, describing an effect in nuclear chromatin stabilization, and studies in rats showed that an excess in copper intake protect against chemically induced carcinogenesis[7]. On the other hand, an augmented amount of Copper induces DNA damage[7].

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If HCC in WD patients is difficult to analyze, as a consequence of its low incidence, the evaluation is even more difficult for the even rarer cholangiocarcinoma (CCC) in WD. Here we report on a case with rapidly developed CCC in a 39-year-old female WD patient who had been followed up and treated with chelating agents throughout nineteen years.

CASE REPORT

This Caucasian female patient was sent to internal medicine consultation at the age of 19 years for presenting jaundice and elevation of transaminases. She was asymptomatic and there were no risk factors for hepatic disease (intravenous drug use, accidental needle punctures or unknown origin cuts, unprotected sexual contacts, alcohol or natural herbal products consumption, and no blood transfusions).

On the objective examination there were no stigmas of chronic liver disease. No hepatomegaly or splenomegaly, and no signs of portal hypertension (no semiology of ascites, and neither visible collateral venous circulation, nor edema). Laboratory tests showed a moderate transaminase elevation (AST 50 IU/L, ALT 96 IU/L) and alkaline phosphatase (158 IU/L), with normal gamma-GT (272 IU/L) levels. Serum bilirubin and blood counts were normal. The Anti-mitochondrial and anti-smooth muscle antibodies were negative. Serologic evaluation of hepatitis B, hepatitis C and HIV were negative. Serum copper (33 µg/dL) and ceruloplasmin (7 mg/dL) levels were both decreased.

Liver biopsy was performed and showed hepatic parenchyma and slightly fibrous portal spaces with inflammatory infiltrate of mononuclear cells. Hepatocytes with focal steatosis, concluding as chronic active hepatitis.

The proper diagnosis of WD was established two years thereafter, based on low ceruloplasmin level (<7 mg/dL), low serum copper (27µg/dL) and increased urinary copper (153 µg/24h). No Kayser-Fleischer rings were seen. Serial abdominal ultrasound showed no abnormalities. The patient remained asymptomatic. She started treatment with D-Penicillamine, presenting a rash that led to his suspension. No proteinuria or neutropenia was observed.

A new treatment was started with Trientine Hydrochloride. There was a subsequent normalization of the transaminases and urinary copper levels remained within the desired range. There was a need for dose reduction during pregnancy, resuming four tablets/day after delivery.

She remained asymptomatic and with normal liver tests due to chelating therapy for seventeen years. The regular ultrasound monitoring did not identify focal liver lesions. Seventeen years later, she returned to the consultation with abdominal pain referred to the right hypochondrium. A new ultrasound study was performed, demonstrating a structural alteration of the liver and a lacunar lesion of about 3 cm. To better characterize the identified lesion, abdominal CT was performed, and the lesion was described as being suggestive of hemangioma.

Six months later, a new ultrasound scan was executed, excluding focal lesions and, at the request of the family doctor, she performed a new CT scan that also excluded focal lesions. After another six months period, she was reevaluated with an abdominal ultrasound that showed an hyperechogenic and heterogeneous images in segment III (3.7cm/1.7cm/3.5cm). Blood counts, alpha-fetoprotein, AST, ALT, GGT and alkaline phosphatase were normal. She performed an abdominal MRI that showed hepatic lesions that were not suggestive of hemangiomas, the most voluminous occupying almost the entire left lobe, associated with left portal vein thrombosis. Nodular lesion of 15mm in the right lobe. The left lobe neoformation was biopsied, with a description of “non-specific fibrosis, negative for malignancy. Parenchyma without neoformation; steatosis and very slight portal inflammation”. The patient was referred to a consultation at the Liver Transplatation Reference Center of our Hospital due to hepatic infarction following portal thrombosis and nodule in the right lobe to be clarified.

A few months later, at the age of 39-years old, she was admitted at the hospital with symptoms of rapidly aggravating abdominal pain in the epigastric/right hypochondrium, with four days of evolution, accompanied by anorexia and asthenia. The following complementary diagnostic tools were performed: Serum bilirubin and blood counts were normal. The tumor markers AFP and CEA were in normal range, but CA125 level was very high (675,8 U/ml).

Abdominal ultrasound: mild ascites. Hepatic dysmorphism, left lobe atrophy and compensatory hypertrophy of the right lobe. In the left lobe there was a massive hypoechogenic solid formation, previously described, of similar volume. Appearance of at least 3 solid, hypoechogenic nodular images in the right lobe with 38, 32 and 17mm, apparently of malignancy origin. Pelvic MRI: Multiple peritoneal implants in the pelvis, more evident in the Douglas bottom and in the left adnexal region, compatible with metastatic implants. Ovaries without lesions suspected of malignancy. No changes in the uterus or endometrium. Abdominal MRI: Predominantly hyperintense area occupying almost all of the left hepatic lobe. Significant increase in nodule size already identified in segment IV (4cm). A second node in segment V with 2.5cm. In the hepatic peri-hilar region, a nodular conglomerate, probably translating adenomegaly agglomerate or even secondary neoplastic implant. Large volume ascites, with multiple peritoneal nodules being identified, and secondary neoplastic implants are likely to be present. Multiple peri-celiac adenomegalies. Hepatic Nodule Biopsy: Morphological findings compatible with hepatic primitive malignant epithelial neoplasia (Cholangiocarcinoma / Hepatocarcinoma). The cellular morphology is identical to that described in the peritoneal. Abdominal biopsy: Morphological findings compatible with malignant epithelial neoplasia. After extensive immunohistochemical study for the marker Hep Par (NEGATIVE) and Keratin (CK7 positive, CK20 positive), we concluded Cholangiocarcinoma.

At the hospital, she stayed hemodynamically stable; maintained ascites in need of evacuation paracentesis. She was oriented to the external consultation of Internal Medicine. She presented a progressive worsening of clinical status with refractory ascites, periods of encephalopathy, anorexia and extreme asthenia. She died a month later.

DISCUSSION

First, as previously reported, WD is a particularly rare illness, and this case, simply by this fact of representing an infrequent condition raised our interest since the beginning, especially when we consider that it had been identified and diagnosed early, corresponding to a young adult, and yet under medical supervision, and with apparently correct therapeutic, the outcome still was unfortunate, with the development of a neoplasm and death.

WD is a diagnose that demands a direct suspicion from the medical doctor that is studying the clinical picture. There were no Kayser-Fleischer rings, which are a usual finding in patients with neurological symptoms, but are commonly absent in exclusive hepatic involvement, and the liver biochemical blood tests weren't the typical either (there wasn't the hyperbilirubinemia that usually accompanies the slight elevation of alkaline phosphatase). In this case, the biochemical presentation of the Copper study (urinary copper and ceruloplasmin) was diagnostic and proper treatment (after different options had been tried) did managed to control and achieve the expected and wanted normalization. There were no comments by the pathologist that read the liver biopsy regarding the diagnosis of WD, but the center where this was performed had no resources to measure the Copper content in dry liver. Still, other etiologies were excluded.

With timely identification and treatment being one of the main goals in order to prevent progression to cirrhosis or other complications, this case, identified without cirrhosis established, provided the (soon to be confirmed as false) security of good prognosis. The patient maintained values of serum and urinary copper controlled under Trientine Hydrochloride and cytolysis markers in the normal range. The appearance of a nodular lesion in the routine ultrasound study, promptly lead to alternative diagnostic exams (with a more detailed characterization by abdominal CT and MRI). Initially described as hemangioma, and under surveillance. Subsequent exams showed the oncologic lesion.

The difficulty in diagnosing and studying this kind of complications, is clearly demonstrated in this clinical setting, where the patient actually performed an initial liver biopsy that was negative for malignancy. Finally, the identification of cholangiocarcinoma (with the aid of abdominal metastatic implants), confirmed the medical team worst expectations.

The hepatic neoplasia most often described in the literature as being associated with Wilson's disease is hepatocarcinoma. CCC related to WD has been described in sporadic case reports, and there is no consensus into its relation or the incidence. In this case there was a rapid growth of CCC despite 19 years of effective therapy and regular ultrasound monitoring.

CONCLUSION

Due to the lack of studies and the existence of conflicting theories affirming both reduced and increased risk of hepatic neoplasia in patients with Wilson's disease, the authors recommend that a preventive approach should be adopted. We consider, and this patient was a particular difficult example, that a preemptive and regular imaging screening should be performed. We agree with the hepatic ultrasound screening, with interval similar to that used in cirrhotic patients (every six month) should be applied, with alternative imaging studies (CT or MR) and shorter intervals (3 months) applied when facing a new and/or undefined nodule. We agree with the common conclusion in the publications related to Wilson disease, that more studies and bigger populations are needed to understand more and better this condition.

Conflicts of interest: the authors declare that there is no potential conflict of interest relevant to this article.

Authors' contribution: Correia, Fernando Rocha and Corga da Silva, Rogério wrote de paper; Andrade, João and Pinto, Alfredo reviewed the paper.

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Síndrome febril indeterminado y paniculitis – un caso raro de linfoma T subcutáneo paniculitis-like

Undetermined febrile syndrome and panniculitis - a rare case of subcutaneous panniculitis-like T-cell lymphoma

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ABSTRACT

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is an extremely rare form of skin lymphoma that primarily involves subcutaneous adipose tissue. SPTCL diagnosis is demanding because of its nonspecific systemic features, such as fever or weight loss, that usually mimic other more common conditions. Further complicating diagnosis, lesion biopsies are often inconclusive. For this matter, patients are frequently seen by different clinicians and may be submitted to various cutaneous biopsies before a definitive diagnosis is reached.

We present the case of a 64-year-old man with a two-month history of fever and subcutaneous nodular lesions scattered by the lower limbs and torso, whose final diagnosis of SPTCL illustrates the main features of the disease as well as the challenge of its identification.

Keywords: cutaneous T-cell lymphoma, panniculitis, diagnosis, biopsy.

INTRODUCTION

Subcutaneous panniculitis like T-cell lymphoma (SPTCL) is a rare cytotoxic T-cell lymphoma characterized by the infiltration of the subcutaneous tissue by neoplastic cytotoxic T cells simulating panniculitis.[1] First described in 1991, only in 2001 the World Health Organization defined it as a distinct nosological entity.[2] It affects women slightly more often than men and can occur at any age.[2,3] We report the case of a patient with a prolonged febrile syndrome associated with panniculitis-type subcutaneous nodules, whose final diagnosis of SPTCL was a challenge.

CASE REPORT

A 64-year-old man was admitted for febrile syndrome associated with subcutaneous nodular lesions on the legs, abdomen and back for the last two months. The patient had a personal history of myelodysplastic syndrome, diagnosed one year before, due to weight loss and moderate thrombocytopenia, classified as low risk according to the International Prognostic Scoring System. For this purpose, he was medicated with prednisolone 5mg id for 9 months and weekly darbopoetin 500mcg for 4 months, due to the subsequent onset of anemia.

Two months before admission, he referred the appearance of papulonodular cutaneous lesions, hard and nontender, scattered over the lower limbs and torso. One of the right leg nodules had been biopsied, revealing small lymphoid cells with nuclear polymorphism, histiocytic cells and necrosis. The lymphocytic infiltrate was CD4>CD8, CD56 - and granzyme – and had no evidence of lobular rimming of lymphocytes. This result was first interpreted as a nonspecific lymphocytic panniculitis, of probable reactive nature and the patient was told to increase the dose of prednisolone to 20mg a day, without clinical improvement. A few weeks later, he started fever, a peak per day. For that matter he was given antibiotic therapy with cefuroxime and clindamycin for a week, maintaing symptoms. About one month after the onset of fever, the patient was hospitalized.

On examination at admission, he had mild cutaneous pallor and multiple subcutaneous nodules on both legs and thighs, abdomen, thorax and dorsal region. He had also a palpable hard, adherent and painless mass on the left maxillar region, confounded with the parotid gland. The remaining examination was unremarkable.

Laboratory exams were performed and are described in Table 1.

A chest-abdomen-pelvis computed tomography was done, but did not reveal any nodules, masses or organ enlargements, although the subcutaneous tissue of thorax and abdomen showed diffuse edematous infiltration (Fig. 1).

Due to the presence of a left maxillary mass, he performed an ultrasound that revealed a solid, heterogeneous formation of 30x17mm, with nonspecific features, likely to be a lipomatous mass.

During hospitalization, the patient maintained fever and new subcutaneous nodules developed. We decided to perform a simultaneous biopsy of the left maxillary mass and one of the left thigh subcutaneous nodules. The maxillary tissue biopsy (Fig. 2) showed diffuse but moderate infiltration of small CD8+/CD4- lymphocytes, and prominent presence of CD68+ histiocytic cells that conferred a pattern of panniculitis. Histiocytes surrounded vacuoles and outlined granulomas. There was also rimming of vacuoles by CD8+ lymphocytes. The biopsy of the subcutaneous nodule of the leg would be identical. Based on pathology results, a diagnosis of SPTCL involving extranodal adipose tissue was made.

The study of bone marrow revealed dysplastic alterations of the erythroid line, with 3.8% of blasts and 7% of ringed si-

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Table 1: Relevant laboratory tests performed during febrile panniculitis differential diagnosis

Laboratory study	Result	Reference range
Hemoglobin	8.5	13 – 17.5 g/dL
Mean corpuscular volume	99.5	80 – 100 fL
Leucocyte count	2380	4 – 10 x 103/µL
Neutrophils	1330	2 – 7 x 103/µL
Linfocytes	760	1 – 3 x 103/µL
Platelets	52	150 – 400 x 103/µL
ESR	57	<20 mm/1st hour
C reactive protein	6.75	<0.8 mg/dL
Creatinine	61.6	64 – 104 mmol/L
Total protein count	60	66 – 83 g/L
Albumin	34	35 – 52 g/L
Total bilirrubin	34.2	5.1 – 20.5 mmol/L
Alanine transaminase	7	< 45 U/L
Aspartate transaminase	31	< 35 U/L
Alkaline phosphatase	42	42 – 150 U/L
Lactate dehydrogenase	489	125 – 220 U/L
Creatine kinase	21	< 171 U/L
Antinuclear antibody	Negative	-
Anti-dsDNA	0.60	Negative < 10 IU/mL
C3	152	88 – 252 mg/dL
C4	43	12 – 72 mg/dL
p-ANCA	Negative	-
c-ANCA	Negative	-
ECA	36	8 – 52 U/L
Blood cultures	Two negative sets	-
Rose bengal reaction	Negative	-
Borrelia antibodies	IgG and IgM negative	-
Leptospira antibodies	IgG and IgM negative	-
Syphilis screening	Negative	-
IGRA	Negative	-
HIV screening	Negative	-
Hepatitis B	Negative	-
Hepatitis C	Negative	-
Parvovírus	IgG positive, IgM negative	-
Cytomegalovirus	IgG positive, IgM negative	-
Epstein Barr virus	IgG positive, IgM negative	-
SPE	No relevant abnormalities	-
Imunoglobulin count	Normal	-
Serum immunofixation	No relevant abnormalities	-
Urinalysis	No relevant abnormalities	-

Legend: ESR: erythrocyte sedimentation rate; Anti-dsDNA: anti-double stranded DNA antibody; C3/C4: complement component 3/4; p/c-ANCA: perinuclear/cytoplasmatic anti-neutrophil cytoplasmic antibodies; ECA: angiotensin conversor enzyme; IGRA: Interferon gamma release assay; HIV: human imunodeficiency virus; SPE: serum protein electrophoresis

Fig. 1. Chest-abdomen-pelvis computed tommography showing diffuse subcutaneous nodular formations and subcutaneous edema (A), resolved 9 months after initiating treatment (B)

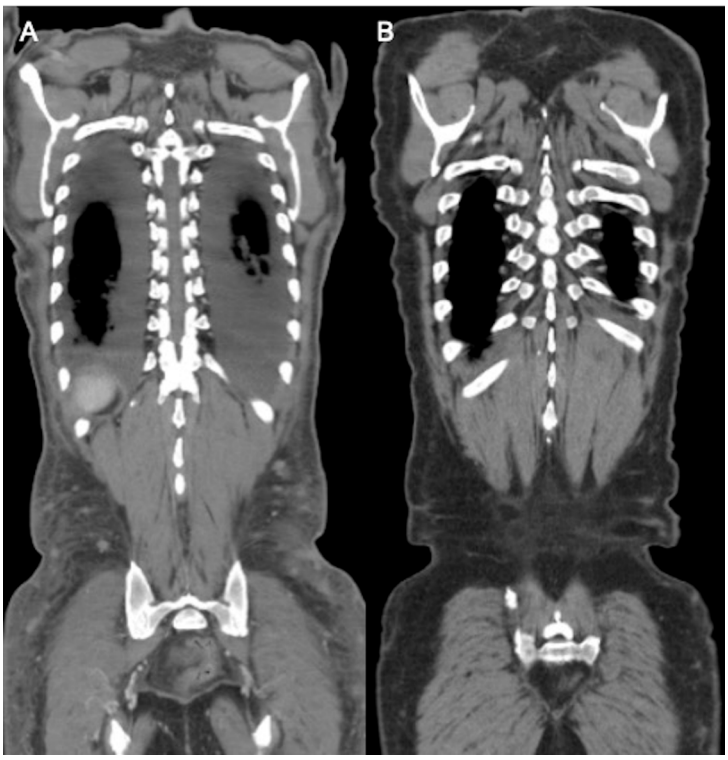
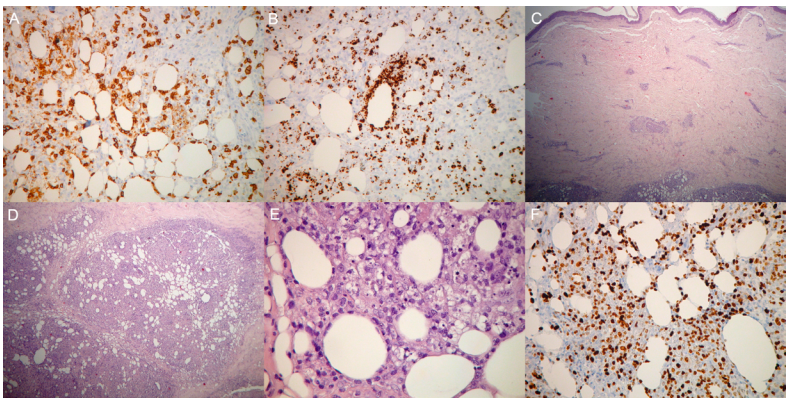


Fig. 2. Biopsy of maxillary subcutaneous nodule. (A) CD8 staining the atypical cells rimming fat space, ×100. (B) Tumour cells have a cytotoxic phenotype and express granzyme. (C) Infiltrate is confined to the subcutaneous tissue with no involvement of the overlying dermis or epidermis, Hematoxylin-Eosin, x40. (D) Predominant involvement of fat lobule by the infiltrate, Hematoxylin-Eosin, x100. (E) Neoplastic cells rim fat cells, Hematoxylin-Eosin, x200. (F) Ki67 expression, x100.



deroblasts, compatible with the diagnosis of myelodysplastic syndrome, but excluded organ involvement by the lymphoma.

The patient started treatment with prednisolone 1mg/kg/day (30mg bid) and cyclosporine 2.5mg/kg/day (75mg bid) with resolution of fever and disappearance of the subcutaneous nodules, as well as recovery of blood cell counts to normal values.

Eighteen months after diagnosis, he is asymptomatic, there is no relapse of subcutaneous nodules neither systemic symptoms related to lymphoma. The dose of prednisolone has been slowly tapered to the current dose of 15mg id, as well cyclosporin that has also been reduced to 50mg bid.

DISCUSSION

SPTCL was initially defined as a cytotoxic T-cell lymphoma with either an αβ or a γδ T-cell phenotype, since both types share a panniculitic presentation.[2] However, a more in-depth knowledge of these diseases showed clinical, histological and immunophenotypical differences. The αβ T-cell phenotype is typically CD4-, CD8+, CD56- and carries a more favorable prognosis. The γδ phenotype is CD4-, CD8- with co-expression of CD56 and is associated with a poor prognosis and much more frequent complications, namely hemophagocytic syndrome.[3] Today, the term SPTCL is applied only to the αβ type.

Patients report the appearance of multiple subcutaneous nodules of varying diameter (1 to 20 cm)[1], more often distributed in limbs and trunk. These are generally painless and rarely ulcerate, a feature most commonly associated with γδ subtype. In early stages, the nodules may disappear spontaneously, leaving areas of lipoatrophy, appearing later elsewhere in the body.[1] Systemic symptoms such as fever, weight loss, sweating and myalgias are common, but only a minority of patients have lymphadenopathies or organomegalies. Evidence of lymphoproliferative disease outside the subcutaneous tissue is rare in SPTCL.[1] Bone marrow involvement is rare but should be excluded.[4,5] In our case, even though bone marrow involvement by T cell lymphoma was excluded, we hypothesize that the myelodisplastic syndrome could be a paraneoplastic manifestion of the lymphoproliferative disease, considering the recovery of platelet count, hemoglobin and leukocytes to normal values when immunosuppressive treatment was initiated.

Differential diagnosis of panniculitis and fever includes autoimmune, infectious diseases and differentiation from other types of cutaneous or subcutaneous lymphomas.

About 20% of patients with SPTCL have an associated autoimmune disease, mostly systemic lupus erythematosus[2,6], although there are reports of association with juvenile rheumatoid arthritis, Sjogren's syndrome or rheumatoid arthritis.

In many cases, patients with SPTCL have a delayed diagnosis due to its presentation with nonspecific symptoms and signs. Additionally, identification of its histological findings requires experience and strong clinical suspicion. Patients are often seen several times by different clinicians and may be submitted to various cycles of empiric antibiotic therapy or cutaneous biopsies of inconclusive result, before a definitive diagnosis is reached.[9]

Due to rarity of this disease, there is no standardized therapy for SPTCL.[7,8] Cyclosporine may be a good option as a first-line therapy even in patients with disseminated disease due to favorable safety profile and ease of administration.[7] Similarly, monotherapy with systemic corticosteroids has achieved complete remission of SPTCL in various case reports.[8] For this matter, recent studies suggest that immunosuppressive drugs should be used as primary therapies for SPTCL patients.[9] Standard chemotherapy remains an option for refractory or relapsed patients. Generally, SPTCL carries a good prognosis, with a 5-year overall survival of 80%.[3]

Awareness of SPTCL is essential in a differential diagnosis of panniculitis, even if features of a different disease are present.

