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CASOS CLÍNICOS

IMÁGENES EN MEDICINA

Plasma cell dyscrasia behavior in a referral hospital in southern Colombia: younger, clinically and paraclinically worse than reported

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ABSTRACT

Objectives: Plasma cell dyscrasias are diseases characterized by clonal proliferation and accumulation of cells producing monoclonal immunoglobulins. These diseases have not been studied in our region and we don't know if their behavior is similar to that reported in the literature. That's why we evaluated multiple characteristics in southern Colombia.

Methods: analytical cross-sectional study of patients with confirmed diagnosis of a plasma cell dyscrasias were included.

Results: 60 patients included in our study, 65% were men, with an average age of 58.8 years (CI 96% 55.8 - 61.93). Bone pain was the most frequent symptom (88%). The most frequent dyscrasia was multiple myeloma and in these patients we found a high percentage of hemoglobin less than 10 mg/dl, creatinine greater than 2 mg/dl and serum calcium higher than 11 mg/dl (77%, 38% and 37 %, respectively). Half of the patients had a time course of symptoms greater than 4 months and 43% had plasma cells in bone marrow greater than 60%. 65% of patients had elevated levels of serum B2-microglobulin (> 5.5 mg/L) and in-hospital mortality was 15%. We found a statistically significant association between mortality and gender (PR 6.5) and between mortality and hemoglobin ($p = 0.039$).

Conclusion: Patients with plasma cell dyscrasia in southern Colombia are younger, consult late, in an advanced stage of their disease, with greater renal damage, hypercalcemia and anemia than reported in the literature, also a high tumor burden due to high plasma cell infiltration into bone marrow and high values of serum B2-microglobulin.

Key words: Plasma cell dyscrasia, monoclonal gammopathy, multiple myeloma, tumor load, Colombia.

INTRODUCTION

Plasma cell dyscrasias constitute a broad spectrum of diseases characterized by clonal proliferation and accumulation of cells producing monoclonal heavy and light chain restricted immunoglobulins (known as paraprotein or M proteins)[1]. These disorders include monoclonal gammopathy of uncertain significance, multiple myeloma (MM) and its variants (asymptomatic multiple myeloma, symptomatic multiple myeloma, plasma cell leukemia, nonsecretory myeloma), plasmacytoma and its variants; osteosclerotic myeloma (POEMS syndrome), immunoglobulin deposition diseases and Waldenstrom macroglobulinemia. In the literature, they are within the spectrum of the same disease, but most reports and studies focus on the Multiple myeloma. Our study tried to collect the whole plasma cell dyscrasia spectrum, nevertheless the symptomatic spectrum of the disease corresponds to multiple myeloma and our data are directed to this particular pathology, due to the low prevalence of the other entities found in our study and their low expression of symptoms[2,3].

MM is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. It`s the most important plasma cell dyscrasia, accounting for approximately 10% of all hematological malignancies[4]. Higher incidence is reported in developed countries, probably owing to the availability of better diagnostic techniques. Also the incidence is higher in black individuals (11.9 per 100.000) and lower in Asian and Hispanic and more prevalent in men than in women[5,6,7].

The diagnosis is based on the presence of a monoclonal protein, bone manifestations and infiltration of plasma cells in the bone marrow. These entities are relatively rare and their prognosis is poor, with less of 2 year survival on the worst scenarios[8].

On the other hand, although associations with strong evidence to reveal clear clinical risk factors in this group of patients have not been elucidated, some frequently encountered conditions have been documented such as advanced age, male gender, african-american race and family history of these diseases[9,10,11]. Despite those clinical risk factors that could lead to a better treatment response the most powerfull prognostic factor is related to genetic abnormalities, principally del(17p) and del(1p32)[12].

Treatment of this hematological malignancy has evolve from corticosteroids and melphalan to high dose chemotherapy associated with autologous stem-cell transplantation and recently immunomodulatory drugs like thalidomide, lenalidomide, proteasome inhibitors and biologic therapies with better outcomes[13,14].

In Latin America, most publications are limited to case reports with manifestations or atypical characteristics of some of these diseases. The few investigations on clinical behavior have been carried out only in patients with multiple myeloma, such is the case of studies carried out in Chile, Cuba, Argentina, Peru, Mexico and Brazil[15], where patients with multiple myeloma have been characterized, reporting statistical data similar to those of the rest of the world, with average age of presentation above 60 years[16].

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No studies have been carried out covering all this group of pathologies in Colombia, and it is unknown if the behavior of this spectrum of diseases in this population is similar at the rest of the world, for which the characterization of this condition was postulated.

MATERIALS AND METHODS

Cross-sectional study, where the demographic, clinical and paraclinical characteristics of patients with plasma cell dyscrasias of the University Hospital of Neiva in a period between January 2005 and December 2016 were studied. Data from the pathology unit and patients whose histological diagnosis met the inclusion criteria were selected. In parallel, patients registered with any of the ICD-10 codes related to the included pathologies were reviewed. Subsequently, and once the patients who entered the study were identified, a search was made on clinical records of the oncology unit, in order to complement and corroborate the information obtained. We included adult patients assessed at the university hospital of Neiva, a tertiary referral hospital in southern Colombia, with a histopathological diagnosis related to some plasma cell dyscrasia available in the database of the pathology unit of this institution during the study period and their respective medical records. Additionally patients with a diagnosis of ICD-10 (International Classification of Diseases, tenth version) related to plasma cell diseases were included.

A convenience sampling was carried out including the total population considering the low prevalence of these disorders.

The sociodemographic data and clinical variables were obtained from the medical records. The review of medical records was carried out by four medical doctors from the University Hospital of Neiva. The data was entered by two independent operators, with subsequent reconciliation of the data by the main researcher, in order to detect erroneous values and missing information.

After the data collection, organization, tabulation and coding variables in the statistical program IBM SPSS 20, a descriptive and inferential statistical analysis was completed and generated information of percentages, averages, proportions of the compared data and measures of association between the different variables.

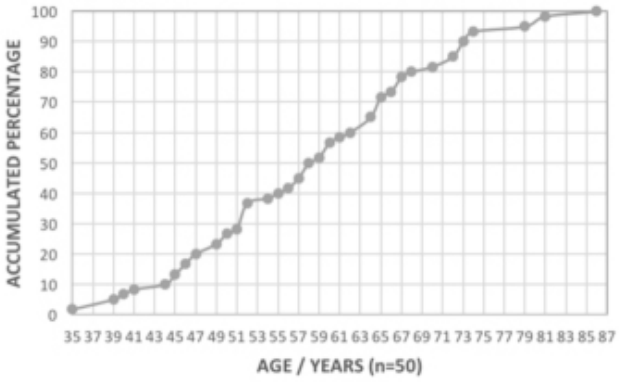
Univariate descriptive analysis were initially completed. For qualitative variables, frequency measurements were calculated; and for the quantitative variables, measures of central tendency, dispersion and position were determined. Normal tests of Kolmogorov-Smirnov and Shapiro-Wilk were performed on all quantitative variables, according to the sample value. Subsequently, a bivariate analysis was performed using different statistical tests according to the type of distribution of the variables, such as Pearson and Spearman correlations between two quantitative variables, the chi-square test between qualitative variables, and t-student and U tests of Mann Whitney between quantitative and qualitative variables.

RESULTS

A total of 95 patients were obtained; 23 medical records were not available in physical or digital file. Nine patients did not correspond to a diagnosis of plasma cell dyscrasia and information was incomplete in three cases, which is why they were not included in the analysis of the information.

The minimum age was 35 years and a maximum of 86 years, with a mean of 58.8 years (IC 55.90-61.9) (Figure 1). 65% of the patients were male, mainly from urban areas (32% vs. 28%). In relation to race, it was found the vast majority of patients were mestizos (95%) and only one patient was African-American. Family history of cancer was found only in 6.8%, with none relation for any type of neoplasia.

Figure 1. Percentage accumulated according to the age of the patients with diagnosis of plasma cell dyscrasia.



Multiple myeloma was the most frequent plasma cell dyscrasia, with 80% (two cases of POEMS syndrome were found (3.3%), two cases of non-secretory multiple myeloma (3.3%). Solitary plasmacytoma was second place in 13.3%; a patient with extramedullary plasmacytoma (1.7%) and an individual with heavy chain disease, also called Franklin's disease (1.7%). After all, 50 patients had multiple myeloma or one of its varieties. No patients were found with Waldenstrom's macroglobulinemia, plasma cell leukemia, light chain deposit disease or primary amyloidosis (Table 1).

Table 1. Distribution according to the type of dyscrasia of patients with diagnosis of plasma cell dyscrasias, n = 60.

Type of plasma cell dyscrasia	Frequency	Percentage (%)
Enf. heavy chains (franklin)	1	1,7
Multiple myeloma	45	75
Multiple myeloma biclonal	1	1,7
Multiple myeloma not secretor	2	3,3
Plasmocytoma	8	13,3
Extramedullary plasmocytoma	1	1,7
POEMS Syndrome	2	3,3
Total	60	100

The clinical manifestations were found in patients with multiple myeloma; bone pain was the most common symptom with an 85%. A little more than a half of the patients also reported weight loss at the time of presentation (57%). Neurological symptoms were a less frequent finding, present in 36.7% of patients. Bone alterations occurred in 88% of patients, with osteolytic lesions predominating (35%), followed by pathological fractures (28.3%). (Figures 2 and 3)

The average time of evolution of the symptoms was 4.5 months until admission, and 20 days for the time from admission to diagnosis. The most common Lab report found was anemia, followed by elevated creatinine and hypercalcemia. 77% of the patients had a hemoglobin value of 10 mg/dl or below. Creatinine greater than 2 mg/dl in 38% of patients and the presence of hypercalcemia (serum calcium greater than 11 mg / dl) was recorded in 37% of cases (Table 2).

Figure 2. Distribution according to the clinical signs of patients diagnosed with multiple myeloma, n = 50.

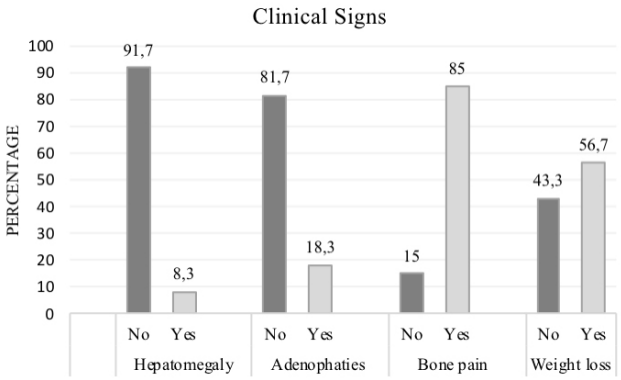


Figure 3. Distribution according to the type of bone alteration of patients with a diagnosis of plasma cell dyscrasia, n = 50.

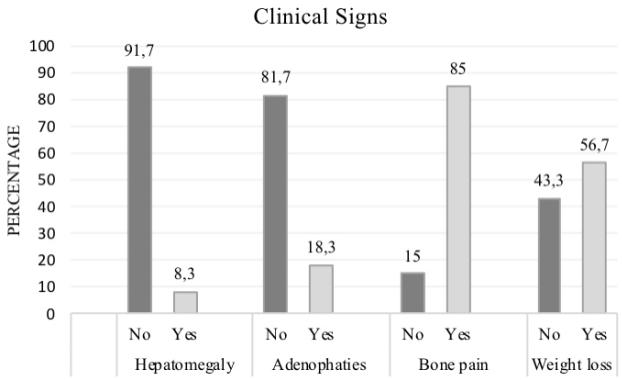


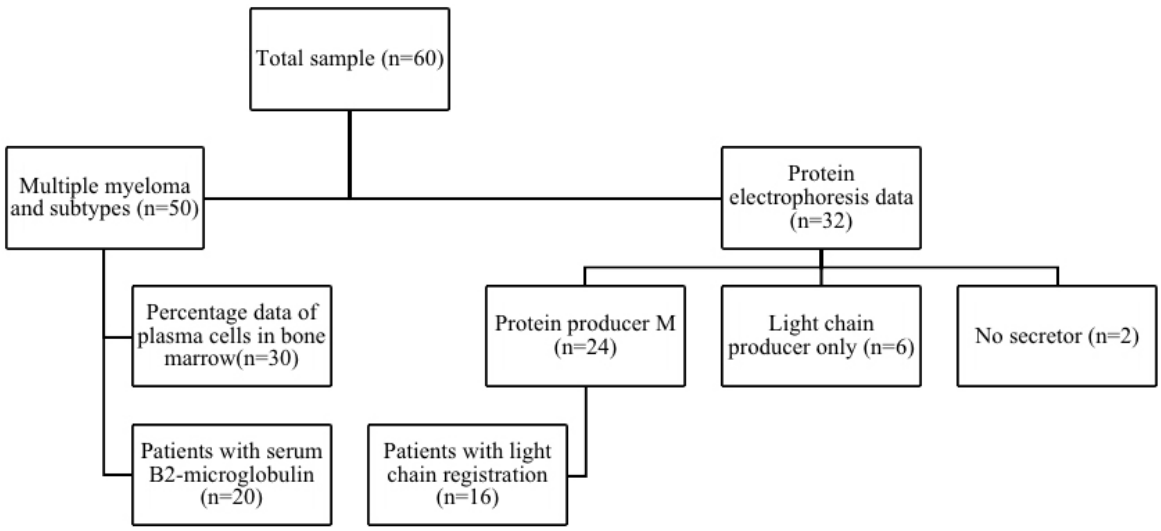
Table 2. Laboratory results in 50 patients with multiple myeloma and its subtypes.

