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## ORIGINAL



## CASOS CLÍNICOS



## IMÁGENES EN MEDICINA

# El anticoagulante lúpico, el factor Von Willebrand y la interleucina-6 como predictores fiables de la necesidad de ventilación mecánica en la COVID-19

## *Lupus Anticoagulant, Von Willerbrand Factor and Interleukin-6 as a reliable predictor of the need for mechanical ventilation in Covid-19*

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## ABSTRACT

**Background:** Coronavirus disease 2019 is characterized by causing thromboembolic events due to a procoagulant state. The possible relationship between lupus anticoagulant and patient's procoagulant state is controversial and no study has specifically evaluated the impact of lupus anticoagulant on noninvasive mechanical ventilation.

**Objectives:** The aim of our study was to analyze the association between lupus anticoagulant and the need for noninvasive mechanical ventilation in 44 consecutive patients hospitalized for Severe acute respiratory syndrome Coronavirus 2 pneumonia.

**Methods:** This was a prospective, multicenter, observational study conducted between January 1 and March 31, 2022, which included a total of 44 consecutive patients, >18 years old and admitted for Severe acute respiratory syndrome Coronavirus 2 pneumonia. The following characteristics were determined: age, gender, blood group and Rh factor, plasma levels of Interleukin-6, Von Willerbrand Factor, lupus anticoagulant at admission, presence of venous thromboembolic disease, need for noninvasive mechanical ventilation, and intensive care unit admission. The relationship between the need for noninvasive mechanical ventilation and the levels of Von Willerbrand Factor and lupus anticoagulant was performed by T-student and its cutoff point was defined by ROC curve. Multivariate analysis was performed to establish worse prognosis factors. SPSS 27.0 statistical software was used, and an alpha error of 0.05 was established.

**Results:** 44 patients hospitalized with Severe acute respiratory syndrome Coronavirus 2 pneumonia (56.8% male, 68.5±17.9 years). 88.6% showed elevated Von Willerbrand Factor. Lupus anticoagulant levels were higher in patients requiring mechanical ventilation versus oxygen therapy (1.32±0.27 vs 1.12±0.17, p=0.011). The cutoff point for lupus anticoagulant levels that were associated with mechanical ventilation was 0.792 AUC (p=0.01). The predictors of noninvasive mechanical ventilation in the multivariate analysis were intensive care unit admission (p=0.02).

**Conclusions:** Plasma levels of Von Willerbrand Factor, lupus anticoagulant and Interleukin-6 can be a very useful prognostic tool for assessing the need for hospital admission to the critical care unit and the need for noninvasive mechanical ventilation. It would be interesting to include these determinations as routine assessments in patients with severe pneumonia.

**Keywords:** Severe acute respiratory syndrome; SARS-CoV-2; pneumonia; lupus anticoagulant; noninvasive mechanical ventilation.

## RESUMEN

**Antecedentes:** La enfermedad por coronavirus 2019 se caracteriza por provocar eventos tromboembólicos debido a un estado procoagulante. La posible relación entre el anticoagulante lúpico y el estado procoagulante del paciente es controvertida y ningún estudio ha evaluado específicamente el impacto del anticoagulante lúpico en la ventilación mecánica no invasiva.

**Objetivos:** El objetivo de nuestro estudio fue analizar la asociación entre el anticoagulante lúpico y la necesidad de ventilación mecánica no invasiva en 44 pacientes consecutivos hospitalizados por neumonía grave por síndrome respiratorio agudo severo coronavirus 2.

**Métodos:** Se trata de un estudio prospectivo, multicéntrico y observacional realizado entre el 1 de enero y el 31 de marzo de 2022, en el que participaron un total de 44 pacientes consecutivos, mayores de 18 años y hospitalizados por neumonía grave por coronavirus 2 del síndrome respiratorio agudo. Se determinaron las siguientes características: edad, sexo, grupo sanguíneo y factor Rh, niveles plasmáticos de interleucina-6, factor Von Willebrand, anticoagulante lúpico al ingreso, presencia de enfermedad tromboembólica venosa, necesidad de ventilación mecánica no invasiva e ingreso en la unidad de cuidados intensivos. La relación entre la necesidad de ventilación mecánica no invasiva y los niveles de factor von Willebrand y anticoagulante lúpico se realizó mediante la prueba T de Student y su punto de corte se definió mediante la curva ROC. Se realizó un análisis multivariante para establecer los factores de peor pronóstico. Se utilizó el software estadístico SPSS 27.0 y se estableció un error alfa de 0,05.