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Síndrome de Cushing ATCH-dependiente durante el embarazo tratado con metirapona

ACTH-dependent Cushing's syndrome during pregnancy treated with metyrapone

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ABSTRACT

Cushing's syndrome (CS) rarely occurs during pregnancy due to the influence of the hypercortisolism on the reproductive axis, with only a few cases described. We present a case of a 32 years-old woman diagnosed with ACTH-dependent CS and no clear pituitary lesion on the MRI. She was on ketoconazole when she discovered she was 8-weeks pregnant. Ketoconazole was stopped and a conservative management was decided. At 26 weeks of gestation, the patient developed gestational diabetes and treatment with metyrapone was started. Metyrapone was well tolerated and the pregnancy proceeded without further complications. She gave birth to a male infant, via cesarean section, at 36 weeks, with no apparent teratogenic effects of metyrapone. Many authors consider surgery as the first-choice treatment in pregnant women with CS but there is no consensus on the best management in such patients. Pharmacological treatment with metyrapone may be a safe and effective alternative.

Keywords: Cushing's disease; Pregnancy; Metyrapone.

Palabras clave: Enfermedad de Cushing; Embarazo; Metirapona.

INTRODUCTION

Cushing's syndrome (CS) is a rare disease in pregnancy because fertility is reduced, due to the hypercortisolism and/or hyperandrogenism[1,2]. Hypercortisolism during pregnancy is associated with adverse maternal and fetal outcomes, such as arterial hypertension, gestational diabetes or glucose intolerance, heart failure, preterm labor and intrauterine growth retardation[2-4]. Because of its rarity in pregnancy, it remains a diagnostic and therapeutic challenge[3]. Surgical treatment is considered to be the most successful option[1,5], although treatment is usually individualized[2]. Some pharmacological drugs, such as metyrapone and ketoconazole, are useful to treat CS in pregnancy[4].

We present a case of a patient who presented with Cushing's disease that became pregnant in the setting of hypercortisolism and was treated during pregnancy with metyrapone.

CASE REPORT

A 32-year-old female was referred to Endocrinology due to severe hirsutism and central obesity. She had a history of non-intentional weight gain of 10 kg (body mass index of 36.6 kg/m^2) and menstrual irregularities over the past 2 years. On examination, she had hirsutism (modified Ferriman-Gallwey Scale score of 15 points) and no florid signs of CS, namely facial plethora, acne, hyperpigmentation or striae. Etiological study was compatible with ACTH-dependent CS (Table 1). Pituitary magnetic resonance imaging (MRI) showed an asymmetry on the left side of the pituitary gland, which could correspond to a pituitary microadenoma (Figure 1). She underwent inferior petrosal sinus sampling, which confirmed left lateralization of the microadenoma. Treatment with ketoconazole 200mg daily was initiated and the patient was scheduled to a pituitary surgery.

A few weeks after treatment initiation, the patient discovered she was 8-weeks pregnant. Ketoconazole was stopped and the case was discussed in an endocrine multidisciplinary team meeting, including Endocrinology, Obstetrics and Neurosurgery specialists. A decision of a conservative management was made considering the risks for both mother and fetus of transsphenoidal surgery during the first trimester and the lack of consistent evidence regarding medical treatment during pregnancy. She was kept under close antenatal surveillance and no complications were documented during the first trimester of pregnancy.

At 26 weeks of gestation, the patient was diagnosed with gestational diabetes following an abnormal oral blood glucose tolerance test and required medical treatment with metformin and glargine insulin. At this point, signs of hypercortisolism,

Figure 1. Pituitary magnetic resonance imaging (MRI) showed an asymmetry on the left side of the pituitary gland, which could correspond to a pituitary microadenoma

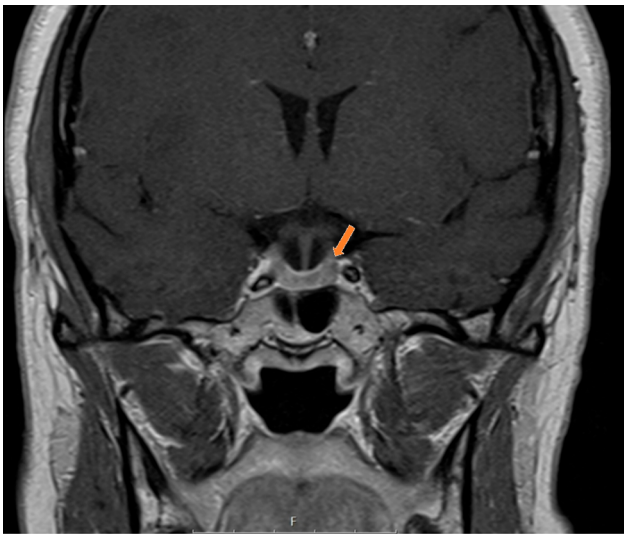

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Table 1. Biochemical results leading to diagnosis of Cushing's Disease

Plasma Measurements					
ACTH 8H: 51.5 pg/mL (reference range: 0-46)					
Cortisol 8H: 21.5 ug/dL (reference range: 6.2-19.4)					
Cortisol post 1 mg overnight dexamethasone suppresion test: 14.1 ug/dL (reference: <1.8)					
Cortisol post combined low-dose dexamethasone-CRH test: 26.1 ug/dL (reference: <1.4)					
Urine Measurements					
Free urinary cortisol: 555.7 ug/24H (reference range: 20-90)					
Bilateral inferior petrosal sinus (IPS) sampling for ACTH levels (pg/mL)					
Reference for localization: pituitary/periphery ratio >2 and >3 after CRH. Reference for lateralization: higher side/lower side ratio > 1.4					
Time	Right IPS	Left IPS	Peripheral	Ratio pituitary/periphery	Ratio left/right
0'	38,8	161,0	31,7	5.1	4.1
3'	116,0	>1250,0	47,6	26.3	10.8
5'	110,0	637,0	92,2	6.9	5.8
10'	110,0	1087,0	89,5	12.1	9.9
15'	113,0	>1250,0	86,5	14.5	11.1

such as striae, became more apparent. She was normotensive and there was a normal development of the fetus, with no obstetric complications. Cushing's treatment options were again discussed in an endocrine multidisciplinary team meeting. The risks associated with pituitary surgery during pregnancy, for both mother and fetus, were considered to be higher than the likelihood of surgical cure, in view of the size and the location of the microadenoma. Therefore, it was decided not to intervene surgically. Because of the risks of hypercortisolism, pharmacological treatment was decided and, at the 27th week of gestation, the patient started taking metyrapone 250mg four times a day, with dose titration every three weeks.

Metyrapone was well tolerated, with no side effects apart from slight exacerbation of the hirsutism. There was a decrease in 24-hour urinary free cortisol levels (until 2-times the upper limit) following treatment with metyrapone (Graphic 1).

She remained normotensive during pregnancy, blood glucose levels were within range with medication and there were no apparent fetal complications. She gave birth to a male infant via cesarean section following premature rupture of membranes at 36 weeks of gestation. The child weighted 3380 grams and had APGAR score of 5 at 1 minute, 8 at 5 minutes and 10 at 10 minutes. The newborn's progress was uncomplicated and no adverse fetal effects of metyrapone treatment were apparent. In the postpartum period, blood glucose levels were within normal range without medication and the patient remained normotensive. There were no maternal complications apart from the healing of the caesarian section, which was impaired and required treatment with vancomycin following the development of cellulitis.

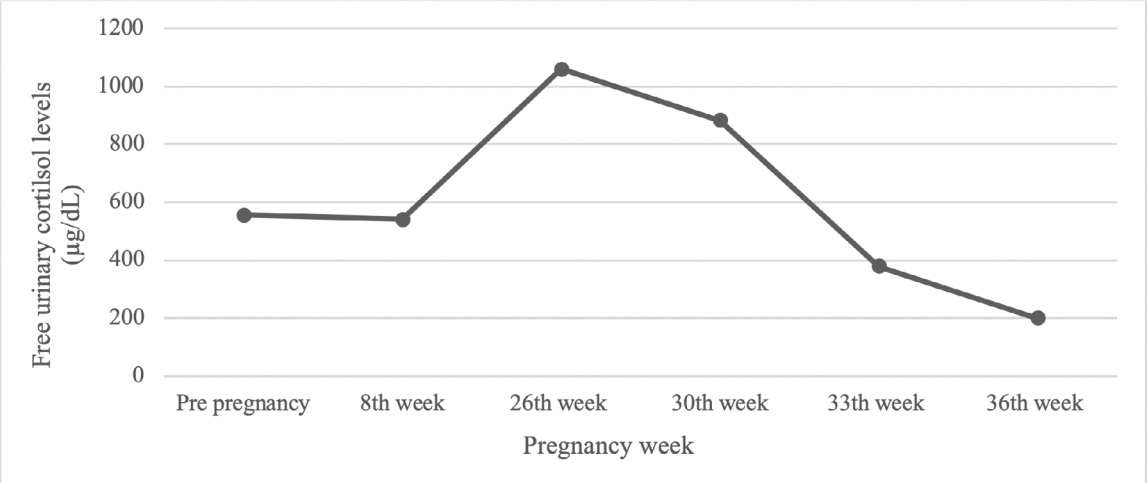
Maternal urinary cortisol excretion increased following delivery, requiring an increase in the dose of metyrapone up to 3000 mg daily. She underwent transsphenoidal surgery and histopathology confirmed a corticotroph adenoma with tumor cells showing a positive staining for ACTH, LH and prolactin. Morning serum cortisol levels following pituitary surgery were 13.8 µg/dL, suggesting maintenance of the disease.

DISCUSSION

CS is a rare disease in pregnancy as hypercortisolism and hyperandrogenism suppress the gonadal axis and ovulatory disorders are common[1,2,6]. The first published case of Cushing's syndrome in pregnancy was reported by Hunt and McConahey in 1953[7], with fewer than 200 cases described in the literature[3]. Contrary to non-pregnant patients, where the most common cause of CS is a pituitary adenoma (70%), in pregnancy the incidence of adrenal adenomas is about 60% whereas pituitary disease accounts for only a third of the cases[4]. Due to physiological changes in the hypothalamic–pituitary–adrenal axis, results of hormonal tests during pregnancy are difficult to interpret, and the diagnosis of CS during pregnancy is remarkably challenging. During pregnancy, corticotropin-releasing hormone (CRH) and ACTH plasma levels increase in the first trimester due to placenta production[4,8]. This results in an elevation of serum, salivary and urinary cortisol levels, but the cortisol secretion maintains its circadian rhythm through the pregnancy[8]. Even taking into account the increase of corticosteroid-binding globulin (CBG) due to high levels of estradiol during pregnancy, which falsely increases serum cortisol levels, serum-free cortisol levels increase during pregnancy by the 11th week about 1,6 fold and urinary free cortisol levels increases up to threefold the normal range[4,8]. It is very important to take these physiological changes into account in order to make a correct diagnosis of CS during pregnancy. Moreover, they are particularly significant during monitoring of treatment of a pregnant woman with CS, once aiming to normalize cortisol levels in pregnancy with pharmacological treatment could result in hypocortisolism of the fetus.

Because of the rarity of this condition, with few cases reported, definite conclusions and recommendations for the

Graphic 1. Excretion of free cortisol levels in 24h urine sample during pregnancy
(normal range in non-pregnant women 20-90 µg/24h)



best management for CS during pregnancy are not available[2]. The chosen approach is usually individualized, depending on the etiology of CS, the severity of hypercortisolism and the pregnancy stage[2]. Equally to non-pregnant women, surgery is the definite treatment in pregnant CS patients and endoscopic transsphenoidal approach or adrenalectomy, ideally between the 12th and 29th weeks of gestation, is often recommended as the first treatment option[1,2,5]. Nonetheless, it is described that most pregnant women with CS didn't receive any specific treatment during pregnancy[2]. In women who were treated during pregnancy, the main treatment of CS was indeed surgery, but as previously mentioned, most cases during pregnancy are adrenal disorders and, to our knowledge, there are only twelve published case reports of transsphenoidal surgery for CD during pregnancy[9]. Taking into account the possible adverse outcomes of pituitary surgery, which is associated with more morbidity and inferior rates of surgical cure compared to adrenalectomy, the patient in our case was treated with transsphenoidal surgery only after the delivery.

When surgery is not possible or contraindicated, conservative medical treatment with steroidogenesis inhibitors are an option in order to control the hypercortisolism and prevent complications[4]. In literature, the most commonly used drug is metyrapone, in 70% of cases, followed by ketoconazole in 15%, aminoglutethimide in 3%, cyproheptadine in 6%, cabergoline in 3%, and mitotane in 3%[2]. In our case, metyrapone was chosen to control the hypercortisolism, starting in the second trimester of pregnancy following the development of gestational diabetes. Although there aren't any available studies in pregnancy, metyrapone seems to be a safe alternative to surgery in the control of hypercortisolism, with only one case described of fetal hypoadrenalism[4,10]. Metyrapone inhibits the last step in cortisol biosynthesis through inhibition of the 11-beta hydroxylase enzyme and the main precautions are due to the adverse effects of the increased levels of 11-deoxycorticosterone, which can cause hypokalemia, edema, hypertension and progression to eclampsia[1,4]. However, these side effects are infrequent and the dose should be tampered until urinary cortisol levels are reduced to the upper limit of the observed in normal pregnancy[4,10]. Ketoconazole, a well-known antifungal agent, is less used during pregnancy because it crosses the placenta and has teratogenic and anti-androgenic effects in animal studies[4]. For these reasons, treatment with ketoconazole was stopped once the pregnancy was confirmed. However, teratogenic and anti-androgenic effects of ketoconazole had not been described in humans and this drug has been used successful in pregnancy without significant side effects[11,13]. In our case, the patient was medicated with ketoconazole during the first weeks of pregnancy, a period in which there is important embryonic development, and no teratogenicity was noted.

Corticotroph pituitary adenomas may express functional dopamine receptors and cabergoline, a dopamine agonist used in the treatment of hyperprolactinemia, has showed to be effective controlling cortisol secretion in nonpregnant patients[14]. Most studies regarding cabergoline treatment during pregnancy didn't show any increase of adverse pregnancy outcomes, however, the majority of studies refer to treatment with low doses of cabergoline and doses used in the treatment of CD are much higher than those used in the treatment of hyperprolactinemia[14,15]. As there are few reports of patients with CS treated with dopamine agonists during pregnancy, cabergoline was not our choice of treatment.

Pregnancy in patients with CS is associated with maternal and fetal complications[2,4]. In our case, our patient remained normotensive throughout the pregnancy, even after metyrapone was started, but developed gestational diabetes that required pharmacological treatment. Moreover, she had a preterm delivery at the 36th week of gestation and presented with abdominal cellulitis following the caesarian section.

As CD is pregnancy is rare, there is no consensus on its best management[2]. We initially opted to manage this patient conservatively by trying to control comorbidities without using specific anti-cortisol drugs, as large studies regarding its safety during pregnancy are not available. We also opted not to perform pituitary surgery during pregnancy, after a multidisciplinary discussion with Obstetrics and Neurosurgery specialists considered the therapeutic risk-benefit for the maternal-fetal outcomes to be unfavorable. The question whether earlier pharmacological treatment or a surgical approach during pregnancy could have prevented the development of gestational diabetes or preterm labor remains; however, even in treated cases, some patients still develop complications, such as premature delivery[4]. We believe that treatment with metyrapone, initiated during the second trimester of pregnancy, reduced hypercortisolism and prevented the development of further complications. Moreover, the newborn's progress following delivery was uncomplicated and no teratogenic effects were noted.

CONCLUSION

Cushing's disease rarely occurs in pregnancy[1,2]. Hypercortisolism negatively impacts on the prognosis of pregnancy and is associated with adverse maternal and fetal outcomes[2,4].

Validated guidelines regarding treatment of Cushing's disease during pregnancy are not available so management is usually individualized[2]. As in non-pregnant women with CS, surgery is considered to the first-line treatment and medical treatment is reserved for situations where surgery is not possible or is contra-indicated[1,2,5,5]. Currently, metyrapone represents the best pharmacological treatment[3].

In our case, treatment with metyrapone was a safe alternative to surgery and prevented the development of further complications. As CD is rare in pregnancy, therapeutic decisions should be made by a multidisciplinary team consisting of Endocrinology, Obstetrics and Endocrine Neurosurgery specialists.

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Enfermedad de Weber-Christian. A propósito de un caso

Weber-Christian Disease. A case report

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ABSTRACT

Weber-Christian disease is a skin condition that features recurring inflammation in the subcutaneous fat layer and systemic symptoms. The disease is a diagnosis of exclusion characterized by a lobular panniculitis without vasculitis in histopathology.

We report an 80-year-old man with constitutional symptoms and relapsing nonsuppurative nodular panniculitis.

The purpose of the case described is to emphasize that rare diseases may occur, therefore their diagnosis can only be made with previous medical knowledge and the delay, or even the absence, in the diagnosis of these pathologies could interfere with the quality of life of patients.

Palabras clave: enfermedad de Weber-Christian, paniculitis idiopática lobular, tratamiento corticoideo.

Keywords: Weber-Christian disease, idiopatic lobular panniculitis, corticosteroid therapy.

INTRODUCTION

Panniculitis refers to a broad spectrum of diseases that involve inflammation of the subcutaneous fat layer of the skin[1]. Weber-Christian disease is an eponym for a form of panniculitis called idiopathic nodular panniculitis and the first cases as a distinct entity were described at the end of the 19th century and the beginning of the 20th century[2]. This disease is characterized by recurrent subcutaneous inflammatory painful nodules, usually located in limbs and torso; systemic symptoms and signs such as relapsing fever episodes, fatigue and polyarthralgia are also frequent and may involve the lungs, heart, intestines, spleen, kidney, adrenal glands, and even orbits[3].

Weber-Christian disease can be described as an autoinflammatory disease affecting adipose tissue and its aetiology is unknown. The key pathologic finding on histological examination is a nodular inflammatory pattern of the fat lobules. When no other cause of lobular panniculitis can be identified (such as systemic lupus, factitious, pancreatic associated, histiocytic cytophagic and alpha1-antitrypsin deficiency panniculitis) Weber-Christian disease can be diagnosed by exclusion[4,5].

It has been reported most frequently in people between fourth to seventh decades of life, and 75% of cases occur in women after the second decade of life. Also, it is an extremely rare condition in children[6].

The medical community still deliberate whether Weber-Christian disease occurs as a unique disease entity or if it is just a substitute for any lobular panniculitis with unknown cause[7].

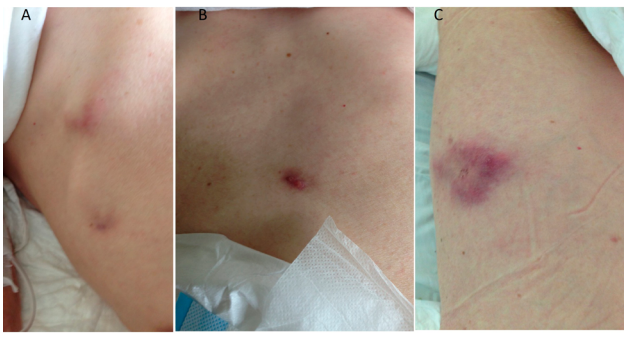
CASE REPORT

We report the case of an 80-year-old Caucasian male, resident in a rehabilitation care facility, with a past medical history of hypertension and vascular dementia. The patient was admitted to the hospital with a two-month history of relapsing fever episodes associated with generalized weakness and recurrent appearance of multiple painful nonsuppurative swellings on the trunk and thighs. Fever had a daily pattern with peaks of 38-39ºC on regular antipyretic drugs. There were no reported changes in the patient's medications nor history of thermal, mechanical or chemical trauma. He had recent travel history and local epidemiologic data were unremarkable. The patient received prior antibiotic therapy with no clinical improvement.

On the physical exam the patient was conscious, alert, pallor, no jaundice and no rash. His vitals were: blood pressure 123/69 mmHg, regular heart rate at 95 bpm, regular respiratory rate at 12 cycle/minute, temperature 38.2°C, oxygen saturation 96% on room air. Chest wall and abdominal examination reveals erythematous, oedematous and tender subcutaneous nodules well circumscribed in the right chest wall as well as in anterior abdominal wall (Figure 1), without fluctuation. There was a depressed and atrophied scar of old incisions over right thigh. Other systemic examinations were unremarkable.

Laboratory investigations showed raised inflammatory markers (C-reactive protein (CRP) 59.3 [<0.5 mg/L], leucocytes 10.300/mL, neutrophils 7000/mL, lymphocytes 2100/mL, elevated erythrocyte sedimentation rate (ESR 68mm/h) and normocytic normochromic anemia (haemoglobin 10.4 g/dL,

Figure 1. Subcutaneous nodules in the right chest wall (A and C) as well as in anterior abdominal wall (B).



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MCV 80.3 fL) with normal differential count on peripheral smear; renal function, liver biochemistry, lactate dehydrogenase, creatin-phosphokinase, pancreatic amylase were normal. Also, values for ANA, ANCA, anti-ds-DNA, serum protein electrophoresis, complement factors C3 and C4, anti-CCP, and anti-MCV were within the normal range or not detectable, respectively. Normal immunoglobulin assay including IgM 62 mg/dL (normal range, 40–230 mg/dl), IgA 372 mg/dl (normal range, 22–159 mg/dl), IgG 1079 mg/dl (normal range, 441–1135 mg/dl) and normal serum angiotensin converting enzyme (SACE) activity. Urine analysis with microscopy and urine culture were normal; three repeated sets of blood cultures were negative. Cultures for bacteria, mycobacteria, and fungi from the swelling in right thigh revealed no growth. The serologies for the following diseases were negative: Toxoplasmosis, human immunodeficiency virus, Epstein-Barr virus, hepatitis viruses, cytomegalovirus, syphilis, Q fever, brucellosis, and leptospirosis.

Posteroanterior chest radiography, transthoracic echocardiogram, sonography abdomen and computed-tomography whole-body scanning with no abnormal imaging findings.