	No. of patiens	Result	Rank	Distribution	% of patiens
Hemoglobin (gr/dl)	50	Mean: 8.8	4.8 – 14.0	< 10	77
Creatinine (mg/dl)	50	Median: 1.26	0.45 – 10.6	> 2.0	38
Calcium (mg/dl)	50	Median: 10.4	7.2 – 16.2	> 11.0	37

In regard of plasma cell percentage, this value was found in 30 of the 50 patients with multiple myeloma or its subtypes (Figure 4). The median was 45% and 43% of the patients had a value greater than or equal to 60% of plasma cells in bone marrow. The B2-microglobulin in this same sample (n = 50) showed a median of 6.0 mg/L and 65% of the patients were above 5.5 mg/L.

32 patients had a record of protein electrophoresis, 24 patients had production of M protein, of which IgG was the most frequent (50%), followed by IgA (18%). In 18%, only

Figure 4. Distribution of patients with plasma cell dyscrasias for the following variables: percentage of plasma cells in bone marrow, M protein, light chain and serum B2-microglobulin value.



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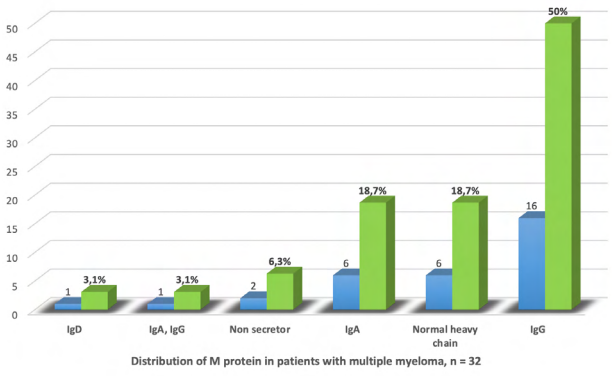
light chain production was also found, being Kappa chain the most frequent (50% Vs 43.7%). One case was treated as biclonal multiple myeloma where Kappa and Lambda chains were identified (Figure 5).

Figure 5. Distribution of M protein in patients with multiple myeloma, n = 32.



In-hospital mortality was recorded in 15%, and 18% in the case of multiple myeloma. When comparing mortality with qualitative variables, a statistically significant association between gender and in-hospital mortality was found using the chi-square test, with a p = 0.04 and a prevalence ratio (PR) value of 6.5, with an interval of confidence (CI) 95% (1.48 - 28.53) for multiple myeloma.

The association between the variables of mortality and hemoglobin performed with t-student test showed that there is a statistically significant difference in the mean hemoglobin between patients who died and did not die (p = 0.039), being lower in the group that died. The patients who died had a mean hemoglobin of 7.7 gr/dl in contrasts with the average of those who survived (9.5 gr/dl). (Table 3)

Significant differences were found between the medians of the patients who died and did not die in the case of the percentage of plasma cells in the bone marrow (80% Vs 40%, respectively), as well as for the serum B2-microglobulin (12.9%). Vs. 6 mg/L)

DISCUSSION

In this study, an average of 58 years of age was found, which is not consistent with reports in the western literature, where an average of approximately 70 years is described on regards of patients with multiple myeloma[17]. It has been shown that only 10% and 2% of patients are under 50 and 40 years old, respectively[18].

Age averages similar to the present research have also been reported, such as in the Egyptian published in 2014, where the average age was 58.5 years[19] and in a Colombian study conducted in the Santa Fe Foundation of Bogota in patients with multiple myeloma finding an average of 58 years, 26% of them were under 50 years old[20].

By gender, the highest prevalence was in men (65%), slightly above the male: female ratio described in the literature (1.8: 1 vs 1.4: 1). This gender distinction is probably important in terms of mortality. The literature reports a higher incidence in black and African-American individuals (approximately 2 to 3 times compared to the white race)[21], which did not correlate with the results, nor was it found that the prevalence of cancer in first-degree relatives was more frequent than the general population.

For patients with multiple myeloma in our study bone pain was the predominant symptom, occurring in 88% of patients, higher than reported in the literature where it is described in approximately 58% of cases. Weight loss was a frequent complaint, found in 57% of our population, more than double what was reported in a registry of 1027 patients diagnosed with multiple myeloma in the Mayo Clinic[17,21,22].

Neurological symptoms are not uncommon in patients with plasma cell dyscrasias, and are the most frequent presentation symptoms in multiple myeloma, after CRAB symptoms (Calcium, Renal failure, Anemia, Bone disease)[23]. Peripheral neuropathy is common and is frequently associated with plasma cell dyscrasias, which may correspond to 10% of patients with idiopathic peripheral neuropathy and as high as 20% in patients with multiple myeloma. In this study, a high neurological compromise was found, with paresis of the lower limbs more frequent[24,25].

Bone lesions visualized on a conventional radiograph, which may include osteolytic lesions or the presence of fractures, are described in 80% of patients at the time of diagnosis. A record similar to that found in this study (74%), where injuries also predominated osteolytic[26].

An average duration of 56 days has been described, from the time of onset of symptoms to the medical consultation for multiple myeloma, representing the longest duration among 10,953 patients with 28 different types of cancer, as reported in a study published in the British Journal of Cancer in 2015. This does not resemble the present results, where 50% of the patients had a medical consultation greater than or equal to 4 months. Situation that may be a reflection of failures in access to health services and lack of education in the general population to consult quickly before the progression of these symptoms, which induce a late diagnosis and poor prognosis[27].

From the point of view of laboratory reports; hemoglobin, serum creatinine and serum calcium values were taken into account, as they are fundamental markers of organic damage and an indispensable condition in the definitive diagnosis of the majority of patients with multiple myeloma[28]. In this way, it was possible to demonstrate that anemia does correspond to the most frequent findings, although the large series only describes it in 35% of patients. Creatinine and serum calcium are also reported lower (19 and 13%, respectively)[17], indicating that our patients presented with greater anemia, kidney damage and hypercalcemia.

The compromise at the spinal level found is similar to reported in the literature, however, it is noteworthy that a large part of

the patients (43%) had an infiltration in the medulla of more than 60%, indicating a large tumor load. Findings in protein electrophoresis were consistent previously described, and for the case of B2 microglobulin it was found that the vast majority of patients had high values, indicating an advanced stage in the evolution of the disease. The high levels of serum B2-microglobulin have been associated with a higher tumor load and it has also been related to renal failure, which in turn leads to an unfavorable prognosis[28,29].

In-hospital mortality was high in our patients, and even more so in those with multiple myeloma. This compared with the study that analyzed 3,107 patients with multiple myeloma evaluated in a medical research center in the United Kingdom, where an early mortality (first 60 days of diagnosis) of 10% was found[30].

A bivariate analysis was performed in which a statistically significant association was found between gender and in-hospital mortality with a value of $p = 0.04$ and a prevalence ratio (PR) of 6.5, posing the hypothesis that women can have a greater chance of dying. Additionally, it was found that the hemoglobin levels were different between those who died and those who did not die, this in a statistically significant way with a value of $p = 0.039$, in such a way that it is possible to hypothesize that having a low hemoglobin, around of 7 gr/dl, significantly increases the chance of death. Large studies such as the one mentioned in the Mayo Clinic have identified some risk factors for adverse prognosis, among which the most significant are the patient's functional status, albumin concentration and age. Hemoglobin less than 10 gr/dl is described, but with a low relative risk (RR = 1.3) and gender has not been reported as a favoring or adverse factor[17].

CONCLUSIONS

The clinical findings and the predominant symptoms are similar to those reported in the literature, as well as the findings in protein electrophoresis. However, in our patients these disorders were diagnosed in younger people and often in advanced stages of their evolution. The proportion of patients with renal damage and hypercalcemia was high and a strong tumor load was shown due to the high levels of serum B2-microglobulin and the high percentage of plasma cell infiltration within the bone marrow in patients with multiple myeloma.

The time of evolution since the beginning of symptoms was prolonged, much longer than described for this type of disease, with a negative impact in the clinical course of the disease.

The main limitations on our research are all those associated with biases of the cross-sectional studies (selection, biases due to prevalent cases, information, cause-effect relationship not always verifiable), and incomplete information in protein electrophoresis reports. However, its main strength was including the spectrum of plasma dyscrasias, in addition to providing an approach to these pathologies of low incidence and prevalence and allow us to raise some possible hypotheses and in a later prospective study perform stratified analyzes, controlling variables of confusion to establish association and risk measures.

Although the nature of our study does not allow the identification of causal relationships, a statistically significant association was found between mortality and female gender, as it was found with low levels of hemoglobin, which raises the initial hypothesis of higher mortality in females and hemoglobin around 7 gr/dl that must to be confirmed in further investigations.

Clinical practice points

- Plasma cell dyscrasias constitute a broad spectrum of diseases characterized by accumulation of immunoglobulins, known as paraprotein or M proteins, within which multiple myeloma is the most prevalent.
- Despite western literature reports multiple myeloma patients were over 60 years old Latin American, and especially in Colombians, clinicians should raise disease suspicion also in younger ones with CRAB symptoms.
- Awareness of risk factors as time of evolution since the beginning of symptoms, female gender, anemia, grade of renal failure and hypercalcemia must be taken in count to a worst prognosis in low income institutions were molecular technology it's not available.
- More research must be done with a bigger sample, including different institutions and cities all over the country to determine specific behavior of plasma cell dyscrasias in Colombia and Latin America.

DISCLOSURE

The authors have stated that they have no conflicts of interest or economic financing.

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Diabetes Mellitus in asians patients: descripticion of one population of one family health unit from the north of Portugal

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The authors declare that they have no conflits of interest.

ABSTRACT

Introduction: Asian Countries contribute more than 55% to the world's diabetic population. Compared with the European population, Asians develop diabetes with lower thresholds of body mass index and abdominal perimeter and at earlier ages.

Material and Methods: An observational, cross-sectional study was conducted based on a population of patients with diabetes of Asian origin enrolled in the USF Rainha D. Amélia. These patients were selected through the MIM@UF® program using the codes of the international primary health classification: T90 and T89.

Results: The population obtained consisted of 20 patients with Type 2 Diabetes, originary in Asian countries. At diagnosis the patients had a mean of 42.6 years, and in 30% (n = 6) the diagnosis was established before the age of 40 years. The mean duration of diabetes was 6.75 years. Pancreatic anti-islet antibodies were determined in 10 users, all with negative results, as well as the C-peptide values, which were within the normal range. There were statistically significant differences for total and LDL cholesterol in patients with glycated hemoglobin> 7% when compared to the group with lower values.

Discussion and Conclusion: Asian populations have a substantial risk of developing diabetes compared to other populations. In addition they develop the disease earlier and with lower body mass index. One possible reason for this difference is that, compared to Caucasians, Asians have more visceral adiposity, which contributes to lipotoxicity, insulin resistance and diabetes development.

Key Words: diabetes mellitus; asians

INTRODUCTION

The prevalence of *Diabetes Mellitus* (DM) has been increasing and is estimated to reach 438 million adults between the ages of 20 and 70 by 2030. This value represents more 153 million than in 2010[1]. Asian countries contribute more than 55% to the world's diabetic population[2], mainly at the expense of type 2 DM[3]. The estimated prevalence in China, India, Bangladesh is 9.7%, 9.1% and 6,3%, respectively[4,5].

The population density of India and China, urbanization, economic growth with changes in dietary patterns and ethnic and genetic background are the major contributors to the high prevalence of DM in Asia. Compared with the European population, Asians develop DM with lower thresholds of body mass index (BMI) and abdominal perimeter and at earlier ages[2]. According to the Joint Asia Diabetes Association, one in five individuals from Asia with DM are diagnosed before age of 40[6]. The onset at an early age conditions long duration of the disease and increases the risk of chronic complications, responsible for the rates of early morbidity and mortality. The main chronic microvascular complications of DM in these populations are renal (urinary excretion of elevated albumin and chronic renal disease); of macrovascular complications cerebrovascular disease is the most relevant. The available literature points to lower rates of peripheral arterial disease and coronary disease, compared to the European population[7,8].

The progressive and early decline in β-cell function, conditioned by a predominant phenotypic pattern of centripetal obesity and insulin resistance in these Asian patients[5], is the main pathogenic mechanism of type 2 DM. Poor control of the disease can be explained by the low adherence to non-pharmacological and pharmacological therapy, a statement supported by a study of compliance assessment that showed that oral antidiabetics, antihypertensive and antidislipidemic drugs were only 40-50%[9] identifying as the highest risk group the younger patients, with more comorbidities and with lower economic status. Language barrier, illiteracy and preference for traditional or alternative therapies may contribute to low compliance in these ethnic groups[10].

The increasing emigration of Asians, particularly to Portugal, makes it urgent to know the particularities of DM in this population, especially as regards the greater difficulty in the therapeutic approach, to which the linguistic barrier also contributes.

Thus, the main objective of this study was to characterize the Asian patients with DM type 2 enrolled in the Family Health Unit (FHU) Rainha D. Amélia in Porto, evaluating demographic, clinical and analytical parameters of this population. The secondary endpoints consisted of comparing patients with uncontrolled or controlled type 2 DM (assuming no control for HbA1c values greater than 7%) relative to therapeutically modifiable variables [blood pressure, total cholesterol, high density (HDL) cholesterol, low density cholesterol (LDL), triglycerides and BMI] and to variables not modifiable by therapeutics (sex, age and duration of DM).

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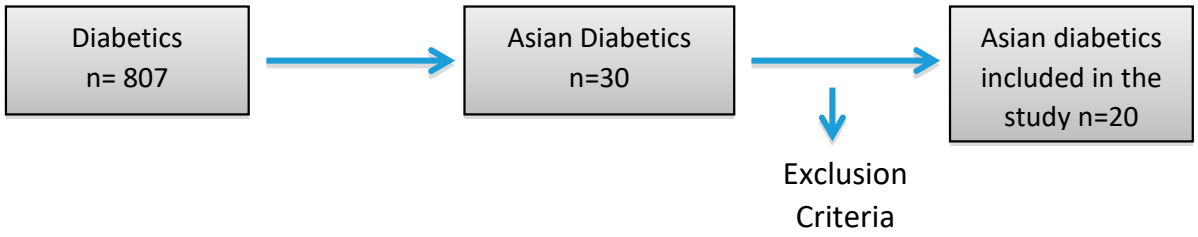
METHODS

An observational, cross-sectional study was carried out based on a population of patients with DM of Asian origin (Bangladesh, India, Pakistan and China) enrolled in FHU Rainha D. Amélia and who had at least one face-to-face consultation in the last four years. These patients were selected through the MIM@UF® program in November 2017 using the International Primary Health Care (ICPC-2) classification codes: T90 - non-insulin-dependent DM and T89 - insulin-dependent DM. Biometric and analytical data were collected through the SClinal® information system. Subsequently, these data were recorded and analyzed using Microsoft Excel 2013® and SPSS version 24.0®. All variables had a normal distribution, so we used the Student's t test to analyze independent samples. The level of significance was set at 0.05.

In the study, the inclusion criteria were those enrolled in the FHU Rainha D. Amélia, with a Family Physician assigned and diagnosed T89 or T90 in the list of problems and originated from Asian countries. The patients without medical consultation in FHU for more tanh 4 years were excluded (Fig. 1).

Figure 1. Selection of study participants



This study was carried out taking into account the principles by which research is conducted, with the individuals included in the sample being duly informed about all aspects intrinsic to the study and only participating after having decided of their own free will, taking into account the the principle of freedom of choice, informed consent and the guarantee of anonymity and confidentiality of the data collected.

RESULTS

The population obtained consisted of 20 type 2 DM patients from Bangladesh (n=12), Pakistan (n=3), India (n=3) and China (n=2) - table 1. Of these, 85% (n=17) were males. The mean age was 49.4 years. At diagnosis the patients had a mean of 42.6 years and in 30% (n = 6) the diagnosis was established before the age of 40 years. The mean duration of type 2 DM in the study population was 6.75 years ranging from 2 to 17 years. The mean value of glycated hemoglobin (HbA1c) at diagnosis was 8.0% (n=14); in 5 patients it was higher than 7% and at the time of the study in 9 patients the HbA1c value was higher than 7% . With regard to microvascular complications, these patients accounted for 20% (n=4) of the patients and 15% (n=3) had macrovascular complications.

In 10 patients the results of the C-peptide, whose value was doseable and within the reference values in all cases (mean of 3.06ng/mL, maximum of 4.45ng/mL, minimum of 1.45ng/mL, for a normal range of 1.1-4.4 ng/ml). Pancreatic anti-islet antibodies were determined in 10 users, all with negative results.

The main therapeutic classes used were biguanides in 90% (n=18) of the cases. Dipeptidyl peptidase 4 (DPPi4) inhibitors were prescribed in 50% (n=10) of patients, sulphonylureas in 25% (n=5) and insulin 15% (n=3).

About 75% (n=17) of the patients were non-smokers, while only 15% (n=3) smoke. Forty-five percent (n=9) of the patients had arterial hypertension (AHT). With respect to BMI, in the 14 patients in whom it was possible to get, they had a mean BMI of 27.6 kg/m^2 and at the time of the study the mean BMI of the total was 27.2 kg/m^2, with 60 % (n=12) to present a BMI ≥25 kg/m^2. Regarding the abdominal perimeter (n=15), all the women in the study population had values greater than 80cm (mean of 103.3cm, maximum of 120cm and minimum of 91cm) and 66.7% of the men had values more than 90cm (mean of 92.7cm, maximum of 102.5cm and minimum of 80cm).

Relatively to lipid profile more than half of the patients had total cholesterol values equal to or greater than 170mg/dL (n=12). It should be noted that in 4 patients a total cholesterol value above 200mg/dL was observed. Regarding HDL cholesterol, 10 of the 17 male patients and 1 of the 3 female patients had a value above 40 mg/dL and 50 mg/dL, respectively.

Table 1: Characterization of the study population according to the demographic, clinical and analytical variables

Variables	Values
Demographic variables	
Sex	Male: n=17 (85%); Female: n=3 (15%)
Age at diagnosis (mean)	42,6 years (maximum 54; minimum 30; SD 5,9)
Age at the moment of study (mean)	49,4 years (maximum 59; minimum 41; SD 5,3)
Country of origin	Bangladesh: n=12 (60%); Pakistan: n=3 (15%); India: n=3 (15%); China: n=2 (10%)
Clinical Variables	
Duration of DM (mean)	6,75 years (maximum17 anos; minimum 2 anos)
AHT	YES: n=9; NO: n=11
BMI at diagnosis (mean)	27,6Kg/m2 (maximum 44,3; minimum 21,6; SD 6,0)
BMI (mean)	27,2Kg/m2 (maximum 44,3; minimum 19,5; SD 5,8)
Abdominal perimeter (mean)	Male (n=12): 92,7cm (maximum 102,5; minimum de 80; SD 6,9) Female (n=3): 103,3cm (maximum 120; minimum de 91)
Smoking habits	YES: n=3 (15%); NO: n=17 (75%)
Microvascular complications	Peripheral Neuropathy: n=2; nephropathy: n=4; retinopathy n=3.
Macrovascular complications	Cerebrovascular disease: n=3; peripheral arterial disease: n=3; Coronary heart disease: n=3.
Therapeutic classes	Metformin: n=18 (90%); DPPi4: n=10 (50%); Sulphonylureas n=5 (25%); Insulin n=3 (15%)
Analytical Variables	
HbA1c at diagnosis (n=14; mean)	8% (maximum 13,1; minimum 6,6; SD 1,7)
HbA1c (mean)	7.57% (maximum 12,8; minimum 5,8; SD 2,0)
Total cholesterol (mean)	177,6mg/Dl
LDL cholesterol (mean)	101,2mg/dL
HDL cholesterol (mean)	Male: 39,2mg/dL; Female: 46mg/dL.
Triglycerides (mean)	176mg/dL

Legend: SD – Standard Deviation; DM – Diabetes *Mellitus*; AHT – Arterial Hypertension; BMI – Body mass index; DPPi4 – Dipeptidyl peptidase inhibitor 4; HbA1c – Glycated haemoglobin; HDL – High density; LDL – Low density.

From the comparative analysis of patients with uncontrolled or controlled type 2 DM, we found that in the group with good glycemic control there is a predominance of men (3 women for 8 men), while the group with inadequate glycemic control is composed only of men (table 2).

Table 2: Charaterization of the population as a function of DM control

Variables	Controlled DM	Not controlled DM
Sex	Male: n=8; female: n=3	Male: n=9; female: n=0
Age at diagnosis (mean)	42,8 years	42,3 years
Age at the moment of study (mean)	48 years	51 years
Country of origin	Bangladesh: n=7; China: n=2 (10%); Pakistan: n=1 (15%); India: n=1	Bangladesh: n=5; Pakistan: n=2; India: n=2; China: n=1
Duration of DM (mean)	5,2 years	8,7 years
AHT	YES: n=5; NO: n=6	YES: n=4; NO: n=5
BMI (mean)	28Kg/m2	26,3 Kg/m2
Abdominal perimeter (mean)	Male (n=7): 89,4cm || Female: 103,3cm	Male (n=5): 97,3cm
Smoking habits	YES: n=1; NO: n=10	YES: n=2; NO: n=7
Chronic complications	Microvascular: n=2 || Macrovascular: n= 1	Microvascular: n=3 || Macrovascular: n= 2
Total cholesterol (mean)	171mg/dL	185,8mg/dL
LDL cholesterol (mean)	95,8mg/dL	107,8mg/dL
HDL cholesterol (mean)	Male: 39mg/dL; female: 46mg/dL.	Male: 39,4mg/dL
Triglycerides (mean)	171,1mg/dL	181,9mg/dL

Legend: DM – Diabetes *Mellitus*; AHT – Arterial Hypertension; BMI – Body mass index; HDL – High density; LDL – Low density.

At age we noticed that the mean was higher (51 versus 48 years) in the group with inadequate glycemic control, although not statistically significant. In the same way, we did not detect significant differences between the two groups regarding the duration of DM (5.2 versus 8.7 years). However, in the group with inadequate glycemic control, almost half (44%) had a duration of DM greater than 10 years. As for the variables modifiable by therapeutics, we detected only differences for total cholesterol and LDL, which was higher in the group with poor glycemic control. Total cholesterol was significantly higher in the group with inadequate glycemic control, p=0.018.

We did not find significant differences between the two groups regarding HDL cholesterol levels (p=0.856), triglycerides (p=0.399) or for BMI, although 77.8% (n=7) of the group with poor glycemic control being obese. As for LDL cholesterol, its value is significantly higher in the group with poor glycemic control, p=0.026.

DISCUSSION

Populations from South Asia present a substantial risk of developing diabetes compared to other populations[11]. In addition, in agreement with the literature, they develop the disease 5-10 years earlier (42.5 years versus 58 years in the Caucasian race)[12], in 20% of cases with early diagnosis (before 40 years)[6] and with lower BMIs[13]. One possible reason for this interethnic difference is that, compared with Caucasians, for any BMI value Asians have more visceral adiposity which contributes to the lipotoxicity, insulin resistance and development of type 2 DM[5]. An Asian epidemiological study demonstrated that patients with type 2 DM had significantly greater secretion and insulin resistance 10 years before the onset of diabetes. In addition, there was an abrupt decrease in insulin secretion during the last 2 years before the onset of diabetes[14].

Simultaneously, some genetic variants have been identified and associated specifically with the Asian diabetic population, which may explain the clinical characteristics of diabetes in this population.

The recognized ethnic disparities regarding the abdominal perimeter, as an estimate of subcutaneous and intra-abdominal abdominal adipose tissue, justified the different cut-offs of the abdominal perimeter of 90cm for men[15]. Additionally, different cut-offs of BMI were defined and adopted by the International Association for the Study of Obesity for these populations, defining an overweight BMI ≥ 23kg/m^2 and an obesity BMI ≥ 25kg/m^2.

The population analyzed included a total of 20 Asians with type 2 DM, predominantly of the male gender, which can probably be justified by the isolated movements of the male (versus the family) for professional reasons and the search for better living conditions.

More than half (60%) of the patients were obese (from the cut-offs of the Asian population), and 66.7% of the men and 100% of the women had an abdominal perimeter greater than 90 and 80cm respectively. Huxley et al.[12] reported a lower association between BMI and diabetes in Asians compared to Caucasians, justified by the risk of DM increasing to normal BMI in Asians, and total obesity (versus central) did not translate a good measure of cardiometabolic risk[12].

Despite the increased prevalence of DM in the Asian population, according to the InterASIA study[16], in the Chinese diabetic population, rates of disease awareness, treatment and control are relatively low. In this study DM control (fasting glycemia <126mg/dL) was achieved in only 35% of the patients, and control rates differed according to the urban / rural context but did not differ for the duration of diabetes.

It was our intention to statistically evaluate the data from the patients included in this study to identify which parameters might be more directly related to the DM control rate in this population so that it is possible for the clinician to identify at the outset which patients which may benefit from tighter surveillance. We obtained statistical significance in some modifiable parameters as in total cholesterol and LDL. The highest values of total cholesterol and LDL were found in the group of diabetics with inadequate glycemic control, which may be related to therapeutic failure.