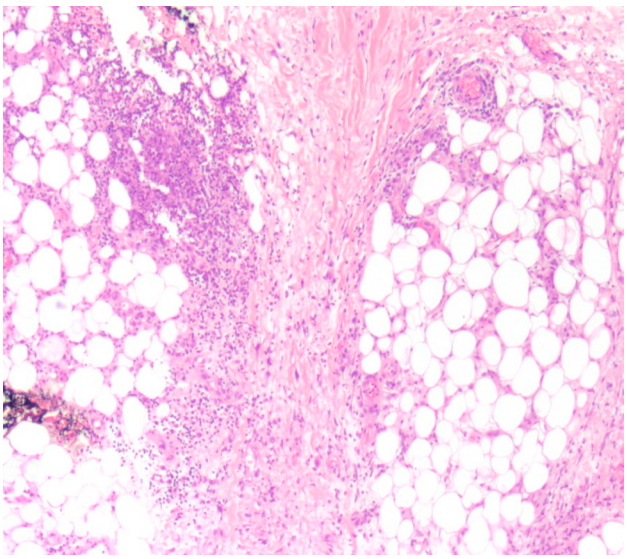
One of the painful nodules was removed and histopathologic findings revealed neutrophilic panniculitis with basophilic degeneration of collagen with haemorrhage and necrosis of subcutaneous tissue, inflammatory cellular infiltrate which was mainly composed lymphocytes infiltrating all layers of skin and band of fibroblasts and inflammatory cells in bloody stroma with no vasculitis or malignant cells (Figure 2).

Based on this clinical findings and results of the diagnostic workup, the final diagnosis of a Weber-Christian disease was established. Following treatment with high dose prednisolone, the patient's condition improved significantly and temperature as well as inflammatory markers returned back to normal levels rapidly. Also, the nodules clearly reduced in size, and the patient only reported minor pain on pressure. Therefore, patient was discharged from the hospital and on a routine check-up in the following month he presented in very good general condition with no more signs of inflammation or relapsing nodules.

DISCUSSION

The term "panniculitis" refers to a group of inflammatory disorders in which the primary site of inflammation is the subcutaneous fat[8]. The diagnosis can be challenging not only because different forms of panniculitis may be present with similar clinical findings, but also many of those are rare[5,9]. Weber-Christian disease is called idiopathic lobular panniculitis because its aetiology is unknown. Indeed, it is a rare condition characterized by an autoinflammatory disease involving adipose tissue, commonly focusing on subcutaneous nodules, inflammatory cells in the fat lobules, and systemic symptoms, such as the presence of relapsing fever[4].

Figure 2. Histopathology section of skin biopsy stained with haematoxylin and eosin showing inflammatory cellular infiltrate which is mainly lymphocytes infiltrating all layers of skin and band of fibroblasts and inflammatory cells in bloody stroma.



Although the pathogenesis of Weber-Christian disease is not finally resolved, elevated levels of circulating immune complexes in some of the patients may suggest an immunologically mediated reaction[11].

However, due to the rarity of this condition it is still under debate, if Weber-Christian disease is a unique disease entity, or if it is just a substitute for every panniculitis that does not fit a common diagnosis[7]. Therefore, increasing study and diagnostic sophistication have differentiated Weber-Christian disease from diseases such as lupus panniculitis, factitial panniculitis, panniculitis associated with pancreatic disease, histiocytic cytophagic panniculitis, and alpha1-antitrypsin deficiency panniculitis[10]. Hence, at this time, the eponym Weber-Christian disease still refers to cases of nodular panniculitis with systemic signs and symptoms that remain idiopathic.

The diagnosis of Weber-Christian disease is an exclusion diagnosis[5,7] with a lobular panniculitis without vasculitis in histopathology as it was demonstrated in our case. In patients with primarily cutaneous manifestations, the clinical course may be characterized by exacerbations and remissions of the cutaneous lesions with minimal systemic complaints for several years before the disorder subsides[13]. On the other hand, this entity has also been described in association with systemic involvement, usually involving liver, spleen, bone marrow and mesenteric adipose tissue[12].

Skin biopsy is necessary to confirm the diagnosis of panniculitis. Indeed, biopsies can provide valuable information and are indicated both in cases in which the diagnosis is uncertain or in cases in which the clinical course of a panniculitis does not proceed as expected[9]. However, the histopathologic findings are often ambiguous. In many cases, clinical correlation and careful consideration of the differential diagnosis are required to arrive at a correct diagnosis[7].

In the present case report, the described symptoms together with lobular panniculitis can also occur in other diseases such as infections, certain malignancies, alpha-1-antitrypsin deficiency, pancreatitis, systemic lupus erythematosus and cytophagic histiocytic panniculitis, rendering Weber-Christian disease an exclusion diagnosis following careful evaluation of the patient. However, all of these diseases, except alpha-1-antitrypsin deficiency, were excluded in our patient by extensive diagnostic evaluation favouring the diagnosis of a Weber-Christian disease. It did not explicitly exclude alpha-1-antitrypsin deficiency, because panniculitis is only observed in patients with severe forms of the disease[8], which would include other symptoms, like COPD and/or liver cirrhosis.

Several treatment options were reported in the treatment of Weber-Christian disease, even though, no specific uniformly effective therapy was recognized. Several reported cases showed patient clinical improvement with the use of the following therapies: fibrinolytic agents, hydroxychloroquine, azathioprine, thalidomide, cyclophosphamide, tetracycline, mycophenolate, and clofazimine[11,13]. Systemic steroids (eg, prednisone) may be effective in suppressing acute exacerbations[14]; and nonsteroidal anti-inflammatory agents (eg, indomethacin) may reduce fever, arthralgias, and other signs of malaise. Involvement of specific organs may require specific supportive drugs[12]. Our patient improved rapidly following corticosteroid treatment. The prognosis of Weber-Christian disease depends on which organs are affected, the severity of organ involvement, and the response to the therapy[13]. Significant morbidity and mortality may occur in patients with inflammation involving visceral organs[12].

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Cetoacidosis diabética euglucémica, un diagnóstico difícil de identificar

Euglicemic diabetic ketoacidosis, an easily missed diagnosis

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ABSTRACT

Diabetic ketoacidosis is a serious and potentially life-threatening acute complication of diabetes mellitus. SGLT-2 inhibitors are recommended as first-line therapy in patients unable to tolerate metformin or as second-line agents after metformin. Their use is increasing as new data show, besides improving glycemic control, weight loss, blood pressure reduction, and beneficial cardiovascular and reno-protective effects. Euglycemic diabetic ketoacidosis is a rare but potential complication of SGLT-2 inhibitors. Physicians including internists, intensivists and emergency physicians should all be aware as this diagnosis can easily be missed in the absence of evident hyperglycemia. We report a case of 61-year-old male admitted in the emergency room because of altered mental status, associated with holocranial headache. He had medical history of type 2 diabetes and had recently started a SLGT-2 inhibitor. Arterial blood gases showed a severe high anion gap uncompensated metabolic acidosis. Blood and urine ketones were high with normal serum glucose levels. The diagnosis of euglycemic ketoacidosis due to SLGT-2 inhibitor was made.

Palabras clave: cetoacidosis euglucémica, iSGLT2.

Keywords: ketoacidosis, euglycemic, iSGLT2.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious and potentially life-threatening acute complication of diabetes mellitus (DM)[1]. DKA diagnosis is based on laboratory testing showing hyperglycemia (glucose > 250 mmol/l), metabolic acidosis (arterial pH < 7.3, and serum bicarbonate < 18 mEq/l), a high anion gap as well as the presence of ketone bodies in the blood or urine[2]. Euglycemic diabetic ketoacidosis (EDKA), unlike classic DKA, presents a glucose level < 250 mmol/L and it is recently associated to sodium glucose cotransporter 2 (SGLT-2) inhibitors[3], a relatively new class of oral anti-diabetic agents which use is rapidly escalating worldwide. It is important for all clinicians to be aware of the risk of developing DKA even in the absence of evident hyperglycemia, as this diagnosis can be easily missed with potentially dangerous outcome.

CASE REPORT

A 61-year-old male with type 2 DM visited the emergency room because of altered mental status, associated with holocranial headache. The patient had no other chronic disease and was medicated with metformin 1000 mg twice a day, gliclazide 60 mg once a day and canaglifozin 100 mg, this one started 5 days prior admission. He had no history of alcohol intake or herbal, illicit drugs exposure. At admission, the patient was confused but cooperative with no focal neurological deficits. Vital signs were 36.7ºC body temperature, blood pressure 153/72 mmHg, pulse rate was 119 beats per minute, was tachypneic with 23/min respiratory rate, with normal heart sounds and pulmonary auscultation. Blood glucose level was 157 mg/dl. Arterial blood gases (ABG) showed a high anion gap uncompensated metabolic acidosis (pH: 7.21, CO2: 22 mmHg, HCO3: 9.6 mmol/L, serum lactate 1.7 mmol/L, anion gap: 22.4 mEq/L). Blood and urine ketones were high (8.0 mmol/L and 150 mg/dl respectively). Renal function was preserved, with no electrolyte disturbances (Table 1).

Other causes of increased anion gap metabolic acidosis were excluded. The diagnosis of EDKA was made and insulin infusion therapy, intravenous hydration with 5% dextrose fluid considering blood glucose and bicarbonate were initiated. The patient was admitted to intensive care unit where in 2 days the EDKA had completely resolved with normalization of acidosis, blood ketones and anion gap. He was then transferred to Internal Medicine ward and discharged home after 3 days without the SGLT-2 inhibitor.

DISCUSSION

Table 1. Admission laboratory tests

Laboratory tests (units)	Patient´s values	Reference value
Random blood sugar (mg/dl)	157	65 - 100
Hemoglobin (g/dl)	15,2	13 - 17
White blood cells (10^9/L)	10,2	4,0 - 10,0
Platelets (10^9/L)	211	150 - 400
Sodium (mmol/L)	139	136 - 144
Potassium (mmol/L)	3,9	3,5 - 5,1
Chloride (mmol/L)	107	98 - 107
Anion Gap (mEq/L)	22,4	
Blood Ketones (mmol/L)	8	
Urea (mg/dl)	87	74 - 106
Creatinine (mg/dl)	1,2	0,7 - 1,2
Arterial Blood Gas:		
pH	7,21	7,35 - 7,45
Bicarbonate	9,6	21,0 - 28,0
pO2 (mmHg)	86	83 - 108
pCO2 (mmHg)	22	35 - 48
Lactates (mmol/L)	1,7	0,0 - 1,3
Urine Ketones (mg/dl)	150	< 5,0
Urine Glucose (mg/dl)	1000	< 30,0

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SGLT-2 inhibitors are recommended as first-line therapy in patients unable to tolerate metformin or as second-line agents after metformin[1,4]. They act by inhibiting the SGLT-2 that are expressed in the brush border membrane of the renal proximal tubular cells and accounts for 90% of total renal glucose absorption, increasing urinary glucose excretion[5].

Their use is increasing as new data show, besides improving glycemic control, weight loss, blood pressure reduction, and beneficial cardiovascular and reno-protective effects. It is expected that SLGT-2 inhibitors use will only increase over time[6].

They are generally well tolerated but have several well-recognized adverse effects that should be considered to optimize their risk to benefit ratio[7].

Ketoacidosis is an adverse effect of SGLT-2 inhibitors use in patients with both type 1 and more rarely type 2 diabetes. Classically is defined as a presence of the triad of hyperglycemia (glucose > 250 mmol/l), metabolic acidosis (arterial pH < 7.3, and serum bicarbonate < 18 mEq/l), a high anion gap as well as the presence of Ketone bodies in the blood or urine[2]. Our patient had ketoacidosis, yet his blood glucose level was far below the usual for the "traditional" DKA. The absence of elevated serum glucose levels can delay the recognition and diagnosis of this life-threatening state by the clinician that can lead to a potentially fatal outcome or longer hospital/intensive care unit (ICU) stay[8].

The mechanism of EDKA[9] has not been fully elucidated. Some authors propose that by increasing urinary glucose excretion, which in turn reduces insulin secretion from pancreatic β-cells, results in a lowering of the anti-lipolytic activity of insulin and consequent stimulation of the production of free fatty acids. These free fatty acids are then converted to ketone bodies by β-oxidation in the liver. Also, there is recent evidence demonstrating the presence of SGLT-2 inhibitors in pancreatic α-cells which directly stimulates glucagon secretion, with further reduction of the insulin-to-glucagon ration, contributing to ketogenesis.

To minimize DKA episodes associated with SGLT-2 inhibitors, prescribing these agents should be avoided in DKA-prone patients, including those with type 1 DM, diabetes-related autoimmunity and those with previous history of DKA. Stopping SGLT2 inhibitors should be considered if patients are under conditions that can precipitate DKA[3,7,9].

Once recognized, the treatment of EDKA is similar to that of DKA and involves rapid correction with intravenous fluids, correction of electrolyte abnormalities and insulin drip with a dextrose solution until anion gap and acidosis normalize[10].

The authors pretend to alert to the possibility of having ketoacidosis with normal glucose levels, which is rare, easy to miss and difficult to diagnosis if not considered, mainly when there is history of SGLT-2 inhibitor use. These patients despite the absence of hyperglycemia should be analyzed with blood gas samples and blood and urine ketones checked.

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Enteropatía asociada a olmesartán

Olmesartan-associated enteropathy

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RESUMEN

La toma de antagonistas de los receptores de la angiotensina II (ARA II) puede desarrollar una enteropatía similar a la enfermedad celíaca, compartiendo incluso el mismo patrón histopatológico. El desconocimiento de esta entidad puede llevar a errores diagnósticos y terapéuticos. Se presenta el caso de un varón de 69 años, hipertenso en tratamiento con olmesartán, que es valorado por presentar diarrea de dos semanas de evolución, junto con pérdida ponderal de 5 kilogramos. Se realizó una biopsia de duodeno, donde se objetivó un patrón Marsh 3c. Tras la retirada del fármaco se confirma la mejoría clínica. Una segunda biopsia evidenció una regresión histológica a patrón Marsh 3.

Palabras clave: olmesartán, enteropatía, enfermedad celiaca, histopatología.

Keywords: olmesartan, enteropathy, coeliac disease, histopathology.

INTRODUCCIÓN

La toma de antagonistas de los receptores de la angiotensina II (ARA II) se ha asociado a una entidad iatrogénica conocida como enteropatía *esprue-like*. Esta tiene una presentación clínica similar a la enfermedad celiaca, consistente en diarrea crónica, cuadro malabsortivo y pérdida de peso. A diferencia de esta patología, el estudio genético de celiaquía resulta negativo y no se produce una mejoría clínica tras la retirada de gluten en la dieta. Anatomopatológicamente, ambas entidades comparten el mismo patrón histopatológico.

CASO CLÍNICO

Se presenta el caso de un paciente varón de 69 años, con antecedentes personales de hipertensión arterial (HTA) en tratamiento con olmesartán, hipertrofia benigna de próstata (HBP) e hipotiroidismo en tratamiento sustitutivo. Acudió al servicio de urgencias por cuadro clínico de diarrea de dos semanas de evolución, en número de 8-9 deposiciones diarias, acuosas, sin productos patológicos, junto con pérdida ponderal de 5 kilogramos. El paciente negaba la introducción de algún nuevo tratamiento farmacológico o viajes al extranjero.

En la exploración física destacaba palidez cutánea y abdomen con dolor generalizado a la palpación superficial, sin signos de irritación peritoneal y con ruidos algo aumentados. En el resto de exploración física no se evidenciaron otros hallazgos de interés. Ante el cuadro clínico que presentaba el paciente, se decidió su ingreso en el servicio de Medicina Interna.

Analíticamente, al ingreso, destacaba hipopotasemia (3,17 mEq/l) y un leve deterioro de la función renal (creatinina 1,24 mg/dL).

Se realizaron estudios microbiológicos de bacterias, parásitos, virus entéricos o *C. difficile*, que resultaron negativos.

El estudio genético y los anticuerpos para enfermedad celiaca (HLA-DQ2/DQ8) fueron negativos.

Así mismo, se realizaron una serie de pruebas complementarias, como colonoscopia, tomografía computarizada abdominopélvica o entero-resonancia magnética, con resultados dentro de la normalidad. Posteriormente se le realizó una endoscopia digestiva alta (EDA), con toma de biopsia de las vellosidades intestinales a nivel duodenal. El estudio anatomopatológico demostró un patrón histológico Marsh 3c (Figura 1 a y 1 b).

Dado que los estudios de celiaquía resultaron negativos, se realizó un diagnóstico diferencial entre las diferentes entidades que pudiesen justificar la asociación de dicho cuadro clínico y patrón histopatológico, encontrándose entre ellos la toma de olmesartán.

Se procedió a la retirada del fármaco, con evolución favorable tras la misma presentado clara ganancia ponderal y descenso de los episodios diarreicos. Tras la estabilización clínica del paciente fue dado de alta hospitalaria con revisión dos meses después en consultas externas, previa realización de nueva EDA con toma de biopsia, demostrándose una lesión histológica Marsh 3a (Figura 2 a y 2 b), llegando al diagnóstico definitivo de enteropatía asociada a Olmesartán.

DISCUSIÓN

Olmesartán es un tratamiento antihipertensivo perteneciente a la familia de los ARAII, el cual es empleado como tratamiento de primera línea en pacientes con diabetes mellitus y enfermedad renal[1].

Su uso se ha relacionado en los últimos años con el desarrollo de enteropatía, cuyo cuadro clínico se caracteriza por diarrea crónica, pérdida de peso y cuadro de malabsorción intestinal. Dicha entidad comparte aspectos clínicos e histológicos con la celiaquía, salvo por la negatividad de los anticuerpos característicos y el HLA predisponente (HLA DQ2/DQ8) de la enfermedad celíaca, además de no presentar una mejoría sintomática tras la retirada del gluten[2].

Respecto a la sintomatología, Tapia *et al*[1] realizaron un estudio en el que se incluyeron 22 pacientes, observándose como clínica más frecuente, una media de deposiciones 6 al día, con pérdida ponderal, distensión abdominal y malabsorción asociada. Esta clínica es compatible con la que presentaba

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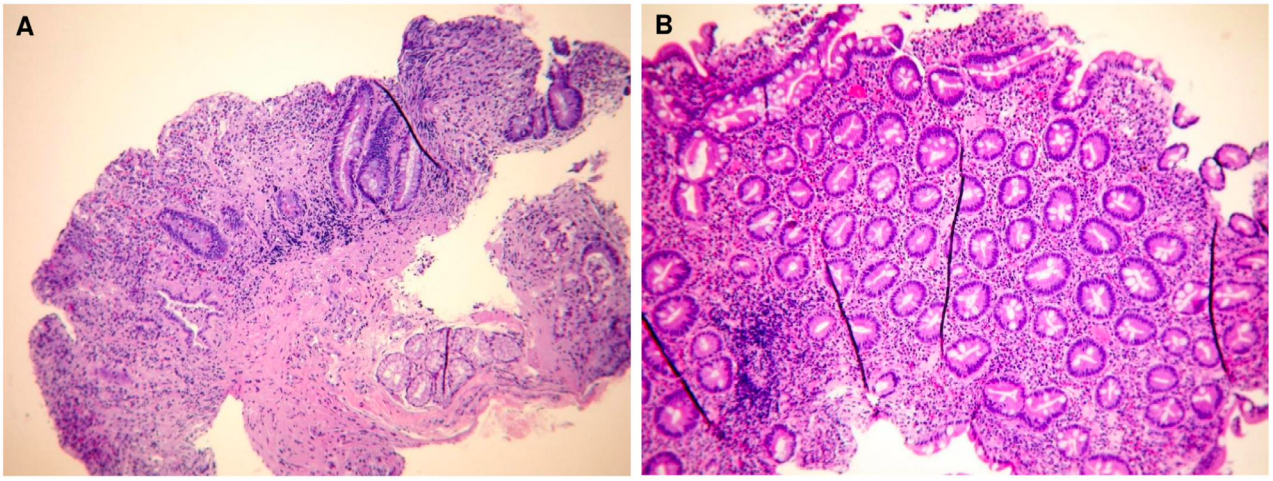
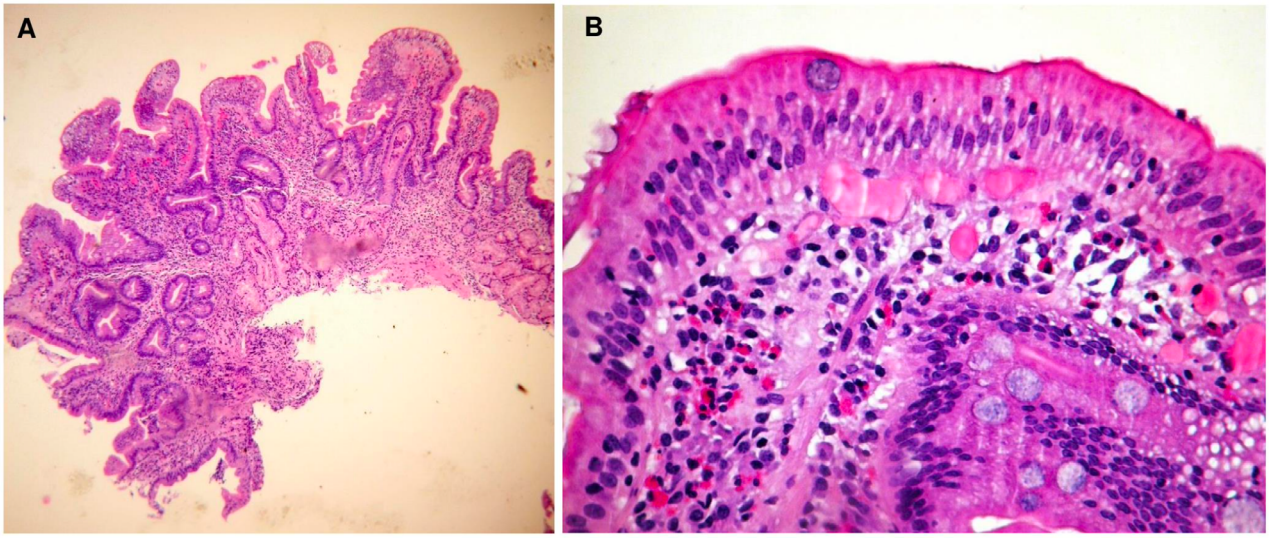
Figuras 1 A y B. Biopsia de vellosidades intestinales con tinción de hematoxilina-eosina coincidiendo con la administración de olmesartán. Se objetiva un patrón histológico Marsh 3c, observándose, en menor y mayor aumento respectivamente, atrofia total de las vellosidades con infiltrado linfocitario a nivel intraepitelial junto a algunos eosinófilos.