As the cardiovascular risk is higher in Asian type 2 diabetics compared to Europeans, the approach also implies an optimization of dyslipidemia[13]. Statins appear to have similar efficacy in lowering cholesterol levels and mean cholesterol levels in South Asians and Europeans with diabetes are also overlapping[13].

Hypertension was observed similarly in the 2 groups. According to Ronald and his co-workers, blood pressure values are similar in South Asia and Europe with type 2 DM, but the use of antihypertensives appears to be lower in the early stages of the disease in the South Asian population, perhaps because of age more early diagnosis and lower rates of obesity[5].

Regarding non-modifiable parameters, although the group with uncontrolled DM was older, we did not obtain statistical significance. The same was observed for the gender and duration of DM, which allows us to infer that, in the analyzed population, these parameters alone do not seem to influence glycemic control.

About half of the Asians with Type 2 DM living in Portugal and with follow-up at FHU Rainha D. Amélia have sub-optimal glycemic control. The lack of knowledge about type 2 DM and awareness and the language barrier may have contributed to these results. Good glycemic control would result in lower cardiovascular risk. Thus, greater efforts and incentives are required for more intensive changes in lifestyle and/or early escalation of therapies in order to reduce progression to chronic complications and morbi-morbility.

The study demonstrates the importance of knowing the ethnic particularities / disparities of diabetes in Asian patients, as it is increasingly discussed with increasing immigration. The present work intends to adopt care aimed at health promotion and prevention of the disease in these populations, at the level of primary health care in Portugal.

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Meningococcal knee arthritis serogroup W-135. Case report

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ABSTRACT

N. Meningitidis serogroup (A, B, C), are main causers of disease. Serogroup W-135 incidence is lower nowadays and, although it is increasing, is such an uncommon infection in adults.

We report a case of a monoarthritis knee due to *Neisseria meningitidis* (W- 135) in an inmunocompetent 50 year- old male.

Palabras clave: *Artritis, Neisseria meningitidis, Serogrupo W-135*

Keywords: *Arthritis. Neisseria menigitidis. Serogroup W-135*

INTRODUCTION

Neisseria Meningitidis is a stationary and aerobic Gram Negative bacteria, exclusive of human being.

Meningococcal arthritis in many cases has a singular joint presentation. A, B and C serogroup are main causers of disease; W-135 serogroup is an exceptional cause of infection in adults. We report a case of an inmunocompetent adult with monoarthritis caused by *N. meningitidis* with this serotype[1,2].

CASE REPORT

50-year-old male with history of right knee meniscectomy. He came to our Hospital because of pain and swelling on his left knee which had started 48 hours ago. One week before he had had an episode of cough and discomfort. At physical examination, pain on his left knee with flex and extension movements, also swollen joint was observed.

Arthocentesis was done, draining 60 cc of cloudy fluid, presenting 95.000 cell/µL (75% polimorphonuclear), and calcium pyrophosphate crystals. At blood test, leucocytosis 10.150 x 10^3 cell/ µl appeared without neutrophilia and RCP was 25,2 mg/dl. He was discharged from Hospital with Colchicine and Eterocoxib 90mg, with favorable evolution of the symptoms.

48 hours later Microbiology service alerts from growth of *N. meningitidis* in joint fluid culture. Hospital admission was decided for treatment; joint lavage by arthroscopy and Ceftriaxone (2g each 12 hours/ IV per 7 days). Contacts received single-dose of chemoprophylaxis with Ciprofloxacine 500mg. Patient presented clinical and analytical improvement, and also swelling of joint decreased.

After intervention, no blood or joint fluid cultures were collected. In control cultures, no new microorganism were isolated.

He was discharged from Hospital after 6 days without any complication. After 10 months of medical supervision, he is still asymptomatic.

DISCUSSION

Meningococcal arthritis is a rare infection disease in our enviroment, being upper airways the main focus in 50% of cases. Diabetes mellitus, joint replacements or patients previously treated with intra-joint steroids are some of the main risk factors to host.

There are some relevant communicable factors such as smoking, viral infections and overcrowded conditions[3]. *Staphylococcus* aureus is the most frequent microrganism in adult septic arthritis both in Europe and USA, followed by *Streptococcus pyogenes* and *S.pneumoniae.*

Pseudomonas aeruginosa and *Escherichia coli* are the most frequent Gram negative microrganisms. Before vaccine period, *Haemophilus influenzae* was the most frequent microrganism isolated founded in children.

Among thirteen *N. meningitidis* serogroups, most frequently responsible for septic arthritis, both in adults and children, are C serogroup (36%), B (30%) and less frequently A serotype. W-135 serogroup is related with meningococcal joint infection, associated with its ET-37 gen (*electrophorethic type 37*), also found at C serogroup; it is considered as a virulent factor in joints[3].

Some arthritis cases in children by this serogroup are described, but they are exceptional at adult age[2].

Prognosis factors are related with host and the microrganism virulence. Higher mortality was associated with W-135 serotype. An early recognition of microrganism and treatment is essential for meningococcal arthritis good prognosis. Mortality index in USA is close to 15%. Empirical treatment is based on third generation cephalosporins or cloranfenicol in case of allergy/intolerance to beta-lactam treatment, although there are some resistent cases wrotten in literature[6].

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Referring to surgical treatment, recommendations are based on restrospective studies with very few patients. Indications depend on development of the infection, the affected joint and abscess.

Aspiration with needle, arthroscopy drenage or arthrotomy are some of the most used options. Surgical drenage is usually indicated on hip, shoulder and prothesic infections. Arthroscopy is usually the first line of surgical treatment for knee and shoulder.

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Severe neutropenia and thrombocytopenia in a young adult: a case-report

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ABSTRACT

We present the case of a 20-year-old male hospitalized with severe neutropenia and thrombocytopenia. After exclusion of other etiologies, it was concluded to be of autoimmune etiology. The prompt and sustained response of both cell lines to corticosteroids, reinforced this diagnosis. This case illustrates a very rare association of severe primary neutropenia and thrombocytopenia. The lack of serological marker makes this diagnosis delayed and resource-consuming.

Keywords: Neutropenia, thrombocytopenia, autoimmune cytopenia

BACKGROUND

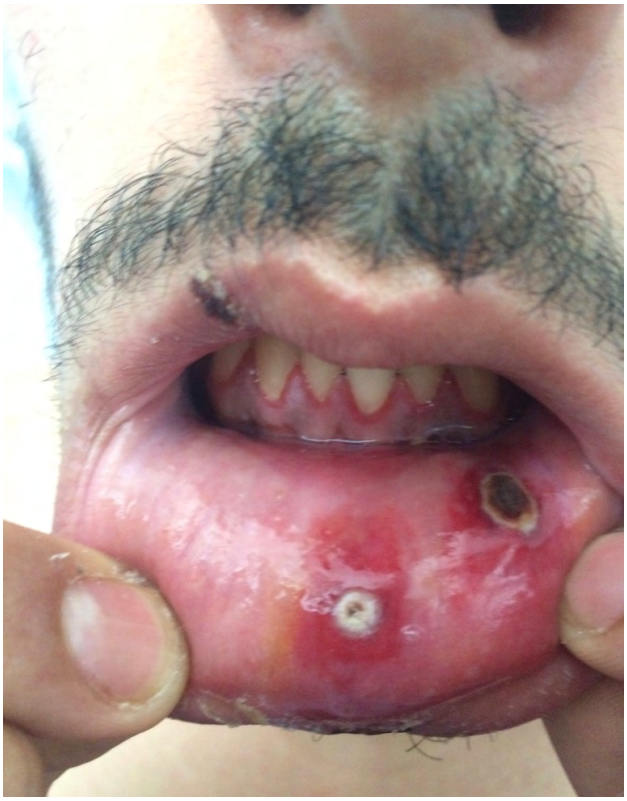
Blood cell cytopenias can be primary or secondary. Primary cytopenias are more common in infants and children, being mostly a benign condition with a self-limited course[1,2]. In 1949 Evans and Duane[3] first reported the association of acquired hemolytic anemia and other cytopenias. Platelets and erythrocytes are known to be the most affected cell lineages, with neutropenia being not so often reported[4,5]. Bux *et al.* describe 8.4% of autoimmune thrombocytopenia in a group of 143 patients with autoimmune neutropenia[6]. Secondary cytopenias are more common and associated with other conditions, such as autoimmune diseases, infections, drugs or hematological malignancies.

We present the case of a young adult with an upper respiratory airway infection that was treated with antibiotics before severe thrombocytopenia and neutropenia were known.

CASE PRESENTATION

A 20 year-old male, with a past history of amidgalectomy and adenoidectomy in 2003 due to recurrent upper respiratory infections, presented to his family doctor with odynophagia and fever (38.5-39.0ºC axillary temperature). Symptoms initially improved and fever resolved after treatment with penicillin G benzathine and azithromycin, but right after he developed labial lesions resembling herpes simplex. Six days after the first medical observation he went to the emergency department because of recurrent fever and appearance of a cutaneous rash and inner lip mucosal lesions (Figure 1). At physical examination he was afebrile (37.1ºC auricular temperature), hemodynamically stable (blood pressure 139/89 mmHg, heart rate 90 bpm), showing no signs of respiratory distress; skin and mucosal membranes were hydrated, pink, with small petechiae through the limbs and trunk; oral cavity showed two ulcerations on the inner surface of the lower lip (one of them with dark appearance) and labial herpes scar on the upper lip (Figure 1); gingival mucosa was friable; otoscopy was normal; oropharynx showed erythema but no exudates;

Figure 1. Mucosal ulceration and friable gingival mucosa.



a right non-tender, soft, about 3 cm long axis axillary adenopathy was palpable; heart and lungs sounds were normal; abdomen was tender and painless, with no palpable masses or organomegaly; no peripheral edema.

Blood tests showed severe neutropenia (0.020x10^9neutrophils/uL) and thrombocytopenia (<10x10^9platelets/uL); hemoglobin level was normal (13.6 g/dL); erythrocyte sedimentation rate was 67mm/1sth and C-reactive protein was 33.7 mg/L; no significant change was found on liver panel, kidney function tests, electrolytes or coagulation tests; no folate or cyanocobalamin deficit. A blood smear confirmed decreased number of leukocytes (showing reactive mono-

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cytes), decreased platelet count (with anisocytosis and megathrombocytes); no evident schizocytes or circulating blasts. Bone marrow was normocellular, with normal megakaryocytes morphology, myeloid left shift with reactive precursors, no blasts excess or maturation stop; monocytes, lymphocytes and eosinophils were morphologically normal; immunophenotyping showed no monoclonal cell populations, but a slight increase in immature granulocytic forms. Immunoglobulin levels and protein electrophoresis were normal. Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) directed antibodies and heterophile antibody test for Epstein-Barr virus (EBV) were negative. Blood cultures and the rest of microbiological study were also negative. Antinuclear antibodies (ANA) titer was 1/100 with speckled pattern and anti-thyroglobulin antibody was slightly above the normal range; no other relevant finding on autoimmune study. Chest X-ray was normal. Abdominal ultrasound showed homogeneous hepatosplenomegaly (18.5 cm and 14.5 cm, respectively, greatest diameter) and computerized tomography scan confirmed the slightly increased liver and spleen (13.6x15.1x5.3 cm). Axillary ultrassound showed a few adenopathies on the right side, the two most evident with 32x17 mm and 35x14 mm diameters. Fine-needle aspiration of one of the enlarged lymph nodes found nothing but reactive changes on cytologic examination and immunophenotyping revealed polyclonal B cell population.

As the patient was clinically stable and no signs of critical illness were present, only supportive treatment was given while performing diagnostic workup. We expected spontaneous recovery after a presumed infectious or drug-related etiology, because of the initial presentation. However, over the time (29 days), blood cell counts showed no improvement. He had no fever or sign of active bacterial infection, besides a catheter-associated phlebitis that he developed later and was treated with flucloxacillin. He presented minor gingival bleeding and small petechiae.

Neutropenia and thrombocytopenia persisted severely decreased, as shown in Figures 2 and 3. After the first week platelets seemed to be spontaneously increasing, but fell right after to values <10x10^9/L. Platelets were transfused whenever thought clinically necessary. With granulocyte-colony stimulating factor (G-CSF), neutrophils would increase but only slightly and fall back to baseline levels (Figure 2). With lack of recovery, at day 14, a new bone marrow aspirate was performed, as well as a bone marrow trephine biopsy. Both exams were consistent with the first observation revealing a reactive marrow and with no signs of a primary hematologic disease or infiltrative process. After 29 days, considering the lack of spontaneous recovery and no evidence of other etiology, corticosteroids were started (methylprednisolone 500 mg during 3 days and prednisolone 1 mg/Kg/day thereafter). A prompt and sustained increase was observed after 1 day on platelet counts, and 5 days on absolute neutrophil counts.

The patient was discharged home with prednisolone 1 mg/Kg/day and, after two weeks, started a slow weaning process that lasted for 6 months. After 8 months with no immunosuppressant drugs, the patient shows normal absolute neutrophil counts of 2.58 x10^9/L and decreased but stable platelet counts of 80 x10^9/L. Autoimmune study was repeated and negative.

DISCUSSION

We present the case of a young patient that showed seriously reduced blood cell counts. Because of the initial upper respiratory infection and use of antibiotics, infection and drug exposure were the first diagnostic hypothesis. Both could result in bone marrow insult or induce peripheral cell destruction. Invasion of blood marrow (e.g. fungal or tuberculous) or bone marrow suppression (e.g. HIV, hepatitis, EBV) could cause decreased hematopoiesis, and EBV could also explain peripheral destruction through splenomegaly[7,8]. Also, mucosal ulcerations suggested a low bone marrow reserve, with inability to deliver neutrophils to the periphery and increased risk of infection, this relation being better stablished in chemotherapy-induced neutropenia[9]. In our patient, bone marrow showed normal cellularity and we found no infectious

Figure 2. Neutrophil count during hospital stay and follow up. *Treatment with G-CSF; • Treatment with corticosteroids.

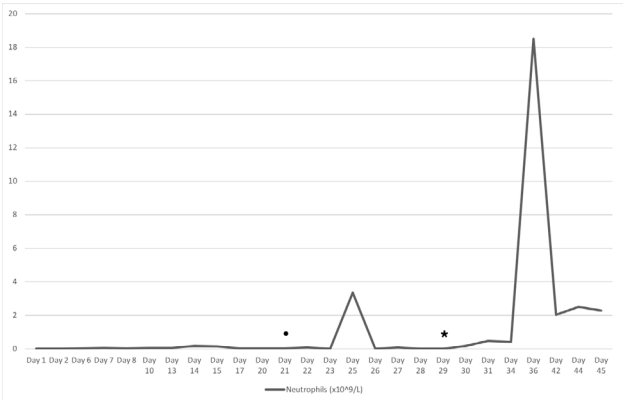
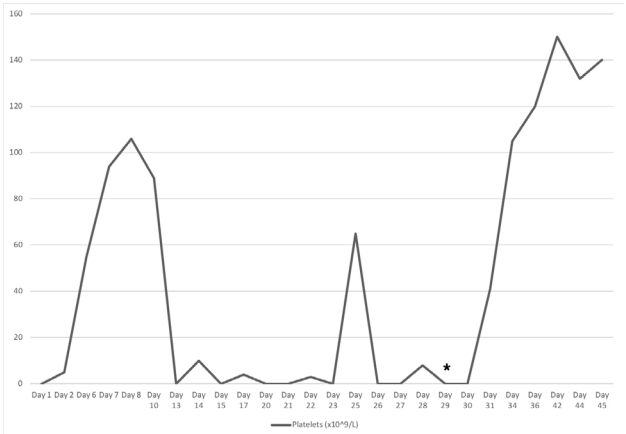


Figure 3. Platelet count during hospital stay and follow up.



responsible agent. There are reports of agranulocytosis after treatment with azithromycin[10], and it is known that penicillin can cause an immune reaction through hapten-induced antibodies, being more often associated with hemolytic anemia and, although rarely, also with thrombocytopenia and neutropenia[11,12]. However, we would expect some recovery after discontinuation of this drugs.

Our patient showed no symptoms suggestive of localized or systemic autoimmune disease and serological markers of autoimmunity were negative, with the exception of slight and non-specific increase in ANA and anti-thyroglobulin antibodies, which were negative during follow-up.

There was no evidence of underlying hematological malignancy: bone marrow and lymph node cytology and immunophenotyping showed no evidence of dysplasia, architectural disruption, infiltrative process or monoclonal population. We did not perform spleen biopsy, but the lack of lymphocytosis in the peripheral blood and in bone marrow, the absence M-protein or monoclonal population, as well as the clinical course, suggested that the presence of lymphoid neoplasms was unlikely. Splenomegaly would be explained by increased phagocytosis of opsonized neutrophils in the spleen or by extramedullary hematopoiesis, which is known to occur in conditions unrelated to bone marrow hematopoietic function but due to increased demand of blood cells, such as infection (like brucellosis or EBV), inflammation (as occurs in systemic lupus erythematosus or rheumatoid arthritis) or hypoxia[13].

Waiting for spontaneous recovery of blood cell counts was crucial to support the autoimmune hypothesis and the need of corticosteroids for recovery, and the immediate and sustained improvement of blood cell counts after immunosuppressive therapy was key for the final diagnosis of primary immune combined cytopenia.

CONCLUSION

Autoimmune neutropenia and thrombocytopenia are a rare association, especially with the severity presented in this case. Our diagnostic workup was performed carefully in order to exclude an underlying disorder. There is no specific serological marker for this condition, and the diagnostic process may be delayed, costly and resource-consuming. Further investigation is needed. The patient should be followed in order to monitor any recurrence of important cytopenia and any other sign of systemic or local autoimmune disease.

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Disseminated gonococcal infection and the inaugural diagnosis of latent autoimmune diabetes in a young adult

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ABSTRACT

Disseminated gonococcal infection (DGI) is a rare and emerging disease that should be considered in individuals who present with acute polyarthralgias, skin lesions and/or tenosynovitis, even in the absence of genitourinary symptoms.

We describe a 29 years old man presenting with fever, arthralgias, skin lesions and signs of tenosynovitis. The diagnostic approach identified a disseminated gonococcal infection and an unrecognized and latent autoimmune diabetes.

We emphasize not only the particularities of diagnostic and treatment approach currently required by this emergent infection, but also the importance of investigation of rare risk factors associated with an underlying immunosuppression. In latent autoimmune diabetes of adults a timely recognition and individualized treatment are fundamental for prognostic.

Keywords: Disseminated gonococcal infection, *Neisseria gonorrhoeae,* Tenosynovitis, Latent autoimmune diabetes in adults, Diabetes mellitus.

CASE DESCRIPTION

A previously healthy 29-year-old man presented to the emergency department complaining of fever, asthenia and migratory arthralgias of wrists, fingers, ankles and toes that started in the previous two days. He also reported swelling of wrists and ankles and painless non-pruritic vesiculopustular skin lesions on both hands thenar eminence. He noted asthenia and a 7 Kg weight loss in the last 6 months. He didn't report neurologic, respiratory, digestive or genitourinary symptoms.

He was single, heterosexual and his last sexual contact had been one month before admission and protected but he recorded multiple partners last year. He worked us a butcher and denied exposure to drugs, ticks, animals or recent travels.

At admission, physical examination revealed a temperature of 39ºC. Cardiac, pulmonary, abdominal and neurologic evaluations didn't show relevant changes. The skin examination revealed macules with central hemorrhagic pustule zone on both hands thenar eminence (Fig 1) and signs of tenosynovitis of both wrists and ankles (Fig.2). There were no signs of meningeal, ocular, genitourinary or rectal involvement. Body mass index (BMI) was 26 kg/m^2.

Laboratory findings reported normocytic anemia (Hgb 11,5 g/dL; normal 13.5-18.0 g/dL), leukocytosis with neutrophilia (17.5 K/µL; normal 4-10 K/µL; 80%), an elevated erythrocyte sedimentation rate (ESR) (90mm/hr) and C-reactive protein (CRP) (98,6 mg/L). Renal, thyroid and liver function test results didn't show any changes and urinary study was normal. Thoracic x-ray, abdominal and renal ultrasound didn´t show any active or suspicious lesion. Blood and urine cultures were performed and he was admitted to the internal medicine department.

As he maintained fever, poliarthralgias with signs of tenosynovitis and skin lesions, an infectious and serological study was required. Venereal disease research laboratory (VDRL) and tests for human immunodeficiency virus (HIV) 1 and 2 (including antibody test and rapid plasma reagin test), Cytomegalovirus (CMV), Herpes simplex virus (ESV), Epstein-Barr virus(EBV), Parvovirus and Hepatitis (A, B and C) were negative. Serology and culture tests for Rickettsia, Coxiella and Borrelia were also negative

Immunological study through the search for autoantibodies (anti-nuclear antibody, anti -double stranded (Ds) DNA, anti-neutrophil cytoplasmic antibodies (ANCA), anti-antinuclear antibody (ANA), Anti-Sjögren's-syndrome-related antigen A (AntiSSA), AntiSSB, Anti- ribonucleoproteins (RNP), and anti-citrullinated peptide antibody) and rheumatoid factor were negative. Coagulation and cardiac studies (including NT-proBNP and troponin I levels) were normal. Transthoracic Echocardiogram and ECG didn't reveal alterations.

On the third day after admission blood cultures revealed the presence of gram-negative diplococcic and 5 days later, *Neisseria gonorrhoeae* was isolated in blood cultures processed on specific (Thayer-Martin) medium (Fig.3).

Imaging via ultrasound showed a moderately sized simple left ankle effusion with marked surrounding edema. Left ankle arthrocentesis was performed, revealing a mildly elevated synovial fluid White Blood Cell count of 30,800 cells/_l (normal below 2,000 cells/_l), and culture of the collected synovial fluid on specific (Thayer-Martin) medium showed no growth.

Mucosal including skin, rectal, pharyngeal, and urethral specimens were submitted for microbiological testing with Nucleic acid amplification tests (NAATs) and only the urethral specimen was positive.

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Figure 1. The skin examination revealing skin lesion with central hemorrhagic pustule zone on the palmar face of the right hand.

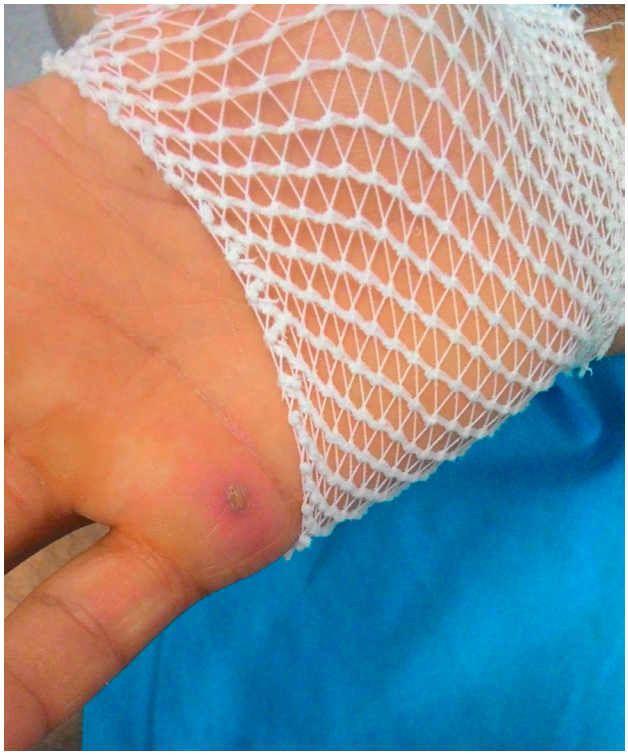


Figure 2. Inflammatory signs of the left ankle visible on admission and associated with pain and edema.

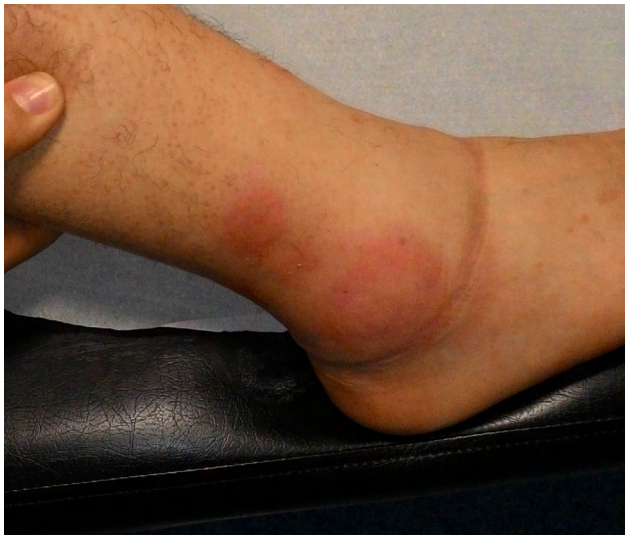
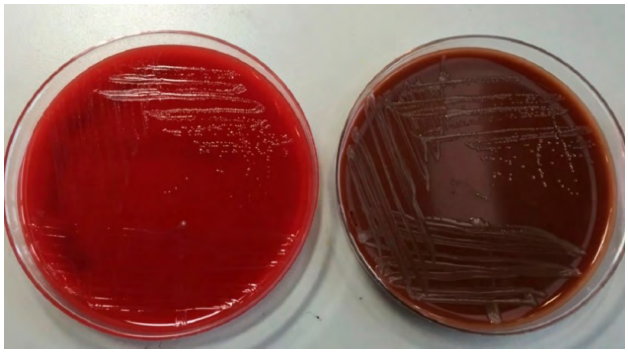


Figure 3. Neisseria gonorrhoeae was isolated in blood cultures processed on specific (Thayer-Martin) medium.