Figuras 2 A y B. Biopsia de vellosidades intestinales con tinción de hematoxilina-eosina tras la retirada de olmesartán. Se objetiva un patrón histológico Marsh 3A, observándose a menor y mayor aumento respectivamente, atrofia parcial de las vellosidades con infiltrado linfocitario a nivel intraepitelial junto a algunos eosinófilos.



nuestro caso, con una media de 8-9 deposiciones, junto con pérdida de peso y cuadro malabsortivo.

Histológicamente, al igual que hemos podido observar en el caso que nos acontece, se caracteriza por la afectación vellositaria de duodeno, estómago o colon, la cual sufre una atrofia junto a un aumento del infiltrado linfocitario intraepitelial[3].

Dentro del diagnóstico diferencial de enteropatía con atrofia de vellosidades en que el estudio de celiaquía resulta negativo, debemos tener en cuenta, entre otras, las siguientes entidades: linfoma, gastritis eosinofílica, colagenosis o infección por *Giardia lamblia*[2].

El mecanismo por el que el uso de ARAII produce esta patología no está aún totalmente dilucidado. Éstos podrían inhibir el factor de crecimiento transformante que se ocupa de mantener la homeostasis del sistema inmune[4]. El tiempo que tarda en producirse los síntomas desde el inicio de tratamiento y la aparición de la sintomatología nos sugiere que dicho daño inmunomediado por células en lugar de roducirse por una respuesta de hipersensibilidad tipo 1[5].

En segundo lugar, existen dos receptores de angiotensina (AT1 y AT2) los cuales se expresan por todo el tracto gastrointestinal. Los tipo AT1 mantienen la homeostasis intestinal y los tipo AT2 inducen apoptosis a nivel de las células epiteliales. Se descubrió que Olmesartán tiene mayor afinidad por los receptores AT1, por lo que pueden producir una saturación de los mismos, y como consecuencia permitir que la angiotensina circulante se una a los AT2 lo que ocasiona una apoptosis celular intestinal y a una atrofia vellositaria[4,6].

La literatura recoge con gran frecuencia casos de enteropatía asociada al uso de olmesartán. Con la intención de descubrir si esta entidad acontece con el uso de otros ARAII, Kamal

et al[7] realizaron una revisión sistemática de todos los casos de enteropatía asociada no solo al uso de olmesartán, sino también de otros ARAII. El resultado fue que, de las 248 casos que encontraron, un 94 % de los casos (233), se debieron a la toma de olmesartán, seguido de telmisartán, irbesartán, valsartán, losartán y eprosartán respectivamente.

El tratamiento de dicha entidad consiste en la retirada del fármaco, como puede observarse en caso de nuestro paciente, el cual, tras la retirada de este, presenta una mejoría no sólo clínica, sino también histológica.

CONCLUSIONES

La enteropatía por olmesartán es una entidad poco frecuente, aunque con un aumento de su incidencia en los últimos años. Es importante tenerla en cuenta en el diagnóstico diferencial de un paciente con cuadro de diarrea crónica con pérdida de peso.

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¿Otra infección urinaria o algo más?

Another Urinary Tract Infection or something more?

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ABSTRACT

Urinary tract infection (UTI) affects mostly women. Any condition that allows stasis or urinary obstruction predisposes to the development of UTI.

The authors report the case of a 37-year-old woman with a recurrent UTI who presented with right lumbar pain irradiating to homolateral inguinal region and genito-urinary symptoms, and a pelvic extensive lesion was shown in the abdominal-pelvic CT in apparent relationship with L5 nerve root compatible with a Schwannoma.

Schwannomas are usually benign tumors that rarely present malignant transformation. Repetitive UTIs may be a consequence of the mass effect or of neurological cause secondary to intraspinal schwannomas that cause urinary retention. Local recurrence or malignant change is possible, so complete tumor resection is important.

Palabras clave: infección del tracto urinario, incidentaloma, schwannoma.

Keywords: urinary tract infection, incidentaloma, schwannoma.

INTRODUCTION

Urinary tract infection (UTI) mostly affects females. Between 20-30% of women with an episode of UTI will have a recurrent episode[1]. The risk factors independently associated with recurrent UTI's in premenopausal women are frequent sexual intercourse, spermicide use, new sexual partner, first episode of cystitis before age 15 and maternal history of UTI[1]. It is the relationship between host, pathogen and environmental factors that determines the clinical outcome. Any condition that allows urinary stasis or obstruction predisposes to the development of UTI.

The authors report the case of a 37-year-old woman with a history of recurrent UTI who presented with right lower back pain with irradiation to the homolateral inguinal region and genitourinary symptoms. An apparent pelvic extensive left lesion was seen on abdominal-pelvic CT in apparent relationship with L5 nerve root, compatible with a Schwannoma.

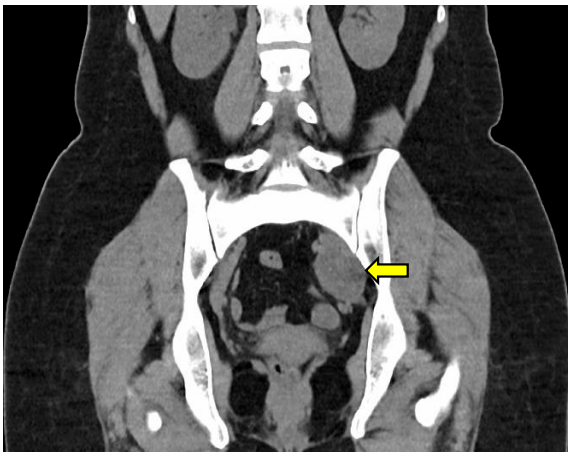
CLINICAL CASE

A 37-year-old female, leukodermic, autonomous in daily life, with a history of recurrent UTI (3 episodes per year), the last one 2 months ago, was admitted to emergency department for constant right back pain with irradiation to the right inguinal region, with 15h of evolution, intensity 8/10 without factors of relief or aggravation, polyuria, vesical tenesmus and urinary urgency.

Upon observation, she presented with pain in the right iliac fossa, without peritoneal reaction, absent renal Murphy. Analytically, she had leukocytosis 15.5x10^3µL with neutrophilia, C-reactive protein 5.6mg / dL. Urinalysis: Leucocytes 4+, nitrites +, blood 2+, proteins 1+.

Abdominal-pelvic CT scan (Fig. 1) showed: left pelvic extensive lesion at least 5x3cm in apparent relationship with L5 nerve root (schwannoma?), without bilateral hydronephrosis, requiring better characterization by MRI (magnetic resonance imaging). Given this result, the patient was admitted to the hospital for etiological study of the imaging finding.

Fig. 1. Abdominal-pelvic CT - Left pelvic extensive lesion (arrow) at least 5x3cm in apparent relationship to L5 nerve root (schwannoma?), without bilateral hydronephrosis.



During hospitalization, she underwent lumbar and sacral MRI (Fig. 2), which confirmed the existence of an extensive lesion originating in the left L5 root foramen segment, extraforaminal and homolateral pelvic extension, fusiform, 77x38x38 mm, hypo/isointense in T1, heterogeneous in T2, with multiple areas of cystic nature, compatible with bulky schwannoma with extradural extension, causing deviation of the left ovary. Smaller lesion with the same signal characteristics involving S1.

She was discharged oriented to Neurosurgery and Internal Medicine consultation. The surgeons have decided to take a "wait and see" attitude because there were no symptoms that warranted surgical intervention.

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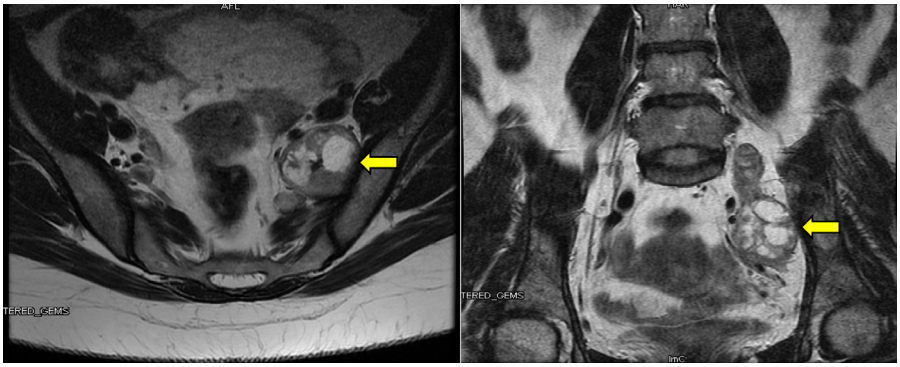
Fig. 2. Lumbar and sacral MRI - Extensive lesion (arrows) originating in the foraminal segment of the left L5 root compatible with bulky schwannoma with extradural extension.



DISCUSSION AND CONCLUSION

Schwannomas are encapsulated solid tumors of Schwann cells and often occur isolated or as multiple tumors in the context of genetic diseases[2]. They are usually benign with rare malignant transformation and are found in the head, neck, posterior mediastinum and extremities[3].

The incidence of spinal Schwannomas, also called neuromas, ranges from 3-4 cases/1,000,000 people annually[4]. There is no difference in prevalence between males and females, and it affects people mainly between 40-50 years old[4].

The cervical and lumbar regions are the most affected, however several clinical cases showed that most schwannomas were located in the lumbosacral region most frequently between L4-L5. In the literature, 15% of intraspinal schwannomas extend through an opening of the dura and present as a mass with an intradural and extradural component[2].

Schwannomas which have a slow growing may be asymptomatic for months or years after their onset. The presence of symptoms depends on the location and size of the tumor and may range from radicular pain, loss of muscle strength or sensitivity and incontinence.

In most cases the reason for the appearance of this type of tumors is unknown. They are sometimes linked to genetic diseases such as neurofibromatosis, schwannomatosis or Carney complex syndrome[5].

Schwannomas can be difficult to diagnose since symptoms may resemble those caused by other diseases. In the reported case, it was initially thought to be acute renal colic due to the clinical presentation, so the tumor found after radiological examination became an incidentaloma. The patient's urinary symptoms could be due either to tumor compression and/or to venous congestion or ischemia. Some authors report that urinary or fecal incontinence rate reaches 5% in patients with spinal schwannoma[6]. In these cases, urodynamic test is mandatory[6]. The preferred exam is MRI, which determines whether the tumor is located outside the nerve or affects the nerve and involves surrounding structures. Tumor biopsy is confirmatory.

Treatment depends on the location of the tumor, the severity of the symptoms and its benign or malignant nature. Usually, patients undergo total surgical resection of the tumor. There are sometimes obstacles that make complete removal impossible, such as adherence to the spinal cord at risk of bleeding or inflammation or adherence to extradural structures. In these cases, radiotherapy is mandatory, but the risk-benefit of its use should always be judged, particularly in women of reproductive age[7].

Apparently, an improvement of urinary symptomatology is rare after tumor excision[6]. In cases such as this described here, a postoperative rehabilitation program is necessary, and a urodynamic test after the surgical intervention may be beneficial for comparison with the previous test. The prognosis correlates with the preoperative neurological condition. Normally complete resection of the tumor is curative and if this is not possible, tumor recurrence is likely[4].

The reported case is relevant since clinicians facing recurrence of urinary tract infections should be aware of factors contributing to their occurrence, such as: frequent sexual intercourse, spermicide use, new sexual partner, first episode of cystitis before age 15, maternal history of UTI as well as anatomical factors such as kidney stones, urinary tract malformations, tumor mass compression or neurological injury[1].

Schwannomas are usually benign tumors that rarely show malignant transformation. It may appear on the head, neck, posterior mediastinum, spine and extremities. Repetitive UTI's in these cases may be a consequence of the mass effect or of neurological cause like intraspinal schwannomas causing urinary retention. Local recurrence or malignant transformation is possible, so complete resection of the tumor is important.

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Ictus isquémico como forma de presentación de una disección aórtica tipo A.

Type A aortic dissection presented as a stroke mimicker

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ABSTRACT

Acute aortic dissection is a rare but lethal cardiac disease involving the aorta and it remains a challenge to diagnose and treat. The range of clinical features is extremely variable. Neurologic symptoms are also present in rare cases but often lead to a misdiagnosis because they mimic stroke. We report a case of a 71-year-old male with aortic dissection presented with acute onset altered mental status and left arm weakness. Aortic dissection presented with neurological symptoms is rare and requires high level of suspicion, especially in cases with unusual presentation.

Palabras clave: disección aórtica aguda, disección tipo A, síntomas neurológicos, ictus, resultados del tratamiento.

Keywords: acute aortic dissection, type A dissection, neurological symptoms, stroke, treatment outcomes.

INTRODUCTION

Acute aortic dissection (AAD) is the most common acute aortic syndrome and a severe cardiovascular emergency with high morbidity and mortality[1]. It is more prevalent in males and in the elderly. Hypertension is the main risk factor[2]. Although sudden onset of severe chest or back pain is the most frequent symptom, other various symptoms may be present[3]. Particularly, acute neurologic symptoms at onset of aortic dissection are not only frequent, but often dramatic and may mask the underlying condition[1,3].

Aortic dissections are usually classified using the DeBakey or Standford classification systems based on anatomical location. In the case reported we use the Stanford classification, which distinguishes two types: type A, more frequent and severe, involves the ascending aorta and requires emergency surgery, whereas type B affects the descending aorta[4].

This paper describes the clinical case of type A dissection with clinical presentation of neurological symptoms and the importance of early diagnosis and timely intervention for type A dissection patients.

CASE REPORT

A 71-year-old Caucasian male, with past medical history of hypertension and obesity presented to the emergency department (ED) with sudden onset of altered mental status and left arm weakness. The patient was assisted by a pre-hospital emergency medicine team requiring orotracheal intubation and mechanical ventilation support (MVS) because of altered mental status. There was no history of trauma and chest pain. Vital signs on arrival to ED were systolic blood pressure 85 mmHg, heart rate of 140 beats/min, temperature 37.1ºC, oxygen saturation 98% with MVS and FiO2 31%. On presentation, neurological assessment noted that the patient was arousable to noxious stimuli with no focal deficits and he showed reactive, mydriatic pupils. Cardiovascular examination revealed muffled heart sounds, jugular venous distention (JVD), narrow pulse pressure and increased capillary refill time. Other systemic examinations were unremarkable. The electrocardiogram revealed a normal sinus rhythm. Due to history of the present illness and neurological symptoms, the patient was treated as a possible stroke and he underwent our center protocol for managing stroke patients. Thus, we performed baseline computed tomography (CT) and CT-angiography of the head that showed supra-aortic trunks with no hypodensity or hemorrhage and no evidence of large vessel occlusion (Figure 1). However, the patient worsened with progression to hemodynamic instability. Based on these clinical findings, acute aortic syndrome or pulmonary embolism were suspected and an emergency CT pulmonary angiography was done, revealing type A dissection (Figure 2A, 2B and 2C) from the ascending aorta until both renal arteries. Furthermore, a hemopericardium (Figure 2D) was also noted and the anteroposterior chest X-ray showed widening of the mediastinum. Bedside ultrasound revealed massive pericardial effusion with signs of cardiac tamponade. Routine laboratory studies were unremarkable. Faced with the diagnosis of AAD with cardiac tamponade criteria, the patient was transferred to a cardiothoracic surgery referral center and urgently submitted to surgical repair with replacement of the ascending aorta. Subsequently, after prolonged hospitalization, the patient was discharge with

Figure 1. Baseline CT and CT-angiography of the head (A). Axial plane revealed no acute hypodensity or hemorrhage (B). An axial reconstruction of the anterior circulation with no evidence of large vessel occlusion (C). In a coronal reconstruction the basilar and posterior cerebral arteries showed no occlusions.

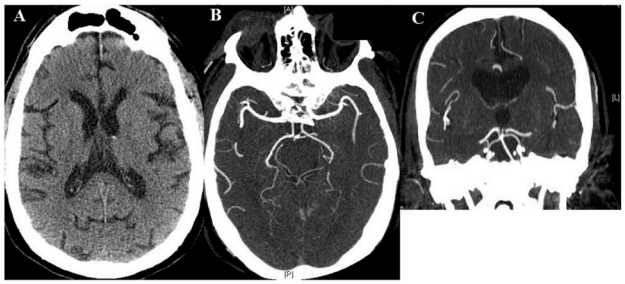

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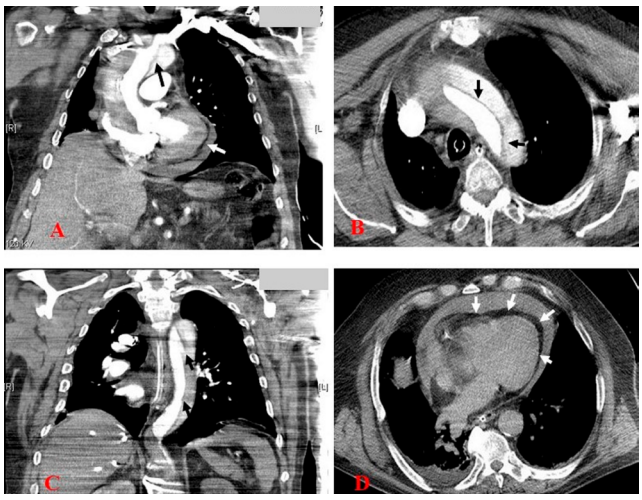
Figure 2. Chest CT-angiography. Coronal plane (A and C) and axial reconstruction (B) revealing an ascending type A aortic dissection showing the intimal flap (D). In an axial plane aortic dissection revealed pericardial effusion.



neurological recover without compromised cardiac function and referral to motor rehabilitation program.

DISCUSSION

Acute aortic syndromes are life-threatening cardiovascular emergencies affecting 3 to 6 per 100 000 individuals a year[1,5], and include aortic dissection, intramural aortic hematoma, penetrating aortic ulcer, and aortic rupture. Approximately 75% of dissections occur in those aged 40-70 years and 70% have hypertension, an important predisposing factor[1,2]. AAD occur when either a tear or an ulcer allows blood to penetrate from the aortic lumen into the media or when a rupture of vasa vasorum causes a bleed within the media[4].

Although AAD classically produces sudden onset of severe chest pain that often has a tearing quality, no sign or symptom can positively identify AAD. The clinical presentation is highly unspecific and an estimated 38% of AAD are missed on initial evaluation[1].

In aortic dissections, the frequency of neurological symptoms ranges from 15–40%[3], and in half of the cases they may be transient. Indeed, major brain injury (i.e. coma and stroke) at the onset of dissection is a complication in 10% of type A acute aortic dissection. Arch vessel involvement was more frequent among patients with stroke[6].

At hospital presentation, one of the most ominous findings on physical examination is hypotension and it is associated with neurological deficits, altered mental status, myocardial and mesenteric ischemia, limb ischemia, or death in 55% of patients[7]. Pericardial effusion alone is an independent predictor of mortality and up to one-third of patients with a large pericardial effusion will progress to cardiac tamponade with shock occurring in 15% of type A AAD[8,9]. AAD can be treated surgically or medically. Emergency surgical correction is the preferred treatment for Stanford type A ascending aortic dissection[4,10].

This case illustrates the dominance of neurologic symptoms in the early stage of AAD, which may make its early diagnosis difficult. However, in our case, the diagnosis of AAD was established based on clinical findings, physical exam and CT pulmonary angiography as diagnostic workup. Our patient had no pain and did not exhibit any of the classic signs of aortic dissection. On the other hand, the physical exam reveals Beck's triad of hypotension, JVD and muffled heart sounds, making cardiac tamponade the most likely etiology. The presented case emphasizes the importance of highlighted the clinical features of AAD which may be present together with neurological symptoms mimicking stroke or others neurological symptoms.

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Endocarditis trombótica no bacteriana y adenocarcinoma de endometrio

Non-bacterial thrombotic endocarditis and endometrious adenocarcinoma

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RESUMEN

Se describe el caso de una mujer de 80 años, con antecedentes de trombosis venosa profunda en tratamiento con apixaban, que presenta clínica focal neurológica. Las pruebas de imagen evidencian múltiples émbolos arteriales en cerebro, riñones y bazo, así como imagen sugestiva de neoplasia uterina. Una biopsia tras histeroscopia, confirma el diagnóstico de adenocarcinoma de endometrio. La ecocardiografía transesofágica constata la existencia de vegetaciones en válvulas cardíacas, siendo los estudios infecciosos negativos. Es diagnosticada de endocarditis trombótica no bacteriana relaciona con una neoplasia. Se cambia apixaban por heparina de bajo peso molecular, confirmando la práctica desaparición de las vegetaciones.

Palabras clave: endocarditis trombótica no bacteriana, endocarditis marántica, adenocarcinoma endometrial, trombosis venosa profunda, apixaban.

ABSTRACT

We present a case of an 80-year-old woman with a history of deep vein thrombosis, treated with apixaban, which has a focal neurological clinic. Imaging tests show multiple arterial ischemic lesions in brain, kidneys and spleen, as well as suggestive imaging of uterine neoplasia. A biopsy after hysteroscopy confirms the diagnosis of endometrial adenocarcinoma. Transesophageal echocardiography shows vegetations in valves, with negative blood cultures. The diagnostic was non-bacterial thrombotic endocarditis related to cancer. The anticoagulant was changed to low molecular weight heparin, confirming the disappearance of vegetations.

Keywords: non-bacterial thrombotic endocarditis, marantic endocarditis, endometrial adenocarcinoma, deep vein thrombosis, apixaban

INTRODUCCIÓN

La relación entre cáncer y trombosis se establece por primera vez en 1866 por Trousseau, y desde entonces han sido publicados multitud de trabajos confirmando dicha asociación. La endocarditis trombótica no bacteriana (ETNB) aparece en situaciones de hipercoagulabilidad, entre las que se encuentra el cáncer. Los tumores que más frecuentemente se asocian con ETNB son los adenocarcinomas localizados en pulmón, páncreas, estómago y ovario[1].

La descripción de ETNB y cáncer de útero no es frecuente, sólo han sido publicados 9 casos[2-10] (en tres de forma simultánea con cáncer de ovario). Se expone un nuevo caso de cáncer de útero presentándose inicialmente con una trombosis venosa profunda (TVP) y una ETNB, con la particularidad de que recibió tratamiento con apixaban antes de presentar fenómenos embólicos arteriales.

CASO CLÍNICO

Mujer de 80 años, ingresada por síndrome confusional en probable relación con infección urinaria y respiratoria. El día del ingreso acude al Servicio de Urgencias por desorientación, tos, disnea, escasa expectoración amarillenta, sin dolor torácico, ni fiebre.