In regard to emerging antibiotic resistance of N.gonorrhoeae (to cephalosporins and azithromycin), an antibiotic susceptibility test (AST) was also performed and he started single dose of azithromycin plus ceftriaxone intravenous 1g/day, completing 7 days of antibacterial therapy. Three days later, AST revealed all strains susceptibility to ceftriaxone, cefepime, cefotaxime and quinolones. Serologic test for syphilis, and NAATs of Chlamydia were negative.

DGI was notified and the identified partners were offered with treatment for both gonococcal and chlamydial infections.

In regard to the apparent absence of some specific host risk factors for DGI and based on association of this systemic presentation with possible immune factors, a study for complement deficiency and immunoglobulins was performed. and was negative. (Complement C3 fraction - 170 mg / dL (VN 90-198); Fraction C4 of complement - 31 mg / dL (VN 10-40); CH50 - 38 mg / dL (NV> 24).

Despite favourable clinical and analytical evolution, it was documented several low magnitude postprandial and basal hyperglycemias (250-300 mg/dl) and after evaluation of endocrinology, Latent autoimmune diabetes in adults

(LADA) was suspected. He was discharged 2 weeks later with insulin therapy. One month after, he was asymptomatic, with negative blood cultures and the diagnostic approach revealed positivity for autoantibodies anti-tyrosin-phosphatase and glutamic acid decarboxylase 65 (GAD65) with normal C-peptide values, supporting LADA diagnosis.

DISCUSSION

This case report is remarkable by its rarity, distinct clinical manifestations, challenging diagnostic approach and surprising evolution. It discloses a previously healthy 31-year-old man, presenting with fever, artralgias, skin lesions and signs of tenosynovitis. The diagnostic approach identified a disseminated gonococcal infection and an unrecognized and latent autoimmune diabetes.

Disseminated gonococcal infection (DGI)

DGI affects 1-3% of patients with gonorrhoea and results of haematogenous spread of Neisseria gonorrhoeae, typically occurring within 2-3 weeks of the primary infection. It demands a difficult diagnostic approach not only because a recent symptomatic genital infection is rare, but also because positive blood cultures are found in only 50% of DGI cases that present with the classic triad of dermatitis, tenosynovitis and polyarthralgias[1-4]. In this case report we emphasize the complete infectious, autoimmune and immunological study performed.

The disseminated form primarily affects young (15 and 30 years), healthy and sexually active individuals like this patient, nevertheless the study for other unrecognized immune factors or diseases as SLE or hypocomplementemia should be performed and was negative[5-9].

However, based on several low magnitude postprandial and basal hyperglycemias, a surprising diagnosis of LADA was made,

which can explain the unrecognized immune factor responsible not only for immunosuppression but also for autoimmunity trigger. We highlight that this represents a relevant new association that has not yet been reported in previous scientific articles with a fundamental impact on the therapeutic approach.

Treatment of DGI depends on manifestations and clinical response. We emphasize the importance of susceptibility testing focused on emerging resistance to cephalosporins and azithromycin. For disseminated infections, combination and parental therapy treatment with ceftriaxone (1 g; 7 to 14 days) along with a single dose of azithromycin is recommended, also treating possible C. trachomatis co infection[1-2].

Latent autoimmune diabetes in adults (LADA)

Latent autoimmune diabetes in adults (LADA) shares clinical and metabolic characteristics with both type 2 and type 1 diabetes and should be suspected on 30-50-years-old individuals, with BMI <25 kg/m2, low magnitude postprandial and basal hyperglycemia and normal or close to normal C-peptide values, not usually occurring with acute hyperglycemic crises[10-13].

Patients defined as having LADA are characterized by genetic, phenotypic, and immunological heterogeneity, highly variability of the β-cell destruction's rate and different degrees of insulin resistance and autoimmunity, likely due to differences in genetic and immune factors[14-16]. Moreover, the great heterogeneity of LADA makes it difficult to determine an a priori algorithm for treatment and personalised therapy for LADA should be implemented[14-20].

Pathogenesis

When compared with classical T1DM, LADA appears like the other extreme of the autoimmune diabetes spectrum, whereby genetic susceptibility, autoimmune response and non-insulin-necessity presentation constitute a mild form of autoimmune diabetes with pathological features closer to those of T2DM than to those of adult T1DM, which is more similar to classical T1DM[10,17,18].

a) Genetic factors

Data available on genetic susceptibility suggest that LADA shows a lower genetic component than T1DM[14,15,21]. However, a recent study carried out in Swedish and Finnish populations, showed that the frequency of T2DM associated CT/TT genotypes rs7903146 in the transcription factor 7 like 2 (TCF7L2) gene was increased in LADA subjects as in T2DM subjects[23], as well as genetic similarities with T1DM have been observed related to HLA, INS VNTR, and PTPN22. These results suggest that patients with LADA may share genetic features with both T1DM and T2DM which further supports the concept that LADA is an admixture of the two major types of diabetes[22].

b) Autoimmunity

As a form of autoimmune diabetes, LADA is characterized by islet-cell specific autoantibody positivity and similar cell-mediated immune response although impairment of β-cells is slower than in classical T1DM[10,12,18]. Another relevant study observed presence of insulitis by pancreatic scintigraphy using interleukin 2 (IL-2) radiolabelled with technetium-99m (99mTc) and contrast-enhanced magnetic resonance imaging[24].

In conclusion and trying to investigate LADA pathogenesis, a recent Italian work suggested that different pathophysiological could explain the heterogeneous phenotypes of LADA[17]. Based on the model presented, in patients with moderate genetic susceptibility to T1DM, specific immunological factors can trigger an autoimmune process against islet cell antigens marked by the appearance of GADAs leading to β-cell apoptosis and insulin deficiency. On the other hand, in obese subjects with genetic susceptibility to T2DM, the low-grade inflammation, typical of visceral adiposity, might trigger a low-grade autoimmune process marked by IA-2 autoantibodies positivity, causing loss of β-cell function and an impairment of insulin secretion.

Regarding our case report we can theorize the importance and significance of infection as trigger factor for insulitis with consequent insulin deficiency and LADA onset. However, given the temporal coincidence, the causal relation can not be concluded, since the patient already had symptoms associated with diabetes and it is impossible to date the beginning of the infection as well as gonococcus dissemination.

Natural history and complications

There are only few studies related to the occurrence of macro and microvascular complications (nephropathy, retinopathy, neuropathy) in LADA and controversial results have been reported, partly due to a substantial heterogeneity regarding disease duration of study's subjects. Limited to patients with a short disease duration, microvascular complications in LADA appear to be less frequent than in patients affected by T2DM. A lower risk of macrovascular complications—including coronary heart disease, stroke, peripheral artery disease—could be postulated on the basis of the healthier metabolic profile of patients with LADA respect to those with T2DM. However, current data showed similar cardiovascular outcomes in LADA and T2DM [25-27].

Nevertheless, this case report highlights the importance of infection susceptibility associated with LADA, disclosing a patient without another identified host factor, diagnosed with a severe disseminated gonococcal infection, that could bring potential severe complications and evolution, beyond possible treatment difficulties regarding bacterial antibiotic resistance.

Treatment

To date, no specific guidelines for treatment of subjects affected by LADA have been published. Therefore, these subjects are mostly treated as affected by T2DM resulting in rapid progression to an insulin-dependent state[17], especially in patients who present with clinical and biochemical features closer to T1DM than T2DM[28,29]. In addition, a correct therapeutic strategy for LADA patients should aim to the preservation of residual β-cell function as well as improvement of glucometabolic control, in order to reduce the risk of long-term complications. Main-

tenance of β-cell function, as demonstrated by the Diabetes Control and Complication Trial, is indeed associated with a reduction of long teen diabetic complications[29].

In this regard, several data showed that insulin treatment, as well as DPP-4 agents, can sustain residual β-cell function[30-38]. Insulin therapy (basal), at low dose can be prescribed to LADA patients with DPP-4 as an additional weapon, whereas sulphonylurea may hasten insulin dependency and should not be used as first-line therapy for patients with LADA.

Preservation of β-cell function: next frontiers in LADA therapy

An intervention intended to preserve β-cell function should be pursued in patients with LADA. Recent immune-intervention trials have achieved promising results in term of preserving stimulated C-peptide levels and improving glycaemic control. However, some drugs currently used for treatment of T2DM might be considered in LADA. Dipeptidyl peptidase 4 (DPP-4) inhibitors represent a class of oral antidiabetic agents frequently used in T2DM which have been shown to preserve β-cell function and reduce insulitis in patients with T2DM as well as in mouse models of autoimmune diabetes[30-34] , suggesting that they might be a valuable treatment option in LADA.

A randomized-controlled study conducted in China[33] has observed that treatment with sitagliptin in addition to insulin preserved C-peptide concentration better than insulin alone in patients with LADA over a 1-year period. Similarly, sitagliptin improved glycaemic control in adults with T1DM[34]. Furthermore, Johansen et al.[35] have reported that another DPP-4 inhibitor, linagliptin, attenuated decline of C-peptide in LADA patients over a 2-year study period. In a post hoc analysis of data pooled from five randomized, placebo-controlled studies[36], saxagliptin was effective in lowering blood glucose levels and well tolerated in GADA-positive patients.

Other interesting findings comes from a post hoc analysis investigating treatment with dulaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1RA)[37] in patients with T2DM among whom there were some GAD antibody positive patients.

As conclusion, in this report we emphasize the importance of LADA diagnosis, supported by positivity for autoantibodies anti-tyrosine-phosphatase and GAD65 and the importance of DGI as a trigger for autoimmunity and insulinitis, which can represent a pathogenesis mechanism in LADA development. Although the possible association between LADA and infection can be suspected, given the temporal coincidence, a causal relation can not be established. On the other hand, we underline the possible association of LADA with greater infection susceptibility and severity in the natural history of the disease, as well as potential impact in antibiotic treatment and bacterial antibiotic resistance.

Finally, we highlight that personalized, controversial and under recent investigation medicine approach to attain optimal metabolic control is fundamental to preserve β-cell function decreasing the risk of long-term diabetes complications.

LEARNING POINTS

- The possibility of Disseminated gonococcal infection (DGI) should be considered in individuals who present with acute polyarthralgias, skin lesions (particularly pustular or vesiculopustular) and/or tenosynovitis, even in the absence of genitourinary symptoms.
- The study of an underlying immunosuppression and the treatment of DGI after appropriate cultures and based on emergent antibiotic resistance is essential and patients should be tested for HIV infection, syphilis and chlamydia.
- Latent autoimmune diabetes in adults (LADA) should be investigated in > 30-years-old individuals with low magnitude postprandial and basal hyperglycemias, with appropriate diagnostic approach, demanding an updated treatment.

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An unusual case of parotid gland B-cell lymphoma complicating Sjögren Syndrome

Un caso inusual de linfoma de células B de la glándula parótida a complicar el Síndrome de Sjögren

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ABSTRACT

Sjögren Syndrome is a multisystemic autoimmune disease that is heterogeneous in its presentation, course and outcome. There is no single clinical, laboratorial or radiological feature that serves as gold standard for the diagnosis and/or classification of this syndrome. The occurrence of lymphoma is known to be one of the most severe complications. We report a case of a 66-year-old female diagnosed with Sjögren Syndrome secondary to systemic lupus erythematous that presented with an enlargement of the left parotid gland consistent with the diagnosis of lymphoma confirmed with biopsy. She received chemotherapy with favorable response and today is asymptomatic with hydroxychloroquine 400mg id. This case report highlights the importance of optimal interventions and active surveillance of Sjogren Syndrome, in order to achieve an early identification of its complications and to prevent worse outcomes of this disease.

Keywords: Sjögren Syndrome, B-cell lymphoma, parotid gland, biopsy

INTRODUCTION

Sjögren syndrome (SS) is a multisystemic autoimmune disease characterized by lymphocytic infiltrates of the exocrine glands leading to loss of secretory function with dryness of the main mucosal surfaces[1]. It's associated with the production and secretion of autoantibodies, related to a consistent immunoregulatory abnormality of B-cell activation[2,3]. The association of SS with Systemic Lupus Erythematous (SLE) was mentioned for the first time in 1959 and it has been reported with a rate of 9-31%, what seems to be related to the difficulties in achieving the diagnosis of both diseases and the different criteria used for that purpose[4].

A multidisciplinary approach is usually required for the diagnosis of SS. Although the disease is usually benign, the majority of individuals have only sicca symptoms, systemic manifestations can occur, with accountable mortality and morbidity, mainly related to extraglandular involvement and haematological cancer[1,2,5,6].

The prompt diagnosis of SS and the acknowledgement of its severe complications allow an early therapeutic intervention in order to slow down the progression of a benign to malignant lymphoproliferation.

CASE PRESENTATION

We describe the case of a 66-year-old female who was referred to our hospital owing to enlargement of the left parotid gland. She had complaints of xeropthalmia and xerostomia for the last 3 years, associated with inflammatory polyarthralgias without arthritis. Photosensitivity was also present as well as malar rash with sun exposure. She denied any other constitutional symptoms or relevant medical, family, and psychosocial history. The physical exam was unremarkable except for a diffuse enlargement of left parotid gland that had developed in the past year. There were no associated preauricular, submandibular or cervical enlarged lymph nodes or masses.

Laboratory analysis were done revealing significant alterations, namely leucopenia (3.53 x 10^3/UL), anti-nuclear antibody (ANA) positive (1:1280; fine speckled pattern), anti-Ro/SSA (614 U/mL) and anti-La/SSB (137 U/mL) positive and low complement levels, C3 0.896 g/L (N 0.90 – 1.80g/L) and C4 0.060 g/L (N 0.1-0.4g/L). Anti-double stranded DNA was negative (9.7 UI/mL; negative < 10 UI/mL) (Table 1). The parotid gland scintigraphy identified a marked functional compromise of both parotid and submandibular salivary glands that had decreased response to the secretory stimulus. In the light of these findings, the diagnosis of SS secondary to SLE was confirmed and the patient started treatment with hydroxychloroquine 400mg and prednisolone 7.5mg once daily. After 6 months there was resolution of the sicca symptoms and of the parotid gland enlargement.

Two years after the diagnosis, in a regular visit, she complained of odynophagia and trismus and had a new enlargement of the left parotid gland with preauricular and infra-auricular

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Table 1. Laboratory routines during follow up. Legend: ANA – anti-nuclear antibody, dsDNA - double-stranded DNA, Hb – hemoglobin, LDH - lactate dehydrogenase, Leuk – leukocytes, Neut – neutrophils, Lymph – lymphocytes, Plat – platelets, R – CVP - Rituximab – Cyclophosphamida-Vincristine-Prednisone, RF – rheumatoid factor.

	1st Appointment	2nd Appointment (hydroxychloroquine 400mg id and Prednisolone 7.5mg id)	After 2nd cycle R-CVP	After last cycle R-CVP
Hb (12-16 g/dL)	14.6	15.0	12.8	12.9
Leuk (4-10 x 103 /UL)	3.53	4.8	4.84	6.82
Neut (2-7 x 103 /UL)	1.79	2.38	2.6	4.91
Lymph (1-63 x 103 /UL)	1.16	1.69	1.37	1.19
Plat (150-400 x 103 /UL)	222	216	195	204
C3 (0.90 – 1.80 g/dL)	0.896	0.958	-	-
C4 (0.1-0.4 g/dL)	0.06	0.082	-	-
ANA's (N<1:160)	1:1280	-	-	-
dsDNA (N<15.0))	9.7	-	-	-
Anti – Ro/SSA (N<10)	614	-	-	-
Anti – La/SSB (N<10)	137	-	-	-
LDH (313-618 U/L)	637	491	486	571
B2 microglobulin (1.09-2.35 mg/L)	-	2.22	-	-
RF (N<15 UI/mL)	32.4	-	-	-
Monoclonal gammopathy	Negative	Negative	-	-

distribution, with roughly 6x7cm, non-mobile and of hard consistency (Figure 1). Two cervical ipsilateral enlarged lymph nodes were observed. A computed tomography (CT) of the neck was performed, revealing a bulky mass in the left parotid gland suggesting malignancy. The biopsy of the parotid gland confirmed the suspected diagnosis of B-cell non-Hodgkin Lymphoma (NHL) – MALT type (Figure 2). Chemotherapy with Rituximab–Cyclophosphamide-Vincristine-Prednisone (R-CVP) was initiated, for a total of 8 cycles. After 10 months, a control neck CT showed normal morphology and dimensions of the left parotid gland. The patient remained asymptomatic for 6 years, medicated with hydroxychloroquine 400mg once daily. There was no evidence of malignancy relapse after stopping chemotherapy.

DISCUSSION

SS is one of the 3 most common systemic autoimmune diseases, along with rheumatoid arthritis and SLE[2]. It is unclear whether SS associated with another autoimmune rheumatic disease represents a distinct overlapping entity or a manifestation in the clinical spectrum of the concomitant rheumatic disorder[7]. Therefore, the expression of SS that coexists with SLE needs to be further addressed.

SS is a good example of a crossroad between autoimmunity and malignant transformation, given the high risk of developing lymphoma. Occurrence of lymphoma is known to be one of the most severe complications of SS, being equivalent for both primary and secondary SS and is estimated to be 10 to 44 times greater than that observed in a comparable normal population[5,6]. B-cell NHL occurs in approximately 5% of the patients[8]. Lymphomagenesis in the setting of SS is considered as a multifactorial process which is not fully understood but there are some clinical features which have been identified has adverse predictors for its development[2,6] (Table 2). In this case, the enlargement of parotid gland was unilateral, fixed and of hard consistency (Figure 1). Even though B symptoms were absent, the presence of cervical lymph nodes occurred later in the course of the disease. Skin involvement was not observed, but when present, is usually linked with cryoglobulinemia. In terms of laboratory findings, the patient had low C3 and C4. Although rare, bone marrow involvement can be present and was excluded.

The therapeutic approach must be adapted to each case. In localized low-grade lymphomas affecting only the exocrine glands, a watchful policy can be an option. However, in order to prevent transformation into a more aggressive type of lymphoma, chemotherapy may be justified[2]. In this case, taking into account the large dimensions of the parotid gland

Table 2. Main classical clinical and paraclinical predictive factors of lymphoma development. Legend: GC – germinal center, RF - rheumatoid factor. The predictive factors present in our patient are in bold.

Clinical predictive factors	Paraclinical predictive factors
Permanent swelling of salivary gland	Cryoglobulinemia
Adenopathy	Lymphopenia
Purpura	Low C4
Raynaud phenomenon	Anti SSA and/or SSB positivity
	RF positivity
	Monoclonal gammopathy
	GC -like structures within salivary gland

Figure 1. Diffuse enlargement of left parotid gland, with preauricular and infra-auricular distribution (6x7cm), hard consistency and immoveable.

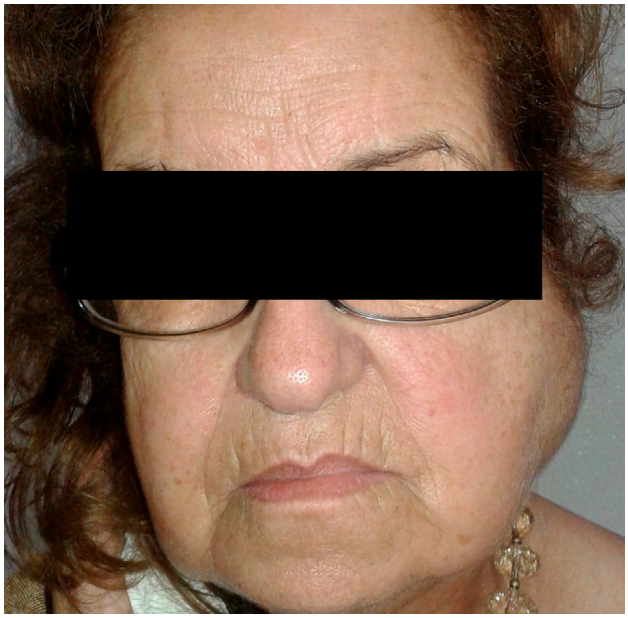
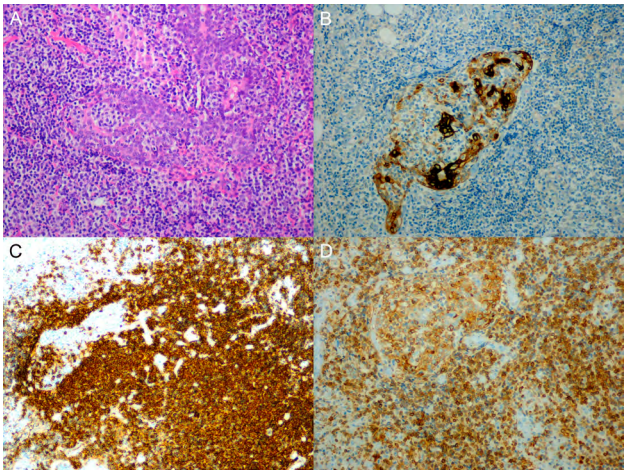


Figure 2. Biopsy of the left parotid gland. A: Hematoxylin-Eosin staining; x200 - Population of lymphoid cells with clear cytoplasm that distort and destroy the glandular/ductal epithelium, compose the lymphoepithelial lesions (B-cell non-Hodgkin Lymphoma – MALT type); B: CK CAM5.2; x200 - Epithelium penetrated by unlabeled lymphoid cells; C: x200 - Lymphoid cells have phenotype B and are CD20 +; D: x200 - Lymphocytes are bcl2 +.



and the involvement of regional lymph nodes, the patient initiated chemotherapy. The best regimen is the combination of rituximab with either alkaline agents (cyclofosfamide/chlorambucil), fludarabine or bendamustine. R-CVP was chosen for this patient with a favorable outcome.

There is no consensus on follow-up of these patients and the strategy should be adapted to the disease activity[2].

SS is a slowly progressive disease with benign course and a negligible mortality. The exception is the evolution of lymphocytic infiltrate in the exocrine gland to an overt lymphoma, comprising a worse prognosis with higher mortality. A close follow-up of the patient is indicated and the active search for risk factors should be included in the management of every case. The management of disease activity should be a primary objective in order to minimize the chronic B-cell stimulation, decreasing the risk of developing lymphoma.

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Cancer Immunotherapy associated with Interstitial Lung Disease

The field of oncology has entered an era of molecularly targeted therapy[1]. Among the many immunotherapeutic strategies, immune checkpoint blockade has shown remarkable benefit in the treatment of a range of cancer types[2]. The broader use of immunotherapy challenges clinicians in the diagnosis and management of side effects which are caused by inflammation generated by the activation of the immune response. Nearly all organs can be affected. Interstitial lung disease (ILD) has been identified as a rare but potentially severe event[3].

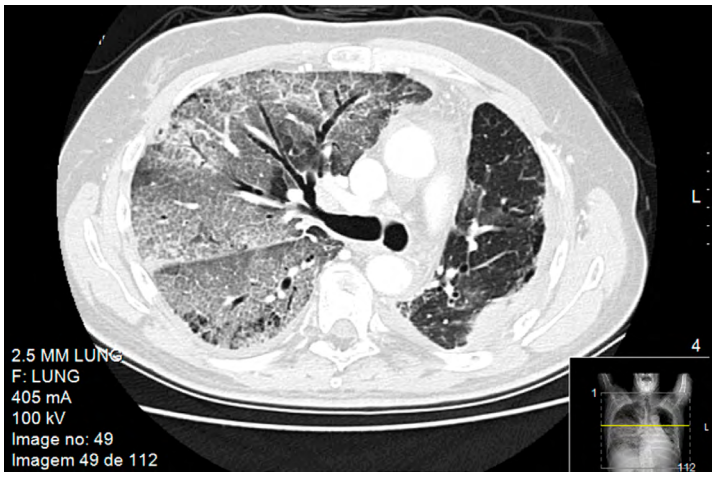
Compared with cytotoxic chemotherapy, agents such as *Crizotinib,* an oral tyrosine kinase inhibitor, offer the promise of improved outcomes with fewer toxicities. However, these agents often target multiple pathways, it is important to recognize both on-target and off-target effects so as to anticipate and treat toxicities that arise[4,5].

This report describes the clinical case of a 57-year-old man, ex-smoker, being treated with *Crizotinib* for a lung adenocarcinoma's recurrence documented in a control CT thorax which showed the progression of the lesion of the lower left lobe of the lung (no more lesions were visible), after an initial scheme with chemo and radiotherapy.

He was admitted to the emergency department (ED) for progressive dyspnea and a dry cough three weeks after the start of immunotherapy, no history of documented fever. In the ED was objectified a severe respiratory insufficiency; given the insidious evolution of neoplasia and the potential for recovery of drug iatrogeny, he was sent to an intensive care unit (ICU) for ventilatory support. A high-resolution chest CT was performed demonstrating findings suggestive of a severe interstitial lung disease. In the medical image presented are visible extensive areas with depolyzed glass densification and thickening of interlobular septa with diffuse alveolar damage type formation.

In the ICU was performed a bronchoalveolar lavage showing a T-lymphocytic alveolitis, microbiological evaluations (viruses, bacteria, fungi and parasites) were negative; the immunological study would also be negative. With adequate ventilatory support the treatment of ILD was achieved with the use of high-dose steroids.

Immunotherapy is becoming a standard approach for many cancer patients. Interstitial lung disease has been identified as a rare but serious and potentially deadly event requiring an early diagnosis, close monitoring and treatment[3,5].