Vive con su familia, con funciones cerebrales superiores adecuadas, siendo independiente para todas las funciones, deambulando con dificultad por artrosis. Tiene antecedentes de hipertensión arterial, dislipemia e insuficiencia venosa crónica con episodio previo de úlcera varicosa resuelto.

Un mes antes de su ingreso es diagnosticada de una TVP en vena femoral superficial derecha. Recibe tratamiento con apixaban a dosis de 5 mg cada 12 horas desde entonces; además como tratamientos crónicos toma valsartán y simvastatina.

A la exploración no se aprecia focalidad neurológica de vías largas, siendo la auscultación cardio-pulmonar y el resto de la exploración normales.

En pruebas complementarias destaca: hemoglobina 11,8 g/dl, leucocitos 8,5x10^9/L, plaquetas 222x10^9/L, INR 1,5, procalcitonina 0,7 ng/ml, PCR 6,6 mg/dl, glucosa 160 mg/dl, creatinina 0,6 mg/dl, con aclaramiento calculado de 47 ml/min. En el sedimento urinario se evidencia leucocituria (16-20 leucocitos/campo) y bacterias escasas. La radiografía de tórax es normal. El ECG presenta un ritmo sinusal sin alteraciones significativas.

La tomografía computarizada craneal (TC) no evidencia patología aguda. Se ingresa, añadiendo al tratamiento amoxicilina/ácido clavulánico vía parenteral. El urocultivo es negativo.

A las 48 horas de su ingreso se objetiva disfasia motora. Una nueva TC craneal demuestra un infarto isquémico agudo en región de arteria cerebral media izquierda.

Los estudios vasculares de troncos supra-aórticos y el holter-ECG no demuestran datos patológicos. Una ecocardiografía transtorácica detecta hipertrofia de ventrículo izquierdo, sin valvulopatías significativas ni datos de endocarditis. Existe elevación de CA 19.9 (180 U/mL) y Ca125 (184 U/mL).

Una TAC tóraco-abdómino-pélvica objetiva infartos en bazo y en riñón izquierdo, así como útero de aspecto nodular, con ocupación de cavidad endometrial, captación heterogénea de contraste y múltiples adenopatías retroperitoneales y en cadenas ilíacas (Figura 1).

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REFERENCIA	EDAD	TIPO DE TUMOR	VÁLVULA AFECTADA	MANIFESTACIONES ISQUÉMICAS	TRATAMIENTO	EVOLUCIÓN DE VERRUGAS
Glass J.P. 1993	42	CARCINOMA DE CÉRVIX	Mitral	Cerebro	Ninguno	Diagnosticadas en autopsia
Numnum T.M., et al. 2006	38	ADENOCARCINOMA ENDOMETRIOIDE DE ÚTERO ADENOCARCINOMA ENDOMETRIOIDE DE OVARIO	Aórtica Tricuspídea	Riñón, Bazo, Cerebro, Cerebelo, manos.	Cirugía Quimioterapia Radioterapia	Cirugía de sustitución valvular
Mir O., et al. 200	40	TUMOR NEUROECTODÉRMICO DE MIOMETRIO	Aórtica	Riñón, Bazo, Cerebro	Cirugía, Quimioterapia.	Cirugía de sustitución valvular
Ito S., et al. 2013	60	ADENOCARCINOMA ENDOMETRIOIDE DE ÚTERO	Mitral	Riñón, Bazo, Cerebro.	Cirugía Quimioterapia Radioterapia	Desaparición
Grecu N., et al. 2014	65	ADENOCARCINOMA MUCINOSO DE ENDOCÉRVIX	Mitral	Cerebro, Cerebelo	No documentado	No documentada
Hottois E., et al. 2014	47	CARCINOMA DE CÉRVIX	Mitral	Cerebro, manos	Quimioterapia Radioterapia	No documentada
Erturk N.K., et al. 2015	56	ADENOCARCINOMA ENDOMETRIOIDE DE ÚTERO ADENOCARCINOMA ENDOMETRIOIDE DE OVARIO	Mitral	Cerebro.	Cirugía Quimioterapia	No Documentada
Orfanelli T.,et al. 2016	63	ADENOCARCINOMA ENDOMETRIOIDE DE ÚTERO CARCINOMA PAPILAR SEROSO DE OVARIO	Aórtica Mitral	No Documentada	Cirugía Quimioterapia	Desaparición
Yokoyama S.,et al. 2016	42	ADENOCARCINOMA ENDOMETRIOIDE DE ÚTERO	Mitral	Cerebro.	Cirugía Quimioterapia	Desaparición
Caso actual	80	ADENOCARCINOMA ENDOMETRIOIDE DE ÚTERO	Aórtica Mitral	Riñón, Bazo, Cerebro.	Ninguno	Desaparición

Se repite la ecocardiografía, vía transesofágica (ETE), a los 15 días del ingreso que demuestra: aurícula izquierda moderadamente dilatada, con orejuela libre de trombos; en la superficie auricular sobre ambos velos mitrales, presenta estructuras de un diámetro de 1,1 cm sugestivas de vegetaciones; en la válvula aórtica se evidencian estructuras compatibles con vegetaciones en cara ventricular de velo no coronario; existe insuficiencia mitral severa; no existen datos de shunt intracardíaco (Figura 2). Se extraen hemocultivos y serologías de *Brucella, Bartonella*, y *Coxiella*, suspendiendo administración de amoxicilina/ácido clavulánico, e iniciando tratamiento antibiótico con ceftriaxona a dosis de 2 g intravenosa (IV) cada 24 horas (durante 15 días), ampicilina 2 g IV cada 4 horas (7 días) y doxiciclina 100 mg vía oral cada 12 horas (15 días).

Los hemocultivos iniciales y las serologías fueron negativos.

El estudio de trombofilia demuestra resultados negativos para anticoagulante lúpico, anticuerpos anticardiolipina, y anti-beta-2-glicoproteína I.

Ante la ausencia de datos clínicos y analíticos que sugiriesen endocarditis infecciosa, y la alta sospecha de ETNB, se cambia apixaban por biosimilar de enoxaparina a dosis anticoagulantes ajustada a peso.

Se repiten los hemocultivos una semana después de la suspensión de los antibióticos, con resultados negativos.

Transcurridos de 18 días del cambio de tratamiento anticoagulante se realiza una nueva ETE, sin apreciarse datos significativos de verrugas, así como con mejoría de la insuficiencia mitral.

Se realiza biopsia de endometrio siendo diagnóstico de adenocarcinoma tipo endometriode. La paciente es valorada conjuntamente por los Servicios de Ginecología y Oncología, decidiéndose alta médica con tratamiento conservador y vigilancia clínica.

DIAGNÓSTICO

Síndrome de Trousseau: Trombosis venosa profunda y endocarditis trombótica no bacteriana relacionadas con cáncer endometrio.

DISCUSIÓN

La presencia de ETNB en pacientes con cáncer presenta datos contradictorios: mientras estudios ecográficos en pacientes vivos con cáncer se evidencia ETNB en un 19% del grupo, los estudios post-mortem, sólo detectan lesiones de ETNB entre el 0,9-1,3%[3].

Las verrugas de la ETNB suelen ser pequeñas, estériles, compuestas de fibrina y plaquetas, friables y fácilmente embolizables. Se localizan de forma mayoritaria en la porción distal de válvulas, en la superficie auricular de la válvula mitral y la superficie ventricular de la válvula aórtica[1,6].

Las manifestaciones clínicas de la ETNB dependen más de los fenómenos embólicos, sobre todo en bazo, riñón, y encéfalo, y menos de la disfunción valvular provocada por las verrugas[1]. El método más sensible para el diagnóstico de las verrugas es la ecocardiografía transesofágica[1].

El manejo terapéutico de la ETNB relacionada con cáncer se debe basar en el tratamiento anticoagulante y en tratamiento del propio tumor. El tratamiento anticoagulante en

Figura 1

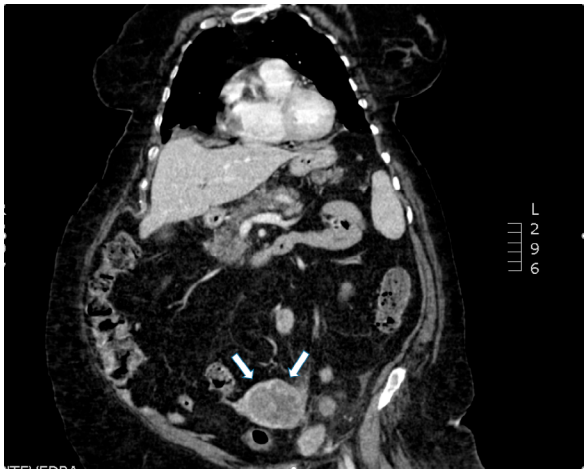
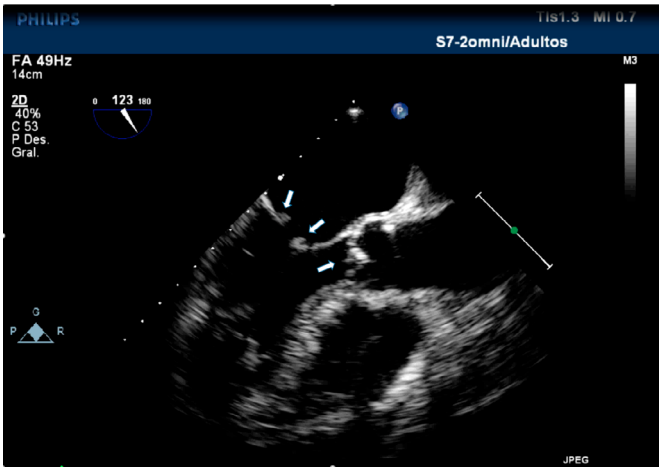


Figura 2



estos pacientes no ha sido definido, aunque se recomienda, bien heparina no fraccionada (HNF), o heparina de bajo peso molecular (HBPM)[1].

En la TVP relacionada con el cáncer, las guías más recientes recomiendan tratamiento basado en anticoagulantes orales de acción directa. Se podría pensar en hacer extensible dicho tratamiento a pacientes con ETNB asociada al cáncer, pero nuestro caso junto con otros similares, ponen en evidencia la mala evolución clínica de estos pacientes tratados con anticoagulantes orales de acción directa (AOAD)[6].

De los 9 casos publicados de ETNB y cáncer de útero (Tabla 1), la evolución clínica de las verrugas mejora y es documentada su desaparición con ecocardiografía en 3 pacientes. De los restantes, en tres no está documentada, dos son sometidos a cirugía cardíaca valvular sustitutiva, mientras que en uno se diagnostica la ETNB en la necropsia. En aquellos pacientes donde se evidencia la desaparición de las verrugas, todos reciben tratamiento anticoagulante con heparina, así como tratamiento oncológico basado en cirugía, quimioterapia, y radioterapia.

En nuestro paciente se evidencia la práctica desaparición de las verrugas sólo con tratamiento anticoagulante basado en HBPM. Creemos que el tratamiento con HBPM hizo disminuir significativamente el tamaño de las verrugas hasta su práctica desaparición.

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El diagnóstico diferencial es fundamental: a propósito de un caso de síndrome de Laugier-Hunziker

The differential diagnosis is crucial: a case of Laugier-Hunziker syndrome

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RESUMEN

El síndrome de Laugier-Hunziker (SLH) es una enfermedad poco frecuente, benigna, no asociada a patología sistémica, cuya forma de presentación en adultos consiste en hiperpigmentación macular mucocutánea que afecta mayoritariamente a labios y mucosa oral, ocasionalmente puede afectar mucosa genital y con menos frecuencia al área palmoplantar. Se encuentra asociada en la mitad de los casos con melanoniquia longitudinal. La importancia de este síndrome es evidente una vez que es diagnóstico de exclusión de enfermedades con significativo riesgo de malignidad. Ante la sospecha de SLH, es obligatorio el despistaje de otras patologías asociadas a hiperpigmentación, lentiginosis y melanoniquia. Los autores presentan el caso de una mujer de 63 años con hiperpigmentación de mucosa oral y de dedos de manos y pies, con el diagnóstico final de SLH. Realizan un resumen del estudio realizado que condujo al diagnóstico. Concluyen subrayando la importancia del diagnóstico diferencial con otras patologías.

Palabras clave: mucosa oral, hiperpigmentación, Laugier-Hunziker, diagnóstico diferencial.

Keywords: oral mucosa, hyperpigmentation, Laugier-Hunziker, differential diagnosis.

INTRODUCCIÓN

El síndrome de Laugier-Hunziker (SLH) es una enfermedad poco frecuente, benigna, no asociada a patología sistémica, cuya forma de presentación en adultos consiste en hiperpigmentación macular mucocutánea que afecta mayoritariamente a labios y mucosa oral, ocasionalmente puede afectar mucosa genital y con menos frecuencia al área palmoplantar. Existe asociación de este síndrome con melanoniquia ungueal longitudinal.

El SLH se considera una enfermedad adquirida benigna que no se asocia a anomalías sistémicas subyacentes ni a factores predisponentes[2,3,5]. La importancia de esta patología se basa en su diagnóstico diferencial. Ante la sospecha de SLH es obligatorio realizar el diagnóstico de exclusión con otras enfermedades con mayor riesgo de malignidad, a través del despiste de todas las patologías asociadas a hiperpigmentación, lentiginosis y melanoniquia[2].

CASO CLÍNICO

Se presenta el caso de una mujer de 63 años, caucásica, no fumadora, seguida en consulta de Medicina Interna en nuestro hospital, derivada desde Atención Primaria por diabetes mellitus tipo 2 de difícil control metabólico con afectación sistémica, a destacar como antecedente patológico personal relevante, la hipertensión arterial.

En la primera consulta nos llamó la atención la existencia de unas lesiones hiperpigmentadas localizadas en mucosa oral (imagen 1) y en dedos de manos y pies (imagen 2 y 3). Según la paciente las primeras lesiones habían aparecido aproximadamente dos años antes, y refería un empeoramiento progresivo sobretodo en las lesiones de los labios y de los dedos de las manos, no presentaba ninguna sintomatología asociada.

Fue realizada una historia clínica detallada siendo excluida historia familiar de alteraciones cutáneas y otros antecedentes familiares relevantes. Tampoco existía historia previa de trauma en las áreas afectadas por las lesiones o toma de fármacos que pudieran causar los cambios descritos.

Fue realizado un examen físico exhaustivo, no fueron encontradas otras alteraciones excepto las ya referidas: existencia de múltiples lesiones lenticulares irregulares de color castaño y negro con dimensiones entre 3-7 mm de diámetro en los labios y mucosa oral, y de menor tamaño en dedos de manos y pies.

Se realizó un estudio analítico completo incluyendo estudio inmunológico, detección de posibles déficits vitamínicos y despistaje de insuficiencia suprarrenal. Todos los resultados obtenidos se encontraban dentro de los parámetros de normalidad.

Ante la sospecha de SLH fue solicitado apoyo de Dermatología para realización de biopsia de las lesiones. El resultado mostró presencia de hiperqueratosis, acantosis e hiperpigmentación de células basales con algunos melanocitos. Se llevó a cabo un estudio complementario extenso para exclusión de otras patologías de mayor potencial de malignidad, ecocardiograma que mostró alteraciones compatibles con cardiopatía hipertensiva, TC de tórax y abdomen que no presentó hallazgos patológicos, estudio digestivo con endoscopia alta y colonoscopia para exclusión de enfermedad gastrointestinal asociada, ambos sin ninguna alteración.

La presentación clínica indolente, la ausencia de hallazgos relevantes en el estudio diagnóstico realizado, junto con la histopatología de la biopsia de la piel condujeron a la confirmación diagnóstica de SLH. Actualmente, después de tres años de seguimiento conjunto en Medicina Interna y Dermatología, no han sido detectadas alteraciones sistémicas asociadas ni evolución para malignidad de las lesiones descritas.

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Figura 1

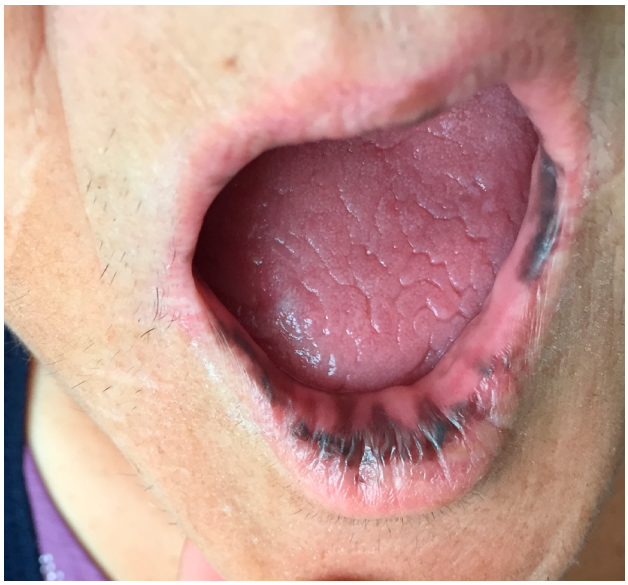
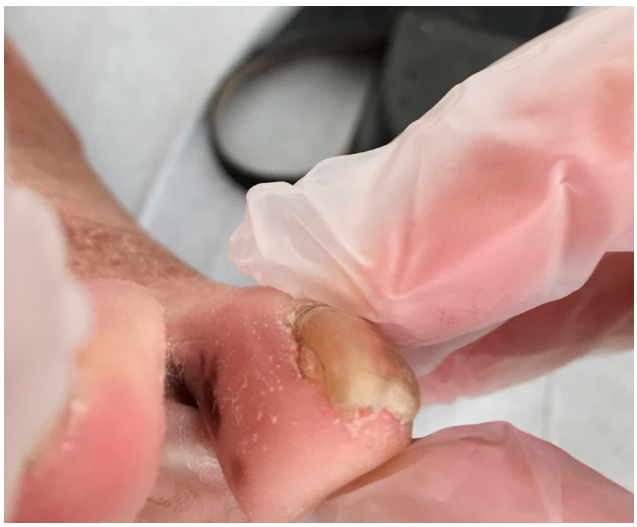


Figura 2

Figura 3



COMENTARIO

La primera descripción del fenómeno caracterizado por la aparición de pigmentación en mucosa oral y genital en adultos fue realizada por Laugier y Hunziker en 1970[1,4]. Posteriormente, Baran[5] relacionó dicho fenómeno con melanoniquia longitudinal y describió la pigmentación ungueal en el SLH, clasificándola en tres tipos. Posteriormente Veraldi et al[2] reportó un cuarto tipo de melanoniquia.

Por su presentación benigna, no asociada a otras manifestaciones sistémicas, Moore et al. propusieron evitar el término "síndrome" para definir la alteración descrita por Laugier y Hunziker, considerando más apropiado la denominación de "pigmentación de Laugier-Hunziker"[8,9]

Desde ese momento y de acuerdo con una reciente revisión de la literatura existen aproximadamente 206 casos reportados (de los cuales dos fueron descritos en España y dos en Portugal). La edad media en el momento del diagnóstico es de 47,5 años, siendo más frecuente en mujeres con una ratio de 1,8:1[3]. La etiología exacta permanece desconocida.

La manifestación clínica consiste en la presencia de máculas lenticulares melánicas en el área labial, la cavidad oral y regiones acrales, identificándose la melanoniquia longitudinal en aproximadamente mitad de los pacientes. En nuestro caso es importante observar la presencia de lesiones en los dedos de los pies ya que se trata de un área descrita como raramente afectada. Los hallazgos dermatoscópicos de las lesiones labiales incluyen presencia de un patrón de surco paralelo con múltiples puntos marrones y alteraciones reticulares regulares, múltiples patrones granulares de color marrón o gris, estrías en arco, similares a escamas de pescado y surcos paralelos en lesiones pigmentarias mucocutáneas. Estos patrones dermatoscópicos se observan frecuentemente junto con vasos lineales y punteados en áreas rosadas blanquecinas[4]. El signo de Pseudo-Hutchison puede aparecer cuando existen alteraciones a nivel ungueal[3].

El examen histológico de las lesiones muestra aumento de los depósitos de melanina en las células basales, siendo que el número, morfología y distribución de melanocitos habitualmente es normal[5]. Con poca frecuencia, a semejanza con nuestro caso, se han reportado hallados como acantosis[7], hiperqueratosis[8] e hiperparaqueratosis[7].

Siendo el diagnóstico de SLH un diagnóstico de exclusión, se obtiene después de la investigación de otras causas de pigmentación oral, labial y ungueal como por ejemplo: Síndrome de Peutz-Jeghers (SPJ), Síndrome de LEOPARD (es un acrónimo de las principales características de este trastorno, que incluye léntigos múltiples, anomalías en la conducción del electrocardiograma [ECG], hipertelorismo ocular, estenosis pulmonar, genitales anormales, retraso del crecimiento y sordera neurosensorial), Enfermedad de Addison, Síndrome de McCune-Albright[10], Síndrome de LAMB o Complejo de Carney[11] (léntigos en piel y mucosas, mixomas auriculares),

Tabla 1. Síndrome de Laugier-Hunziker: diagnóstico diferencial

Máculas melánicas	Melanoniquia
Síndrome Peutz-Jeghers	Onicomicosis
Síndrome Cronkhite-Canada	Infección bacteriana
Neurofibromatosis tipo 1	Hematoma subungueal
Síndrome McCune-Albright	Melanoniquia fisiológica racial
Enfermedad de Addison	Traumatismo
Complejo de Carney	Inducida por drogas
Sindrome LEOPARD	Nevus
Inducida por drogas	Melanoma
Melanosis del fumador	Enfermedad de Bowen
Melanoma	Pigmentación exógena
Nevus melanocitico intraoral	Asociada a liquen plano

Síndrome de Cronkhite-Canada[12], Neurofibormatosis tipo 1, hiperpigmentación inducida por drogas; incluidas en este grupo tetraciclinas, antimaláricos (cloroquina e hidroxicloroquina), antifúngicos (ketoconazol), quimioterápicos (ciclofosfamida, doxorrubicina, hidroxiurea), amiodarona, psicotrópicos (clorpromazina) y anticonceptivos orales, las máculas melánicas consecuentes al uso de tabaco, pigmentación causada por infección bacteriana, onicomicosis, melanoniquia traumática o melanoma (Tabla 1).