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PULSE PARA VOLVER AL ÍNDICE

Un caso raro de lesiones faciales: granulomatosis orofacial

A rare case of facial injuries: orofacial granulomatosis

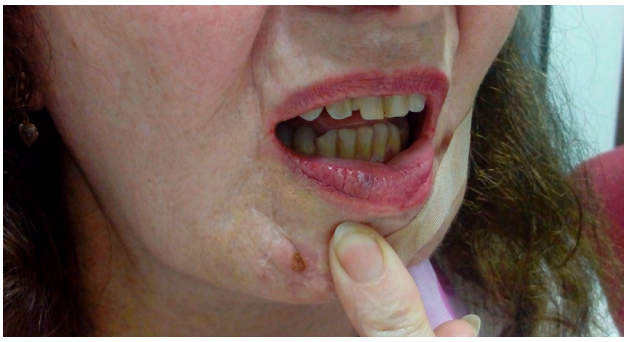
Mujer de 61 años, sin antecedentes de interés que acude a consultas externas de Medicina Interna derivada desde el Servicio de Maxilofacial. Refiere que desde hace unos 40 años, presenta lesiones papulosas eritematosas, circulares y edematosas, que van aumentando de tamaño (imágenes 1 y 2), hasta que en el centro se abren dejando salir un filamento (imágenes 3 y 4). Las lesiones aparecen sobre todo en linea media facial, aunque dos aparecieron en mucosa oral y labial. Las lesiones son autolimitadas, en un primer momento sobreelevadas y edematosas, pero desaparecen dejando la piel atrófica. Mientras estuvo a seguimiento por Maxilofacial se le extirparon varias lesiones, y las biopsias aportadas demostraban granulomas no caseificantes con infiltración perivascular de linfocitos y los filamentos estaban compuesto de estructuras queratinizantes sin una estructura homogénea (a diferencia de un pelo).

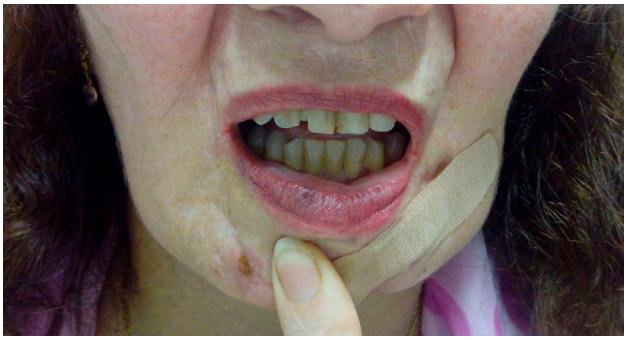
Ante estos hallazgos el diagnóstico diferencial es amplio, ya que incluye todas las enfermedades que cursan con granulomas no caseificantes, tales como enfermedades infecciosas granulomatosas (tuberculosis, lepra u otras micobacterias, sífilis, enfermedad de Lyme) y enfermedades sistémicas granulomatosas (enfermedad de Crohn, vasculitis y sarcoidosis). En nuestro caso, las pruebas complementarias nos descartaron estas enfermedades y la historia no orientaba a clínica sistémica, ya que toda la afectación era circunscrita a esa zona, por lo que el diagnóstico fue de granulomatosis orofacial.

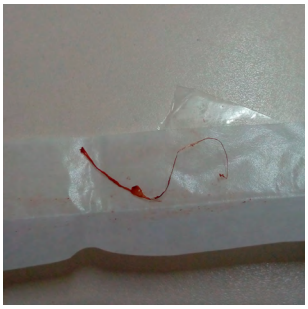
La granulomatosis orofacial es una entidad poco frecuente y de etiología desconocida. Se define como una inflamación granulomatosa crónica persistente o recurrente de tejidos blandos del área oral o maxilofacial. Puede cursar con inflamación en labios, úlceras en cavidad oral y multitud de afectación clínica a este nivel. Existen diferentes variantes clínicas: síndrome de Merkelsson-Rosenthal (parálisis facial periférica, edema orofacial y lengua fisurada), queilitis de Miescher (edema de labio inferior) o puede ser secundaria a una enfermedad sistémica (enfermedad de Crohn, cuyo cribado está recomendado en pacientes jóvenes).

Se trata de un diagnóstico de exclusión. En la anatomía patológica se observan granulomas no caseificantes, pero su ausencia no la excluye. El tratamiento depende del tipo de lesiones y la severidad de las mismas y se basa en corticoides tópicos, intralesionales, sistémicos o bien inmunospupresores tópicos o sistémicos. La respuesta al tratamiento es muy variable.

En nuestro caso llama la atención la presencia de los filamentos con queratina, no encontrando precedentes en la búsqueda bibliográfica.







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Presentación benigna de anomalia potencialmente maligna

Benign presentation of potentially malignant anomaly

Palabras Clave: Anomalía congénita coronaria, Angiografía por tomografía computarizada cardíaca, Muerte súbita de origen cardiaco.
Key words: Congenital coronary anomaly, Cardiac computed tomography angiography, Cardiac sudden death.

A 57-year-old female with no past medical history and no symptoms, who was referred to the Internal Medicine Consultation for the presence of albuminuria with a creatinine clearance of 87.3 mL/min. It was detected grade II arterial hypertension and started indapamide and perindopril. The complementary study carried out evidenced a horseshoe kidney on renal ultrasound and a double contour image in the aortic root (anterior Valsalva sinus) on transthoracic echocardiography (Fig. 1), besides left atrial enlargement. To clarify this lesion, a cardiac computed tomography angiography was done (Fig. 2). This showed a common origin of the coronary arteries in a single ostium in the right coronary sinus, in which the common trunk of the left coronary artery has a long trajectory between the right ventricular outflow tract and the aorta. There was no evidence of extrinsic static compression images and no evidence of atherosclerotic disease. She underwent a cardiac stress test that not showed signs of myocardial ischemia or dysrhythmias. A conservative approach was adopted with vigilance and control of arterial hypertension and cardiac frequency with perindopril, indapamide and bisoprolol. Current follow-up of 5 years without intercurrences.

Coronary anomalies are rare and mostly asymptomatic as they are often diagnosed incidentally. Its clinical significance depends on the origin, course and amount of perfused myocardium. The symptoms result from myocardial ischemia and manifest as angina, arrhythmias, syncope, infarction or sudden death[1].

The single coronary artery is a very rare congenital anomaly with an incidence between 0.0024-0.044%[2]. The obstruction of this single vessel is devastating due to the absence of collaterals. In addition, the inter-arterial pathway may, in the presence of a hypertensive peak, compromise myocardial perfusion and thus culminate in sudden death[1]. The surgical revascularization can be considered in these cases mainly if there is evidence of ischemia[3].

The interesting point of our patient is that she has two potentially malignant anomalies (single coronary artery and inter-arterial course of the left coronary artery) and have none cardiovascular event so far.

Figure 1. Transthoracic Echocardiography: a double contour image at the aortic root - anterior Valsalva sinus (orange circle)

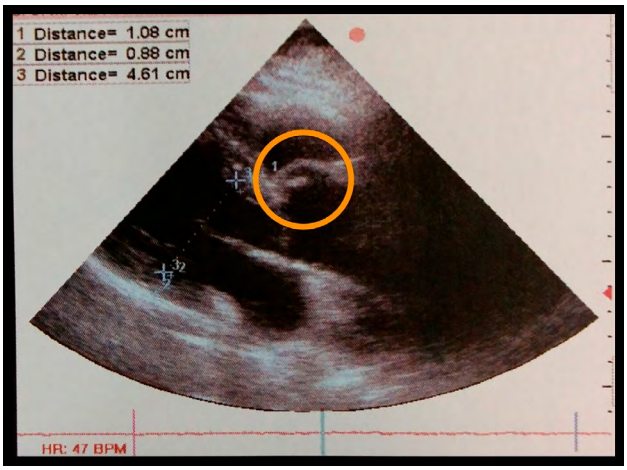
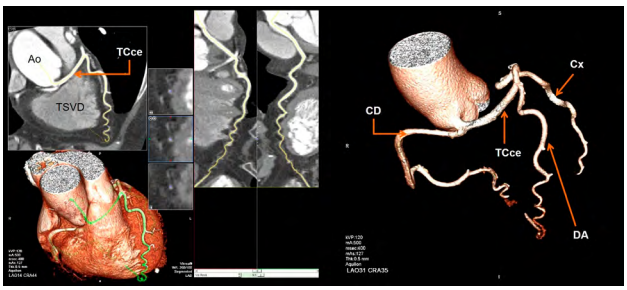


Figure 2. Computed tomography angiography: common origin of the coronary arteries in the single ostium in the right coronary sinus. Common trunk of the left coronary artery with a long pathway between the right ventricular outflow tract and the Aorta. Ao - Aorta. CD - Right Coronary Artery. Cx - Left Circumflex Artery. DA - Left Anterior Descending Artery. TCce - Common trunk of the Left Coronary Artery.



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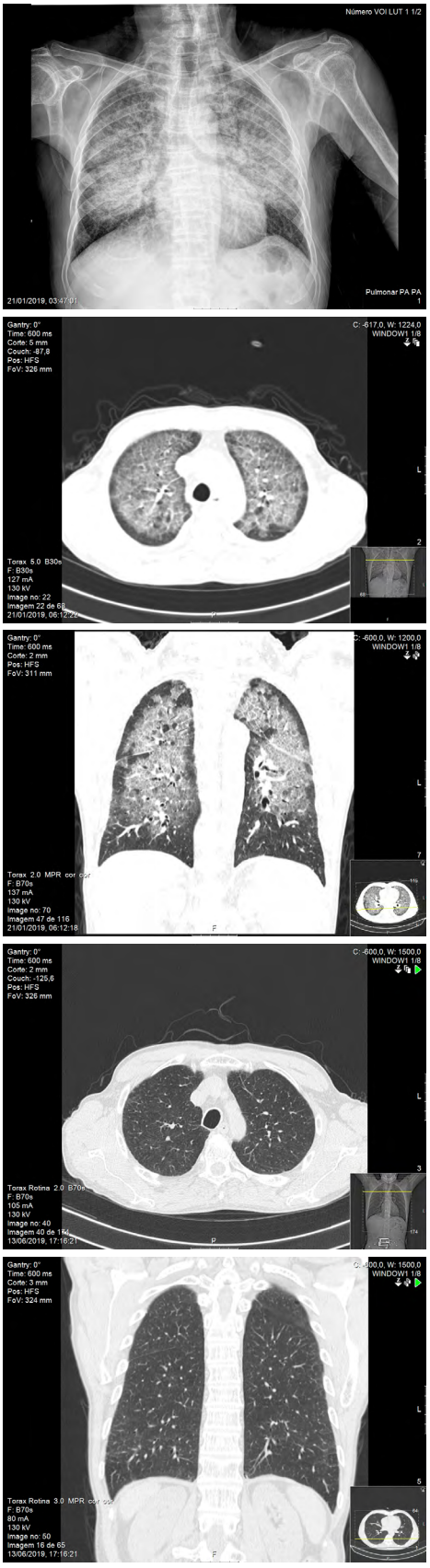
Crazy paving whom's fault?

Crazy paving is a pulmonar high resolution computed tomography pattern of disease where areas of ground glass attenuation with superimposed septal thickening are observed. It is frequently observed in several types of pneumonia (caused by atypical agents, in patients with chronic microaspirations due to gastrointestinal pathologies), in pulmonary tumors, in sarcoidosis and at alveolar proteinosis.

The next images shows a 61-year-old man with personal history of smoking habits and a prostatic tumor (Gleason 7 that underwent radical prostatectomy, without pharmacological therapy at he moment) that appears to the emergency department due to dyspnea, fever and cough with two days of evolution. At pulmonary auscultation there were no alterations. He performed some complementary diagnostic tests that showed elevated inflammatory parameters (PCR 382mg/L, VSG 70mm/h), respiratory insufficiency (pO2 56mmHg, pCO2 31mmHg) and a chest X-ray with bilaterally dispersed infiltrate. Important to notice that he was a negative HIV test, a negative anti-neutrophil cytoplasmic antibodies, a negative antinuclear antibody and a negative angiotensin converting enzyme. He performed a thoracic computed tomography that showed a bilateral infiltrated pattern – "crazy paving like". The patient was hospitalized with the diagnosis of suspected atypical pneumonia in an immunosuppressed patient. He was medicated with azithromycin 500mg/day/5days (initially with ceftriaxone during 3 days, without steroids therapy), with improvement of clinical status and resolution of the clinical situation.

The patient performed a bronchofibroscopy without significant macroscopic changes. Bronchoalveolar lavage revealed macrophages and inflammatory cells without PAS positive material. The IgM Mycoplasma pneumonia serology was positive and IgG was negative (the PCR of Mycoplasma was not performed). After 1 month he performed another thoracic computed tomography with resolution of the bilateral infiltrated and repeated Mycoplasma pneumonia serology with IgG positive.

Keywords: Crazy-paving, atypical agent, Mycoplasma pneumonia, immunosuppressed.



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