En casos confirmados de SLH es importante asegurar al paciente la naturaleza benigna de las lesiones y la importancia de las medidas de protección solar para evitar el empeoramiento y recurrencia de estas. El tratamiento, que es meramente cosmético, debe considerarse sólo en los casos graves con compromiso estético y/o afectación psicológica. En la actualidad, existen múltiples opciones disponibles que incluyen láser de neodimio, itrio y aluminio (láser Nd-YAG), láser Alexandrita Q-switched. Se han descrito casos de tratamiento efectivo con criocirugía.

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Neumotórax desarrollado durante el curso de una neumonía por SARS-CoV-2

Pneumothorax developed during the course of SARS-CoV-2 pneumonia

CASE REPORT

Coronavirus disease 2019 (COVID-19) is a recent outbreak in mainland China and has rapidly spread to multiple countries worldwide[1,2].

The largest case series of chest imaging described multilobar involvement of rounded and peripheral airspace opacities. The occurrence of pneumothorax is rare in SARS-CoV-2 pneumonia[3-5].

We are reporting a case of a male who developed a pneumothorax secondary to SARS-CoV-2 pneumonia.

We present a 70-year-old male patient who was admitted to Emergency Department complaining of productive cough with mucopurulent sputum, dyspnea, fever with maximum temperature of 38.4ºC and diarrhea for seven days. He had no smoking or alcohol consumption. He didn't have contact with anyone known to have COVID-19. His personal pathological history included hypertension, type 2 diabetes mellitus and dyslipidemia. He denied known structural pulmonary pathology. On physical examination, the patient was febrile (38.6ºC), peripheral oxygen saturation (SpO2) was 88% in room air and a rude vesicular murmur and bilateral intermittent wheezing were identified.

Pertinent laboratory results showed increased inflammatory parameters (leukocytosis of 10,4x10^9 cells/L with neutrophilia of 91% and CRP of 32mg/dl) and acute kidney injury (creatinine 1,95 mg/dl and urea 100 mg/dl). Arterial gasometry with FiO_2 24% revealed acute type 1 respiratory failure, with PaO_2 73mmHg. Chest radiograph showed right lower lobe intersticial infiltrate (image 1) and chest computed tomography (CT) scan showed bilateral ground glass opacities and extensive areas of alveolar consolidation with air-bronchogram. Influenza A and B were negative, as well as Legionella pneumoniae antigenuria and serology for Mycoplasma pneumoniae. Oropharyngeal and nasopharyngeal swab test for SARS-CoV-2 by qualitative real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay was positive.

The patient started empirical antibiotherapy with ceftriaxone and azithromycin as well as hydroxychloroquine and lopinavir/ritonavir.

On the 5th day of hospitalization, the patient was on a 31% venture mask. His chest radiograph which showed a spontaneous left pneumothorax, and therefore a 16F caliber chest tube was placed in the 5th left intercostal space. Total pulmonary re-expansion was observed 48 hours later, and chest tube was removed.

The patient was discharged after 3 weeks of hospitalization without further respiratory complications.

Image 1

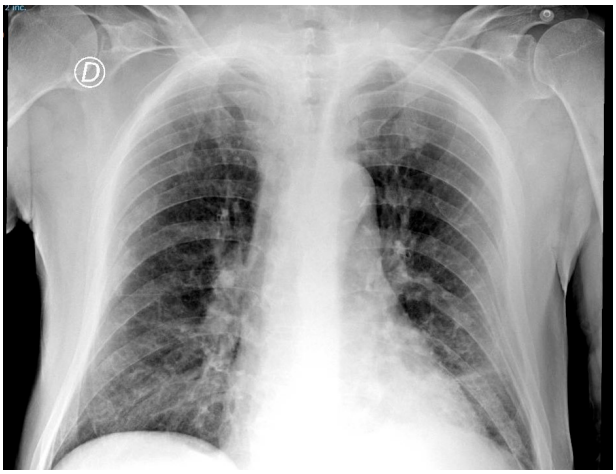
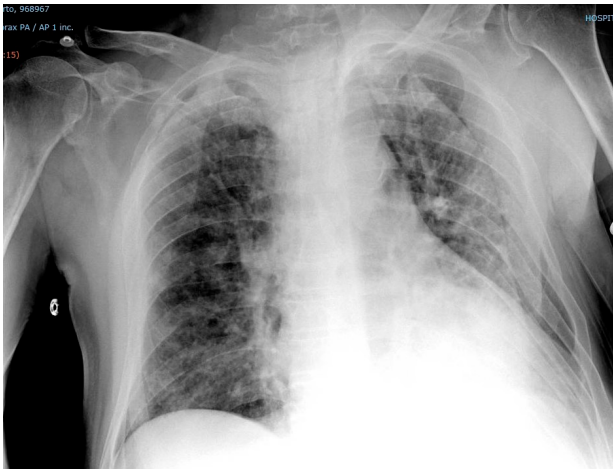


Image 2



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Palabras clave: COVID-19, coronavirus, neumonía, complicación, neumotórax
Keywords: COVID-19, coronavirus, pneumonia, complication, pneumothorax.

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La importancia de la radiografía de tórax en el diagnóstico de la neumonía en la COVID-19

The value of thorax X-Ray in the diagnosis of COVID-19 pneumonia

CASO

En diciembre de 2019, se produjo el primer brote de síndrome respiratorio agudo grave causado por el SARS-CoV-2 en China y se extendió por todo el mundo. El 11 de febrero del 2020, la OMS nombró oficialmente la enfermedad como COVID-19[1]. Dado que la mayoría de los pacientes infectados por COVID-19 fueron diagnosticados de neumonía con patrones característicos, los exámenes radiológicos se han vuelto vitales en el diagnóstico temprano y en la evaluación del curso de la enfermedad. Numerosos artículos demuestran la importancia de la TC en el diagnóstico rápido y temprano[2,3].

En este artículo, presentamos el caso de un varón de 87 años, dependiente para todas las actividades diarias por antecedentes de demencia, si bien no se conocen otros antecedentes personales. El paciente no tenía antecedentes de exposición o contacto cercano con pacientes confirmados o sospechosos, por lo que la imagen de la placa de tórax y la clínica nos hizo sospechar una infección por coronavirus.

El paciente ingresa en el Servicio de Urgencias el 19 de marzo por fallo respiratorio. El cuadro clínico se había iniciado 3 días antes con tos y fiebre.

A su llegada, presentaba disnea y taquipnea. A la exploración destacaba la auscultación pulmonar con roncus dispersos en todos los campos pulmonares.

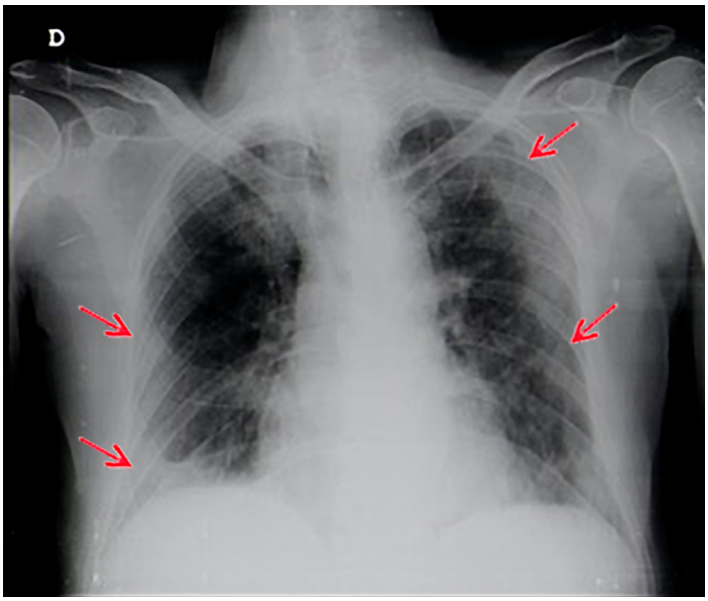
Los estudios analíticos, que incluyeron hemograma, pruebas de función renal, pruebas de función hepática, búsqueda de antígenos Streptococcus pneumoniae, Legionella pneumophila del grupo 1 y búsqueda del SARS-CoV-2, se demostró leucocitosis (22,210/Ul), trombocitosis (646,000/Ul), insuficiencia renal con un nivel de creatinina de 6,81 mg/dL y una PCR de 234,9 mg/L. La búsqueda de SARS-CoV-2 por biología molecular del exudado nasofaríngeo fue positiva.

Se realizó una placa de tórax donde se pudo ver infiltrados difusos bilaterales de características alveolares, pero sin condensaciones definidas, de claro predominio periférico. Sin derrame asociado.

Durante su ingreso, el paciente presentó deterioro progresivo del estado general produciéndose la evolución a muerte en 24 horas, verificándose la sexta muerte por coronavirus en Portugal.

CONCLUSIÓN

A pesar de ser un paciente con antecedentes epidemiológicos desconocidos, la aparición clínica e imagen típica nos hizo sospechar de COVID-19, lo que nos ha permitido establecer el diagnostico rápido y sencillo sin necesidad de recurrir a la TC. Ante esta sospecha, se pudo aislar al enfermo y optimizar su manejo antes del resultado de la búsqueda del virus. Sin embargo, para la mayoría de los pacientes la placa de tórax es limitada y es necesario recurrir a la TC.



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Palabras clave: radiografía de tórax, COVID-19, síndrome respiratorio agudo grave.

Keywords: thorax X-ray, COVID-19, Severe Acute Respiratory Syndrome.

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PULSE PARA VOLVER AL ÍNDICE

Paresia aislada de la mano secundaria a ictus isquémico en la hand knob area

Isolated hand paresis due to ischemic stroke of the hand knob area

CASE REPORT

A 77-year-old man with past medical history of hypertension, coronary artery disease and hyperlipidemia presented to the emergency department with sudden onset of left-hand weakness for past two hours. Denied any dizziness, loss of consciousness and any weakness or loss of sensation in any other extremity. His vitals at triage were blood pressure 146/91mmHg, heart rate 76 beats per minute, respiratory rate 15 breaths per minute, temperature 36.5°C, oxygen saturation 100% on room air. On neurological examination he was alert and oriented in time, place, and person. His gait and cranial nerves were intact. Motor examination demonstrated weakness of left wrist and fingers extensor muscles with a muscle strength grading of 2 without sensory impairments. Strength and sensation in the other extremities were normal. Other review of systems was normal. Laboratory workup were unremarkable, and electrocardiogram was normal sinus rhythm. Computed tomography (CT) scan of the head was normal at admission (Fig. A and B). However, for suspected peripheral nerve damage also performs cervical CT scan that revealed multiple degenerative changes of the cervical spine. It was observed by neurosurgery that suggested to isolated motor deficit, but clinical picture not compatible with spine-radicular compression. Therefore, has repeated cranial CT scan 12 hours after admission, showing a small cortical hypodensity in the right precentral gyrus (Fig. C and D), the hand motor cortex - "hand knob area". We assumed the diagnostic of ischemic stroke with clinical presentation of isolated hand paresis.

Acute isolated hand or foot paresis is a rare symptom of stroke. It corresponds to less than 1% of all ischemic strokes, and the precentral gyrus, referred to as "hand knob" area, is the most frequent site[1]. Early diagnosis is challenging because the clinical presentation can be confused with peripheral nerve injury[2]. Isolated hand/fingers palsy is not included in the NIHSS because it is a rare type of stroke[3]. The most prevalent risk factors are hypertension and atherosclerosis, with embolic aetiology being the most likely underlying pathophysiological mechanism[4].

In conclusion, clinicians should be aware of this clinicopathologic entity and its clinical presentation, particularly when neurological examination reveals an acute, isolated hand palsy without sensory deficit in patients with vascular risk factors.

Fig. A and B: CT head without contrast done at the time of admission shows no ischemic stroke.

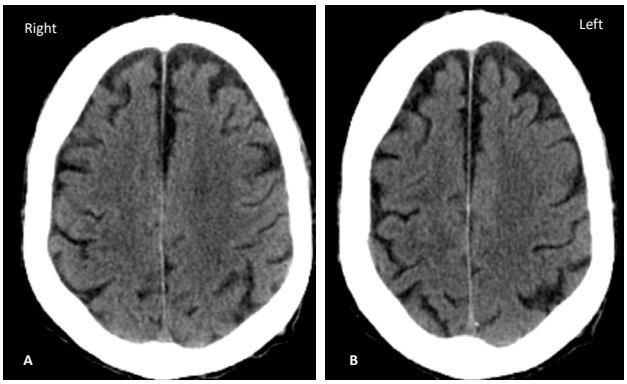
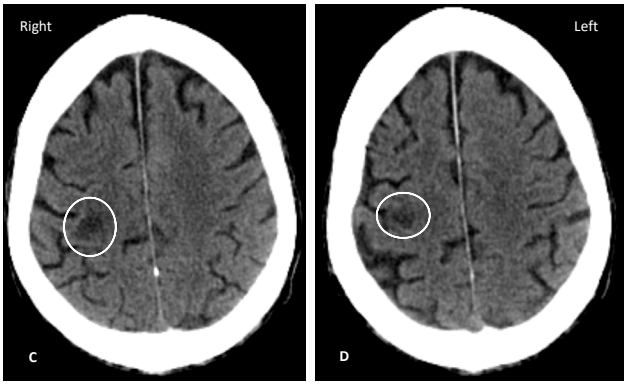


Fig. C and D: CT head without contrast done 12h after admission shows cortical hypodensity in the right precentral gyrus.



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Palabras clave: ictus, monoparesia aislada, hand knob, corteza motora de la mano.

Keywords: stroke, isolated monoparesis, hand knob, hand motor cortex.

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Necrosis de pies y manos en el shock séptico por Klebsiella pneumoniae

Necrosis of the feet and hands in septic shock due to Klebsiella pneumoniae

CASO CLÍNICO

En los cuadros de sepsis grave y shock séptico se producen una serie de mecanismos inflamatorios y vasculopatía que da lugar a manifestaciones cutáneas. Los microorganismos más implicados en estas lesiones incluyen a Neisseria meningitidis y Neisseria gonorrhoeae. Sin embargo, no son cuadros exclusivos de estos microorganismos, sino que también están descritos por otras bacterias como Klebsiella pneumoniae[1].

Presentamos el caso de una mujer de 74 años con antecedentes de hipertensión arterial y miocardiopatía hipertensiva con FEVI preservada, enfermedad renal crónica estadio 3 e hipotiroidismo que acudió por síndrome miccional y fiebre de 5 días de evolución.

A la exploración física, la paciente presentaba una presión arterial de 99/62 mmHg, FC de 114 lpm, fiebre de 38ºC, auscultación cardiaca normal, crepitantes bibasales, mínimo dolor a la palpación profunda del abdomen de manera difusa sin datos de peritonismo y sin edema en piernas.

Analíticamente destacaba leucocitosis con neutrofilia y ligera plaquetopenia, actividad TP 31%, INR 2,41 y resto de los parámetros de coagulación normal, creatinina 4,47 mg/dl, PCR 185 mg/dl y lactato 6 mmol/L. En TC abdominal se evidenció uropatía obstructiva secundaria a litiasis ureteral, por lo que se colocó catéter doble J. Con el diagnóstico de shock séptico de origen urinario, se inició piperacilina-tazobactam. En hemocultivos y urocultivo retirados se aisló *Klebsiella pneumoniae* que confirmó el diagnóstico.

Debido a la situación de inestabilidad hemodinámica y el fallo multiorgánico fue necesario el ingreso en UCI con el empleo de aminas. Al séptimo día del ingreso la paciente presentó isquemia con necrosis de los dedos de las manos y de los pies (Figura 1-2).

Durante el ingreso fue valorada por el Servicio de Cirugía Vascular y Angiología que indicó amputación de las zonas necrosadas que la paciente rechazó. La evolución clínica fue lentamente favorable hasta la recuperación del cuadro clínico.

El shock séptico se define como un síndrome que se caracteriza por hipotensión arterial en el contexto de sepsis, que persiste a pesar de una adecuada administración de líquidos, lo que da lugar a alteraciones de la perfusión y por tanto se produce disfunción multiorgánica[2].

Las manifestaciones cutáneas en el contexto de un shock séptico son muy variadas. El mecanismo fisiopatológico que las produce está relacionado con 4 factores principales: coagulación intravascular diseminada (CID), invasión directa de pequeño vaso por los microorganismos, vasculitis inmuno-mediada y embolismos sépticos[1].

En la bibliografía actual, se ha conoce que algunas cepas de Klebsiella pneumoniae producen enterotoxinas que actúan lisando las células dando lugar a necrosis de tejidos[3,4,5]. Por lo tanto, las manifestaciones cutáneas en el shock no sólo dependen de la vasculopatía, el estado inmunológico y comorbilidades del paciente, sino que también están relacionadas con microorganismo causante[1].

Figura 1. Necrosis de dedos de la mano derecha

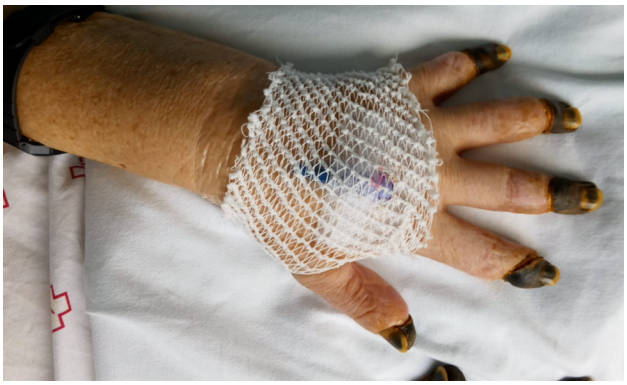
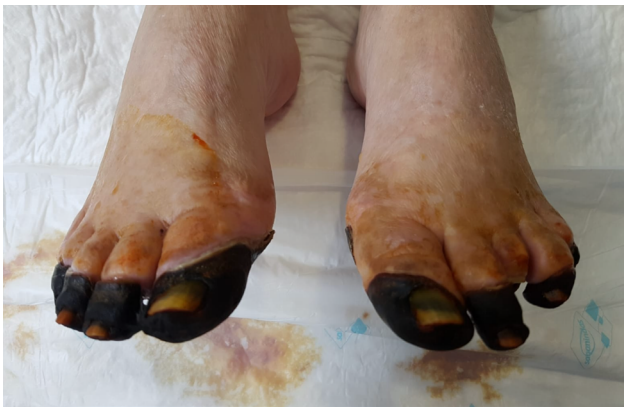


Figura 2. Necrosis de los dedos de los pies



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Palabras clave: necrosis acral, shock séptico, Klebsiella pneumoniae.

Keywords: acral necrosis, septic shock, Klebsiella pneumoniae.

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PULSE PARA VOLVER AL ÍNDICE

Pioderma gangrenoso: una causa poco frecuente de úlcera orbitaria

Pyoderma gangrenosum: a rare cause of an orbital ulcer

CASE

A 46-year-old Caucasian male presented with progressive swelling of the right supraciliary complicated with skin ulceration for the last 2 months. He had had an accidental trauma in that area about 4 years ago with an iron cable. He denied fever, vision loss, headache, arthritis and weight loss. He had a past medical history of obesity, alcoholic chronic hepatic disease and smoking. He did not take any chronic medication. He had no history of recent travels, lived in a rural area and worked as a merchant. Upon clinical examination, he had skin nodules that subsequently formed erosions and a non-exudative skin ulceration of the right eyelid; no lymphadenopathies or others alterations were found. Magnetic resonance revealed an expansive lesion extending to the plane of the superior orbital fissure and the optic nerve canal, involving the medial rectus muscle and intra-conical fat (figure 1).

A diagnosis of orbital cellulitis was assumed and the patient performed multiple antibiotics (ceftriaxone, ciprofloxacin, clindamycin and amoxicillin-clavulanic acid) without improvement. There were no microbiological isolates, either on blood cultures or skin swab. Lesion biopsy excluded both neoplasia (including lymphoma) and infection (including mycobacteria, leishmania, spirochetes and fungi). Histology revealed neutrophilic dermatosis. The injury worsened with time (figure 2). The patient was tested and negative for Human Immunodeficiency Virus, Syphilis and Hepatitis B and C. Immunological tests were also negative. A prothrombotic state was discarded. By then, a diagnosis of *pyoderma gangrenosum* was presumed and the patient started on prednisolone 1mg/kg/day and azathioprine 100 mg/day, after excluding concomitant rheumatological, hematological and neoplastic disease. Unfortunately, the patient died after a few months.

Pyoderma gangrenosum is a rare neutrophilic dermatosis, inflammation and ulceration. The most common presentation is an inflammatory papule or pustule that progresses to a painful ulcer with violaceous borders and purulent base. It is an exclusion diagnosis, made after discarding other inflammatory or ulcerative cutaneous disorders. There are no pathognomonic findings[1,2]. Although there is a risk of biopsy-induced pathergy, the need to rule out other diagnosis supersedes that. Since most patients have an associated systemic disease, like inflammatory bowel disease, arthritis or hematologic disorders, they need to be excluded [2,3].

Figure 1. Magnetic resonance imaging, T2 axial section. Left frontal soft tissue lesion in continuity with right orbital lesion, accompanied by local vasogenic edema. Extension of the lesion for right ethmoidal chambers.

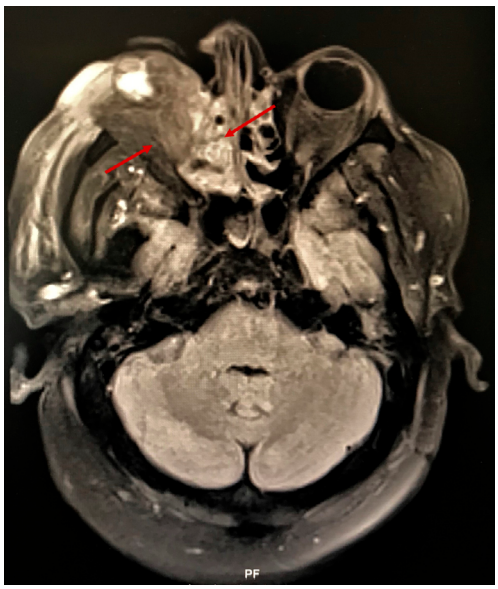
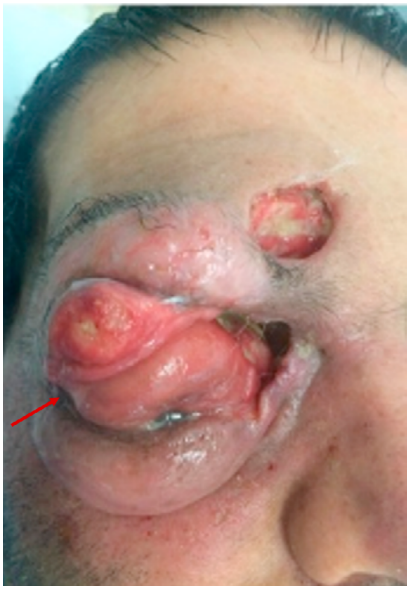


Figure 2. Orbital lesion appearance after 30 months of evolution and two skin biopsies.



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Palabras clave: Pioderma gangrenoso.

Keywords: Pyoderma gangrenosum.

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Un caso atípico de tos y estornudos

An atypical case of cough and sneezes

CASE REPORT

A 68-year old male with prior hypertension and hypertensive nephrosclerosis was admitted in the emergency department after a fully recovered transient episode of loss of consciousness of about 1 minute. He referred a fit of sneezing before losing consciousness and there was no evidence of seizures, chest pain, shortness of breath or palpitations. Clinical examination including neurological exam was normal and there was no evidence of postural hypotension. Further cardiologic evaluation for syncope, including electrocardiogram, echocardiogram and cardiac monitoring, was normal. A more detailed story revealed that the patient had recurrent headaches for at least 6 years, triggered by coughing and sneezing with spontaneous recover after a few minutes. A computed tomography scan of the brain was performed reveling a large extra axial lesion in the left fronto-temporo-parietal region, suggestive of an arachnoid cyst with shift of the median structures, confirmed by magnetic resonance imaging (Figures 1 to 4). The patient refused resection of the cyst and is under periodic surveillance imaging. Headaches and syncope might be explained by the disruption of Monro-Kellie's theory: there is an additional and transient increase in intracranial pressure provoked by Valsalva maneuvers in a patient with a large cyst that also causes obstruction to normal cerebrospinal fluid and blood flow dynamics. Valsalva triggered symptoms are rarely reported as the first presentation of intracranial neoplasms and a high index of suspicion is required to achieve the correct diagnosis. Patients with non-cardiac syncope and cough-headache should be evaluated for an intracranial lesion[1,2].

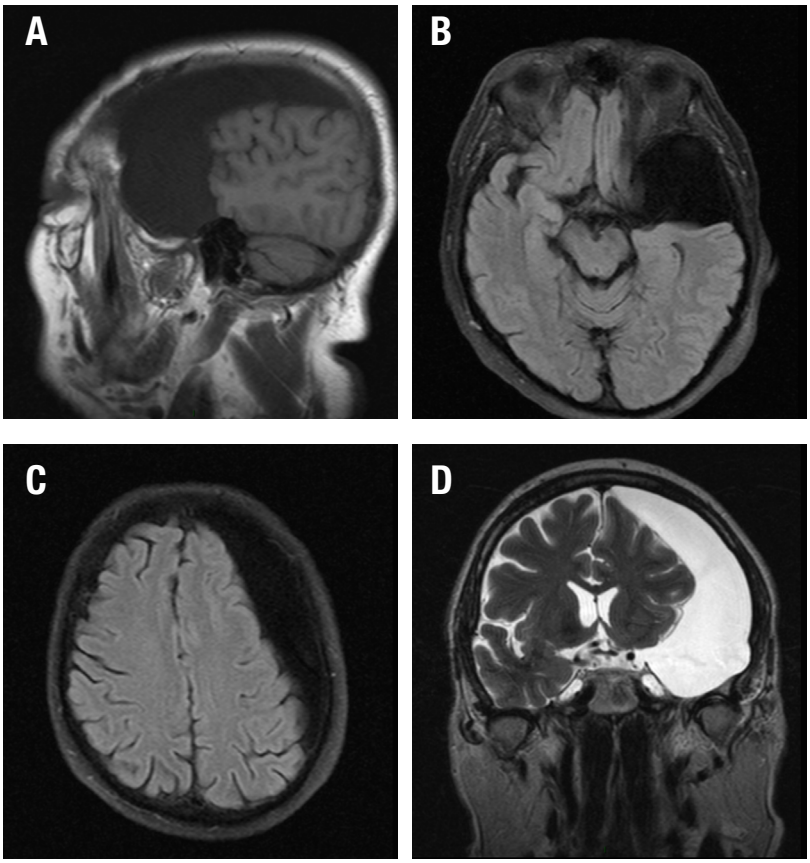

Fig. 1 Brain MRI showing left-sided fronto-temporo-parietal extra-axial cyst with cerebrospinal fluid intensity. A: T1-weighted sagital view. B and C: T2 TIRM dark fluid transverse views. D: T2-weighted coronal view

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Palabras clave: quistes aracnoideos, presión intracraneal, teoría de Monro-Kellie.

Keywords: arachnoid cysts, intracranial pressure Monro-Kellie's theory.

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PULSE PARA VOLVER AL ÍNDICE

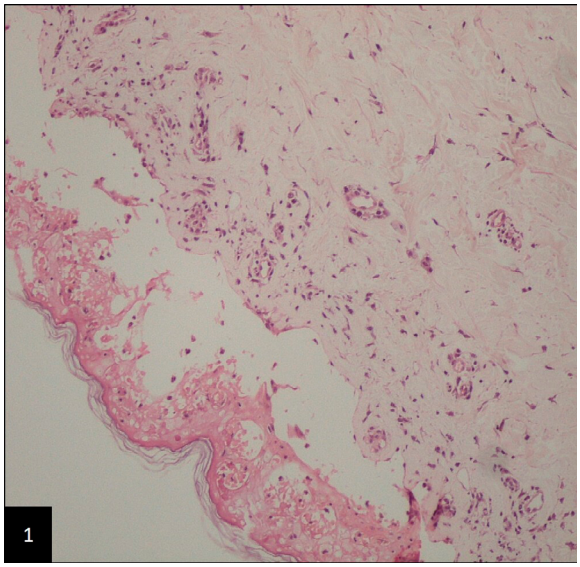
Superposición de síndrome de Stevens Johnson/necrólisis epidérmica tóxica inducida por alopurinol

Allopurinol-induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis overlap syndrome

CASE REPORT

A 45-year-old Caucasian female was admitted to the Emergency Department with a diffuse maculo-papular erythematous and pruritic rash that developed over the last four days. In addition, she developed oral mucocutaneous painful hemorrhagic blisters and hemorrhagic crustations over the eyelids. She was medicated with allopurinol 300 mg once a day for the first time about 10 days ago for asymptomatic hyperuricemia. About three days prior to presentation she became feeling photophobia, conjunctival itching, pain on swallowing, myalgias and fever. She had no prior history of a similar reaction or allergies. Upon examination, she was febrile and there were widespread, irregularly shaped erythematous and purpuric macules with blistering on more than 20% of the body surface area (BSA), including palms and soles and mucous membrane of mouth, anal canal and vagina. Nikolsky's sign was positive. Laboratory evaluation had mild leukocytosis without other relevant changes. A skin biopsy revealed keratinocyte necrosis of full-thickness of the epidermis with dermo-epidermal detachment and a scant, perivascular and inflammatory infiltrate of mononuclear cells in the superficial dermis (Image 1). The temporal association of allopurinol use and subsequent rash in addition of histologic and clinical findings suggested the diagnosis of allopurinol-Induced Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS / TEN) overlap syndrome.

As per the Naranjo Adverse Drug Reaction Probability Scale, the score of 5 indicated a probable adverse drug reaction. Allopurinol was withdrawn immediately. Patient was monitored closely in an isolation room with nutritional and intravenous fluid therapy, oral hygiene, analgesia and daily observation by Ophthalmology. Dressings, topical antibacterial agents and emollients were used to cover cleansed wounds. Despite controversial, corticosteroid therapy was initiated with gradual diminished and healed up of lesions in about 20 days (Image 2). SJS and TEN are rare but potentially life-threatening and severe mucocutaneous reactions, characterized by extensive necrosis and detachment of the epidermis[1]. SJS/TEN overlap described patients with skin detachment of 10%-30% of BSA. Medications are the leading trigger of SJS/TEN and allopurinol is the drug most commonly associated[2]. Diagnosis is clinical and confirmed with skin biopsy. Identification and removal of the precipitating agents should be done as early as possible and aggressive supportive measures should be taken to avoid mortality and morbidity[3]. Patients must not be exposed to the trigger drug, avoid sunlight during healing and moisturize their skin.



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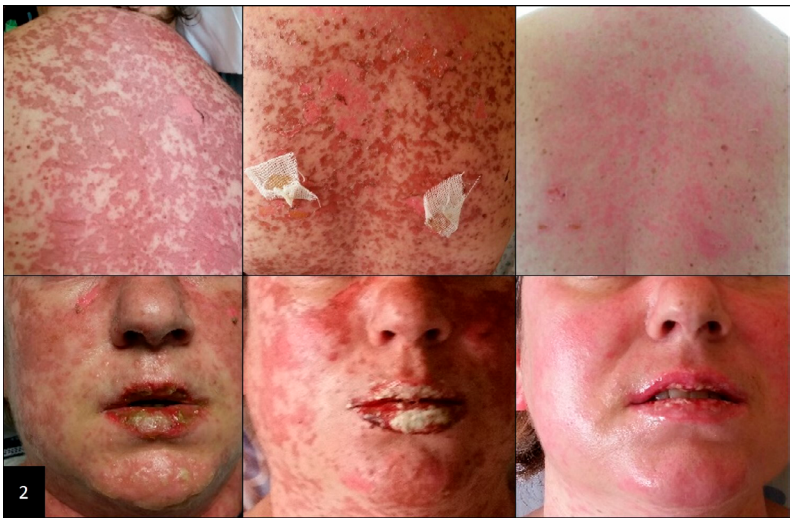

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Palabras clave: alopurinol, reacciones cutáneas adversas graves, síndrome de Stevens-Johnson, necrolisis epidérmica tóxica.

Keywords: Allopurinol, Severe cutaneous adverse reactions, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis.

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Melanoniquia longitudinal inducida por hidroxiurea en policitemia vera

Hydroxyurea-induced longitudinal melanonychia in polycythemia vera

CASE REPORT

A Caucasian 79-year-old female was referred to the Internal Medicine Consultation for etiologic investigation of erythrocytosis (haemoglobin 20.5 g/dL, hematocrit 62%) and segmental pulmonary thromboembolism. Her past medical history included arterial hypertension, dyslipidemia and obesity. After the complementary study carried out, the diagnosis of polycythemia vera was made (heterozygous V617F mutation in the JAK2 gene). The patient was then referred to the Hematology Consultation and started hydroxyurea (initially 500mg twice daily), along with phlebotomies. She was already under systemic anticoagulation. The patient had a good response, with hematocrit control.

After 5 months of beginning with hydroxyurea, she developed asymptomatic and progressive longitudinal dark brown bands involving all her fingernails (Figure 1) and toenails (Figure 2). The bands were well-defined and with different widths. In some fingernails, the pigmentation bands spread proximally underneath the translucent cuticles, but the nail folds were not affected (Pseudo-Hutchinson's sign). There was no nail thickening or atrophy. No history of trauma and there was no history of melanoma in her family. It was assumed drug-induced longitudinal melanonychia due to hydroxyurea. No other side effects of the drug were seen, so it was decided to maintain the drug due to the risk of another thrombotic event with the suspension.

Hydroxyurea is a cytostatic drug typically used for the treatment of myeloproliferative disorders and is generally a well-tolerated drug[1]. Melanonychia is a rare side effect of this drug that occurs only in 4.3% of the patients[2]. Besides, the involvement of all 20 nails is even rarer and only five cases were reported[1,2,3,4]. The time between the initiation of hydroxyurea and the onset of the melanonychia varies from 4 weeks to 5 years[5]. Other differential diagnoses should be considered such as physiological causes, repetitive trauma, onychomycosis or underlying systemic disease[5]. In the case of a single affected nail, subungual melanoma should be ruled out, especially in the presence of the Hutchinson's sign (nail pigmentation affecting also the cuticle and nail fold)[6]. So, this drug side effect should be known to avoid misdiagnosis. After discontinuation of hydroxyurea, melanonychia generally disappears as the nail grows. However, the decision to stop therapy needs to be pondered because of the risk of thrombotic events. If no more serious cutaneous effects occur, we think the drug should not be discontinuing.

Figure 1

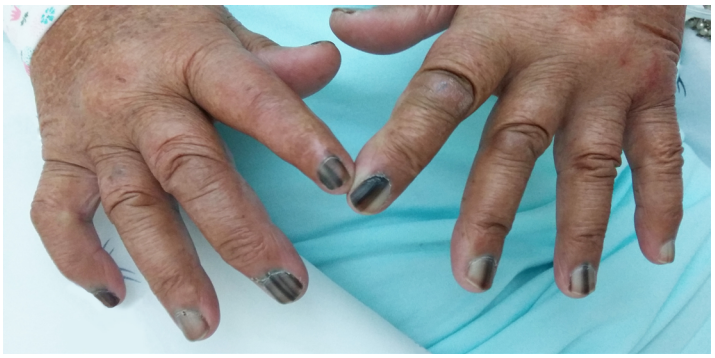
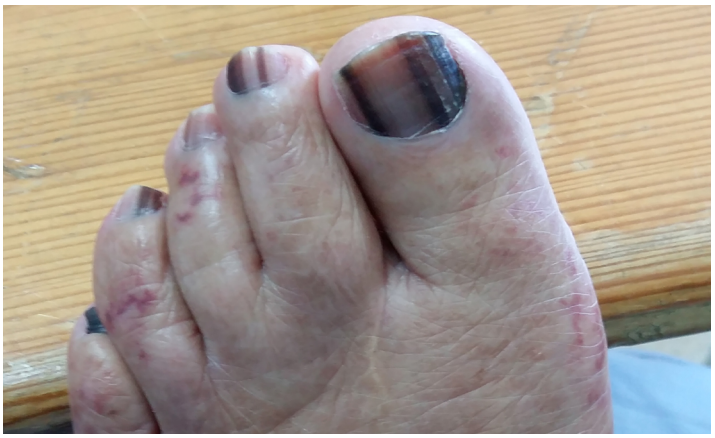


Figure 2



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Palabras clave: enfermedades de las uñas, hidroxiurea, policitemia vera.

Keywords: nail diseases, hydroxyurea, polycythemia vera.

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PULSE PARA VOLVER AL ÍNDICE

Síndrome de Klippel - Trenaunay – a propósito de un caso

Klippel - Trenaunay Syndrome – case report

INTRODUCTION

Klippel - Trenaunay Syndrome (KTS) is a rare condition that can be classified as a combination of vascular malformations affecting the arterial, venous and lymphatic systems. It is characterized by a clinical triad that includes cutaneous capillary malformations, venous malformations and bone/soft tissue extremity hypertrophy[1]. The etiology in unclear but it is presumed a disruption into mesoderm that compromises angiogenesis[2]. Some investigators suggest that deep venous obstruction/atresia causes chronic venous hypertension, leading to the onset of hemangiomas, varicose veins and limb hypertrophy. Although KTS is a sporadic condition, studies report familial cases that were not inherited from Mendelian pattern, suggesting a multifactorial inheritance[3]. Studies conducted later by Happle suggested that inheritance of a single defective gene could explain the development of KTS as well as the occurrence of sporadic and familiar cases. KTS has an equitable geographical, racial and gender distribution[4]. Clinically there may be changes in the upper or lower limbs, rarely the trunk. Patients may have symptoms ranging from moderate bone hypertrophy, hemangiomas and varicose veins. Occasionally they may have hematuria and hematochezia[5]. Treatment should be adjusted individually for each patient as well as clinical course and prognosis.

CASE REPORT

A 31 year-old male diagnosed with KTS appealed to the emergency department with asthenia and hematochezia (with dejections) with 2 months of evolution. He denied nausea, vomiting or weight loss. At the examination he presented cutaneous hemangioma in the left shoulder, left flank and left thigh (Images 1 and 2). He also had exuberant varicose veins in the left lower limb. The rectal touch was performed without evidence of blood. The study performed showed hemoglobin of 6.7 g/dL, VCM 81 fL, iron 28 g/dL, total iron fixing capacity 287 g/dL, transferrin 220 mg/dL, ferritin 51.4 ng/mL. He was hospitalized due to the needed of transfusion support and to clarify the clinical situation. The study carried out at the hospital revealed an anuscopy with large, congestive and friable internal hemorrhoids that needed an elastic ligation. At the colonoscopy there were no significant endoscopic changes. Upper digestive endoscopy and capsule enteroscopy revealed erythema of the duodenal bulb mucosa and a small ulcer/erosion of congestive edges in the terminal ileon (histologic study revealed no malignancy). The patient underwent thoracic, abdominal and pelvic computed tomography without significant changes (without visceral involvement of KTS). For iron deficiency anemia began oral iron supplementation with progressive improvement.

DISCUSSION

Klippel - Trenaunay Syndrome usually affects a body segment and has a wide range of clinical manifestations[6]. The presence of two of the abnormalities initially described are sufficient to the diagnostic; however, all changes are commonly present, in most patients, at birth or during childhood. The lower limb is the most common site of presentation but there are cases of involvement of more than one body segment, like our patient. Visceral involvement also occurs in about 20% of cases[7]. The involvement of gastrointestinal system by

Figure 1

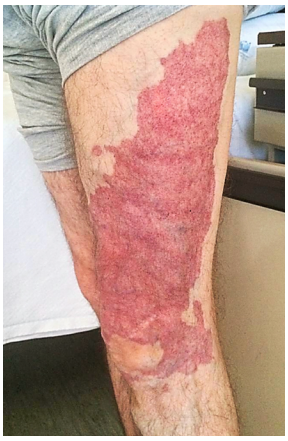
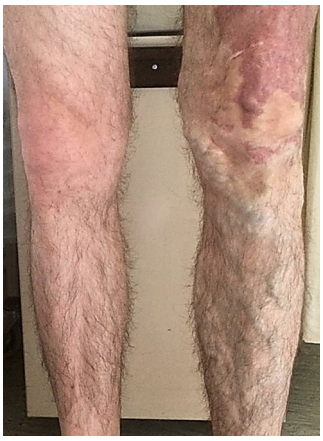


Figure 2



KTS is characterized by the presence of varicose veins (especially in the rectum and sigmoid) that may bleed, as described for our patient[9]. The diagnosis of this pathology is clinical; however some complementary diagnostic tools help to investigate the involvement of various systems and organs by KTS.

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Palabras clave: síndrome de Klippel-Trenaunay, malformaciones capilares cutáneas, malformaciones venosas, anemia, hematoquecia.

Keywords: Klippel-Trenaunay syndrome, cutaneous capillary malformations, cutaneous capillary malformations, anemia, hematochezia.

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Úlcera cutánea fatal en un paciente en hemodiálisis tras fracaso de trasplante

Fatal skin ulcer in a patient on hemodialysis after renal allograft failure

CASE REPORT

A 76-year-old female with history of end-stage renal disease due to IgA nephropathy, submitted to a kidney transplant 28 years before, secondary hyperparathyroidism under vitamin D analogue, chronic anaemia, diabetes mellitus, arterial hypertension, atrial fibrillation (anticoagulated with warfarin) and peripheral venous insufficiency presented with a 1-month history of a skin ulcer on the left lower limb. Five months before, she had to go back on haemodialysis by central venous catheter because of renal allograft failure by chronic dysfunction. Her residual urine output was 1L/day and she was still on low-dose prednisone. Physical examination revealed a distal, 4-centimetre, skin ulcer on the left leg, with inflammatory signs and purulent discharge. Distal pulses were absent, but ultrasound image showed no alterations in biphasic flux of both anterior and posterior tibial vessels. The patient was started on amoxicillin-clavulanic acid, but the ulcer worsened: it became bigger and more painful. One week later, she was readmitted to the emergency department hypotensive, prostrated and with thoracic pain. Acute coronary syndrome was excluded. Laboratory tests showed worsened anaemia (hemoglobin 7g/dL, previously 10g/dL), leucocytosis (16080 leucocytes/microliter, normal value 4000-11000 leucocytes/microliter), high C-reactive protein (87mg/L, normal value <5mg/L), high parathyroid hormone (246pg/mL, normal value 10-65pg/mL), hyperphosphatemia (5.4mg/dL, normal value 2.7-4.5mg/dL) with normal calcium (2 mmol/L, normal value 2-2.6 mmol/L). She was afebrile. Blood cultures were requested.

Multi-resistant *Staphylococcus epidermidis* was isolated in blood cultures; vancomycin was started ant the central venous catheter switched. Infective endocarditis was excluded. Nevertheless, the ulcer grew bigger and evolved to necrosis (image 1). A leg radiography and a skin biopsy were performed. Leg radiography showed calcified vessels surrounding non-calcium-containing radiolucent tissues (image 2). Skin biopsy revealed extensive necrosis of epidermis, dermis and subcutaneous tissue; areas of recent thrombosis of hypodermic vessels and calciphilia of small vessels of the subcutaneous tissue (image 3). Unfortunately, the patient died of septic shock before the result of the skin biopsy.

Calciphylaxis or calcific uremic arteriolopathy is a rare, life-threatening condition, that is usually

Figure 1. Skin lesion appearance after two weeks of hospital admission (at time of skin biopsy).

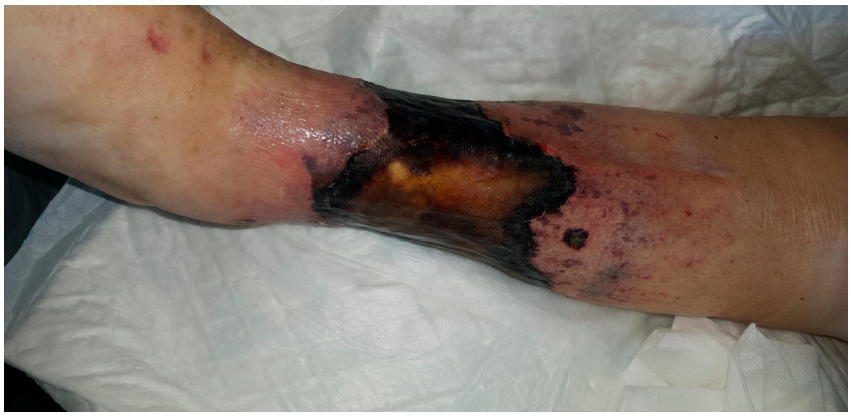


Figure 2. Frontal profile view of left leg radiography showed irregularity of the soft tissue and vascular calcification in the medial-distal region.

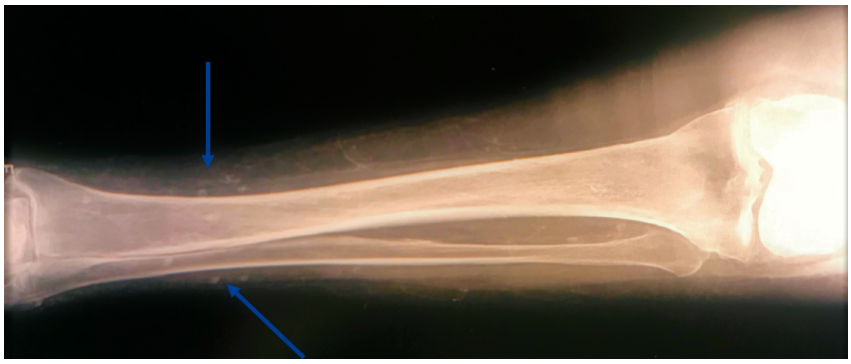
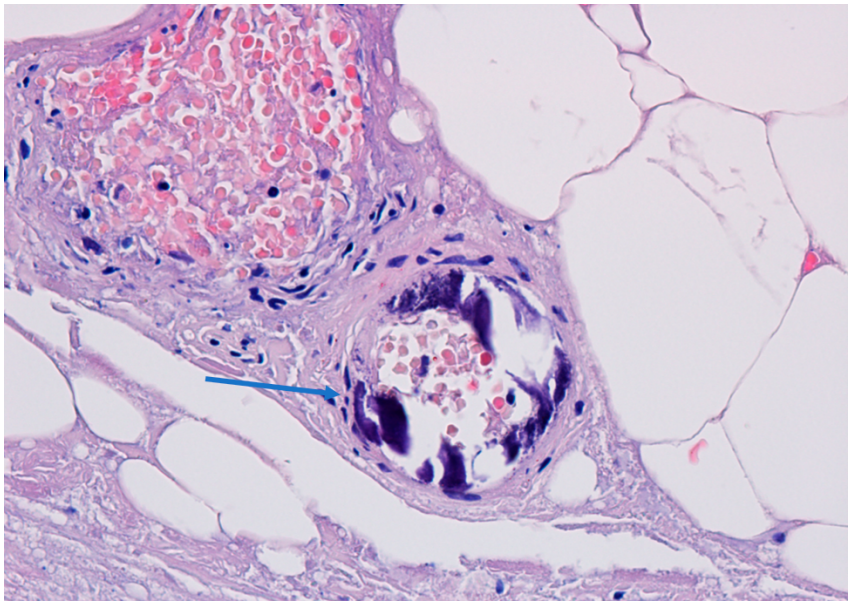


Figure 3. Skin biopsy showed extensive necrosis of the epidermis, dermis and subcutaneous tissue with areas of recent thrombosis of the hypodermis vessels and calciphilia in vessels (amplification 400x, coloration eosin-hematoxylin).



PULSE PARA VOLVER AL ÍNDICE

associated to end-stage renal disease. Less frequently, it can also occur in renal transplant recipients and other patients, denominated nonuremic calciphylaxis. Most patients present with painful lesions that can progress to ischemic/necrotic ulcers and become superinfected. Vascular calcifications can occur in other localizations[1]. Histology reveals dermal and pannicular arteriolar calcification, subintimal fibrosis and thrombotic occlusion. Risk factors include hyperphosphatemia, warfarin use, calcium-based binders, vitamin D analogues, systemic glucocorticoids, female sex, hypoalbuminemia and diabetes mellitus.[2] Optimal treatment is unknown, but sodium thiosulfate, wound care and pain control are reasonable options. Abnormalities in blood calcium and phosphate should be treated[3]. Delayed diagnosis can lead to sepsis-related morbidity and mortality, as in this case we report[1].

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Palabras clave: calcifilaxis, trasplante de riñón, úlcera cutánea.

Keywords: calciphylaxis, kidney transplant, skin ulcer.

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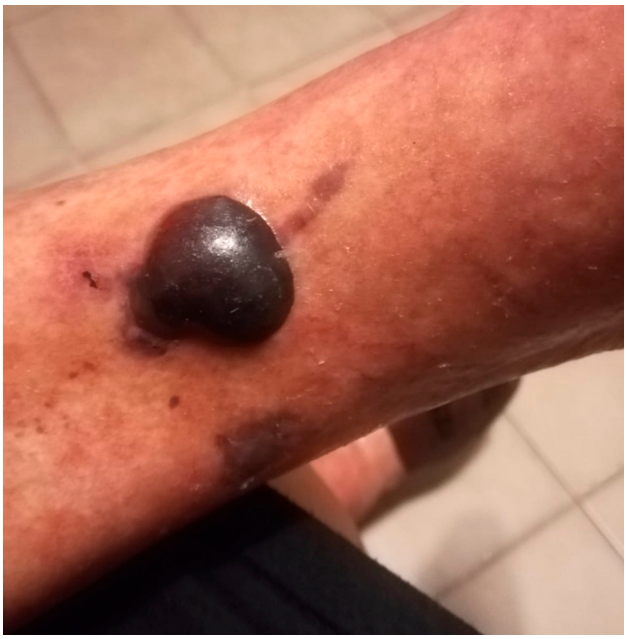
Dermatosis bullosa hemorrágica inducida por enoxaparina: a propósito de un caso

Bullous hemorrhagic dermatosis at distant site induced by enoxaparin: a case report

Enoxaparina es un fármaco ampliamente utilizado en la prevención y tratamiento de la enfermedad tromboembólica venosa. Las manifestaciones dermatológicas observadas por este tratamiento acontecen principalmente en el lugar de la inyección en forma de hematomas, equimosis, necrosis cutánea, dermatosis de contacto o urticaria. No obstante aunque entre las manifestaciones cutáneas frecuentes destaca la urticaria, prurito y eritema, hemos de conocer otras poco frecuentes como es la dermatosis bullosa hemorrágica a distancia inducida por heparina.

La dermatosis bullosa hemorrágica (DBH) inducida por enoxaparina, es un efecto adverso inusual en el que los mecanismos implicados y los factores de riesgo no están claramente establecidos, acontece de manera autolimitada, resolviéndose entre 2-3 semanas, no siendo necesario suspender el tratamiento.

Presentamos el caso de una paciente de 85 años con antecedentes de doble lesión mitral (estenosis mitral leve-moderada e insuficiencia mitral grado II), doble lesión aórtica (estenosis aórtica leve e insuficiencia aórtica grado II) y fibrilación auricular de nuevo diagnóstico. Inició tratamiento con enoxaparina 60 mg subcutánea subcutánea (sc) cada 12 horas, desarrollando a los 3 días del inicio del tratamiento una ampolla hemorrágica tensa de 2x2 cm, no dolorosa, en tercio distal de extremidad inferior izquierda (Figura 1), motivo por el que se recomendó disminuir y mantener la dosis de enoxaparina 20 mg (sc) cada 12 horas. Tres días después, se produjo una ruptura de la lesión no pudiendo ser biopsiada. El control analítico mostraba un recuento plaquetario y una coagulación normales. La paciente mantuvo el tratamiento indicado desapareciendo de forma espontánea la lesión en 2 semanas.



La dermatosis bullosa hemorrágica es una entidad poco frecuente en la práctica médica diaria. Tras la descripción inicial detallada por Perrinaut et al[1] en 2006, se han publicado distintas series de casos que identifican esta entidad, caracterizada por la aparición de ampollas tensas, hemorrágicas, distantes al lugar de la inyección del fármaco con un curso clínico favorable tras la disminución, suspensión e incluso mantenimiento de la dosis del fármaco[2]. Aunque su patogenia es desconocida, se ha descrito su asociación con diferentes mecanismos, entre los que se incluyen reacción de hipersensibilidad retardada tipo IV favorecida por un estado de anticoagulación/antiagregación adicional, trombocitopenia inmunomediada, reacción alérgica tipo I, necrosis de piel y pustulosis[3]. Esta entidad, se ha relacionado con diferentes heparinas de bajo peso molecular (dalteparina, enoxaparina, tinzaparina) y heparinas no fraccionadas, sin embargo, enoxaparina es la que más se ha asociado con DHB.

El diagnóstico diferencial debe plantearse con otras entidades que cursan con lesiones cutáneas de características hemáticas y clínica similar, como aquellas entidades que producen trastornos en la hemostasia. Para ello, nos apoyaremos en una anamnesis detallada, estudios analíticos y anatomopatológicos complementarios. La actitud terapéutica es variable, definido por la suspensión transitoria del fármaco, disminución de la dosis del tratamiento o suspensión y reintroducción de otra terapia anticoagulante[2,4,5]. Puesto que el uso extendido de estos fármacos es un hecho habitual en la práctica clínica diaria, y probablemente esta entidad se encuentre infranotificada, creemos que el diagnóstico de esta entidad deberá ser tenido en cuenta por el clínico y que, por lo tanto, debería conocer.

Este caso se ha notificado al Centro de Farmacovigilancia de Castilla-La Mancha.

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Palabras clave: dermatosis hemorrágica, enoxaparina, heparina de bajo peso molecular.

Keywords: hemorragic dermatosis, enoxaparin, low molecular weight heparin.

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PULSE PARA VOLVER AL ÍNDICE

Pelagra: lesiones dermatológicas típicas

Pellagra: typical dermatological lesions

Pellagra, as all vitamin deficits, is still a prevalent disease in developing countries. In Western Europe there is no data about its prevalence. The few cases reported are associated to alcoholism or malabsorption1.

We present a case of a 37-year-old homeless man, with history of alcohol abuse. He was admitted to the emergency department after the appearance of non-pruriginous lesions of the skin on his face, neck and upper limbs. A month before, he presented a behavioral change, meaningless speech and diarrhea, without fever. He denied any recent burns or exposure to chemical products.

On admission, he had a photosensitive scaly dermatitis on his face, dorsal part of the neck, forearms and hands (Image 1). He was disoriented to person, place and time, and had psychomotor agitation and aggressive behavior. Meningeal signs were negative. The laboratory tests were normal (hemogram, renal function, ionic levels, C-reactive protein), human immunodeficiency virus 1/2 was negative. Cerebral computed tomography scan did not reveal any alteration. He started on niacin 100mg QD. On day 3, the gastrointestinal transit was restored. He also showed progressive improvement of cutaneous lesions and neurological symptoms with total resolution on day 7 (Image 2).

The neurological, dermatological and gastrointestinal involvement defines the niacin deficiency, also called pellagra2,3. The response to treatment with niacin confirms its diagnosis4.

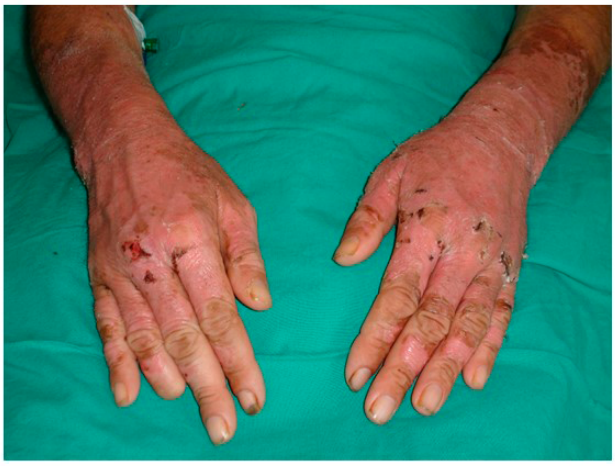

Image 1: Pellagra before treatment with niacin

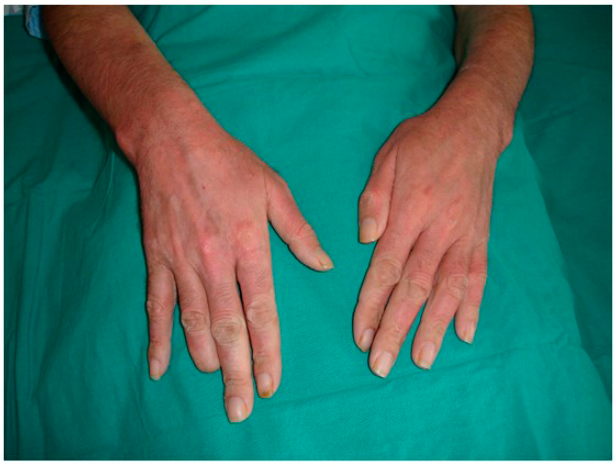

Image 2: Seven days after treatment with niacin

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Palabras clave: pelagra, lesiones dermatológicas, niacina.

Keywords: pellagra, dermatological lesions, niacin.

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Un caso de exantema fijo medicamentoso causado por diclofenaco y naproxeno

A case of generalized bullous fixed drug eruption caused by diclofenac and naproxen

CASE REPORT

Fixed drug eruption is an adverse drug effect that characteristically recurs in the same locations upon re-exposure to the offending drug, more frequently non-steroid anti-inflammatory drugs (NSAIDs) and antibiotics[1]. It usually presents with a single or a small number of dusky red or violaceous plaques that resolve, leaving post-inflammatory hyperpigmentation. Generalized bullous fixed drug eruption (GBFDE), is a particular form of fixed drug eruption characterized by widespread blisters and erosions and can be confused with Stevens-Johnson syndrome and toxic epidermal necrolysis[2].

We report a case of a 74-year-old woman with medical history of hypertension, lumbar spine osteoarthritis and cutaneous hypersensitivity reaction to diclofenac three years ago, that manifested by erythematous bullous patches over the back, abdomen lower and upper limbs that resolved spontaneously leaving a residual hyperpigmentation. The patient was admitted at the emergency department due to similar erythematous pruriginous plaques of varied sizes, some bullous, over the back, lower and upper limbs, on the same locations of the previous lesions and hard palate, with no other significant findings on clinical evaluation. Those cutaneous lesions appeared about 6 hours after naproxen intake due to back pain. Regarding the recurrence of those lesions with similar pattern distribution, the diagnosis of generalized bullous fixed drug eruption was extremely probable. She initiated treatment with prednisolone and a skin biopsy of a lesion on the left tight was performed after she was admitted on Internal Medicine Ward. The diagnosis was later reassured by histopathologic findings and the patient was discharged and instructed to avoid naproxen, diclofenac and other NSAIDs.

This case highlights the importance of an effective clinical evaluation and medical questionnaire, since GBFDE can mimic serious medical conditions.

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Palabras clave: exantema fijo medicamentoso, naproxeno, diclofenaco.

Keywords: fixed drug eruption, naproxeno, diclofenac.

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Fig. 1. Bullous eruption on the hard palate.

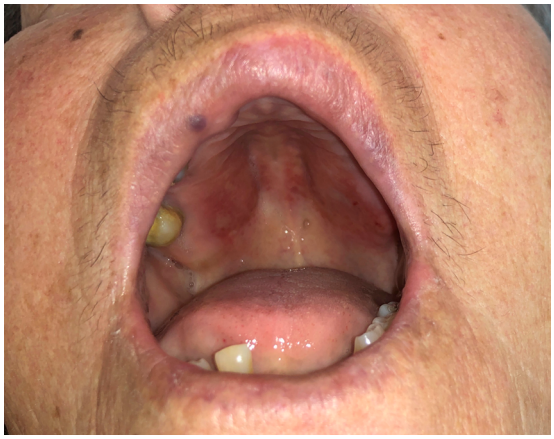


Fig. 2. Bullous eruptions on the left hand and residual hyperpigmentation on the left wrist.

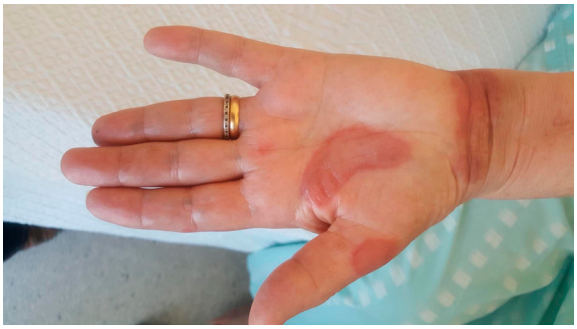


Fig. 3. Dusky patches, with bullae and residual hyperpigmented lesions on the right leg.

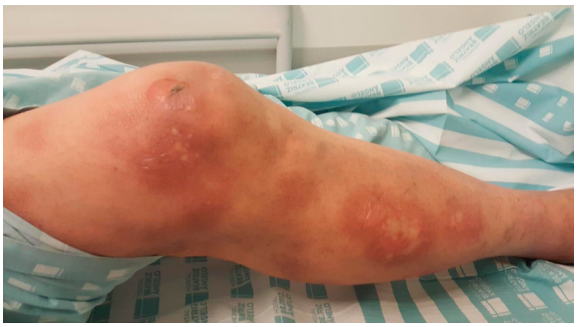
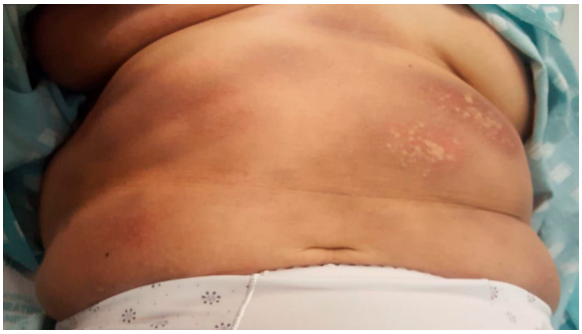


Fig. 4. Erythematoviolaceous, oval macules and patches affecting the abdomen, with residual hyperpigmented lesions with associated skin discoloration.



PULSE PARA VOLVER AL ÍNDICE

Linfoma de Burkitt axilar

Axilar Burkitt lymphoma

CASO CLÍNICO

Varón de 50 años con diagnóstico de infección por VIH, conocida desde junio de 2018, en estadio A3. Actualmente en tratamiento con dolutegravir/abacavir/lamivudina con carga viral indetectable y niveles de CD4 superiores a 1.000/mm^3. Acude por cuadro de 1 semana de evolución de bultoma axilar derecho doloroso, adherido a planos profundos, de consistencia dura y crecimiento rápido; no presenta fiebre ni cuadro constitucional acompañante.

Se realizaron pruebas de imagen y analíticas, así como biopsia de la lesión para estudio anatomopatológico, siendo diagnosticado de linfoma difuso B de rasgos morfológicos e inmunohistoquímicos compatibles con Linfoma de Burkitt.

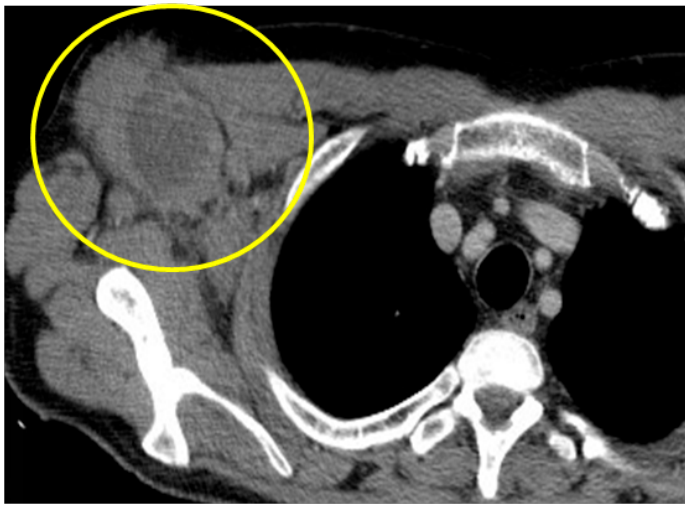
El linfoma de Burkitt es el tumor humano de crecimiento más rápido. Se trata de un linfoma no Hodgkin de células B, debido a la translocación cromosómica (8;14) y disregulación del gen MYC, lo que lleva a un alto índice de proliferación.

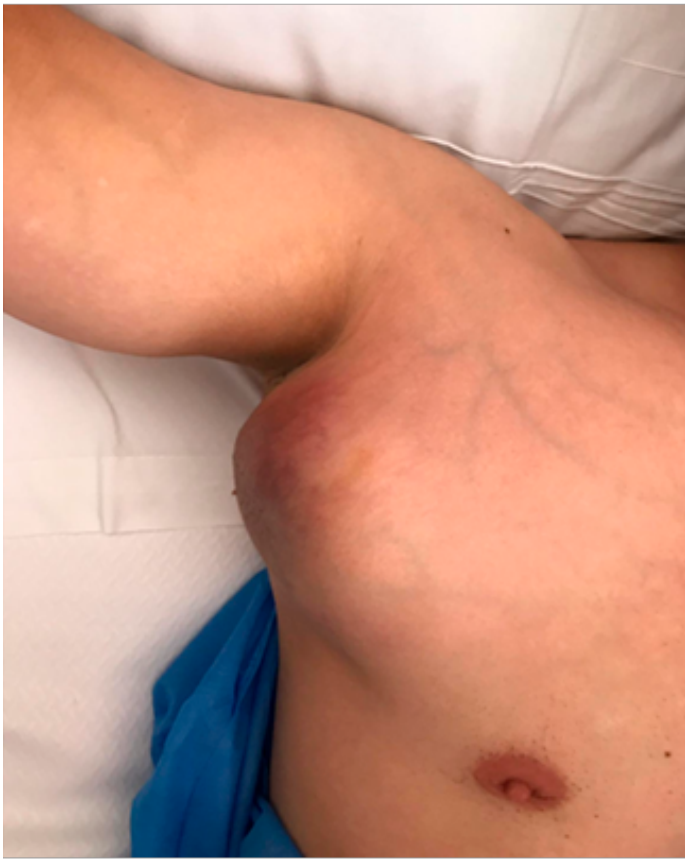
Se describen tres variantes (africana o endémica, esporádica y asociada a inmunodepresión). En pacientes VIH es un criterio de estadio SIDA.

El diagnóstico se establece mediante la anatomía patológica en la que aparece la imagen típica de "cielo estrellado". El estadiaje mediante PET - TC y el estudio de médula ósea y LCR debe realizarse rápidamente dada la rapidez de replicación de las células tumorales.

Palabras clave: Linfoma de Burkitt, VIH, adenopatías.

Keywords: Burkitt lymphoma, HIV, adenopathy.





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