**Resultados:** 44 pacientes hospitalizados con neumonía por coronavirus 2 del síndrome respiratorio agudo grave (56,8 % hombres, 68,5 ± 17,9 años). El 88,6 % presentó niveles elevados del factor Von Willebrand. Los niveles de anticoagulante lúpico fueron más elevados en los pacientes que requirieron ventilación mecánica frente a los que recibieron oxigenoterapia (1,32±0,27 frente a 1,12±0,17, p=0,011). El punto de corte para los niveles de anticoagulante lúpico asociados a la ventilación mecánica fue de 0,792 AUC (p=0,01). Los predictores de ventilación mecánica no invasiva en el análisis multivariante fueron el ingreso en la unidad de cuidados intensivos (p=0,02).

**Conclusiones:** Los niveles plasmáticos del factor Von Willebrand, el anticoagulante lúpico y la interleucina-6 pueden ser una herramienta pronóstica muy útil para evaluar la necesidad de ingreso hospitalario en la unidad de cuidados intensivos y la necesidad de ventilación mecánica no invasiva. Sería interesante incluir estas determinaciones como evaluaciones rutinarias en pacientes con neumonía grave.

**Palabras clave:** Síndrome respiratorio agudo grave; SARS-CoV-2; neumonía; anticoagulante lúpico; ventilación mecánica no invasiva.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is characterized by triggering thromboembolic events due to a procoagulant state. There is sufficient evidence that SARS-CoV-2 is a proinflammatory and prothrombogenic virus with a high mutagenic profile, which produces active infection of variable duration in various organs and systems (lung, digestive system, central nervous system, skin...)[1]. The first complete necropsy studies performed show multiple and severe vascular involvement in the lungs, heart (myocarditis, vasculitis, and myocardial cell necrosis), liver with focal necrosis and neutrophilic infiltrates, and the same in the kidney, with microthrombi and fibrotic foci in the renal interstitium. Also, in the brain there is cerebral hyperemia and edema with glial degeneration[2]. The degree of endothelitis is almost imperceptible in light microscopy but sufficiently relevant to produce the well-known symptoms in the various organs and systems. Since the onset of the disease, patients have been observed to be at increased risk of venous, arterial, and microvascular thromboembolic disease, associated with the development of a hypercoagulable state.[3]

Emerging evidence prove that the ongoing pandemic of coronavirus disease 2019 (COVID-19) is strictly linked to coagulopathy even if pneumonia appears as the major clinical manifestation. The cumulative incidence of venous thromboembolism was 27% (95% CI 10%-47%), 4% (95% CI 1%-12%) for arterial thrombosis and 29% (95% CI 12-49%) for arterial thrombosis[4], so that a relative significant number of studies have been performed to explore thrombotic risk in COVID-19 patients. Cytokine storm, mediated by pro-inflammatory interleukins, tumor necrosis factor α and elevated acute phase reactants, is primarily responsible for COVID-19-associated hypercoagulopathy. Also, comorbidities, promoting endothelial dysfunction, contribute to a higher thromboembolic risk. Many of the mechanisms by which this prothrombotic state occurs are unknown, although it has been related to the overexpression of procoagulant factors and the generation of a proinflammatory state, endothelial activation and dysfunction that increases interleukin 6 (IL-6) levels, vWF and lupus anticoagulant (LA) all generating microvascular inflammatory thrombosis and producing the dreaded thrombotic episodes associated with the disease and its sequelae in different vascular territories.[3,5,6]

A high prevalence of antiphospholipid antibodies (aPL) has been reported in COVID-19 patients, however, the association of the same with thrombotic events in COVID-19 is very heterogeneous and thrombosis occurs later in patients with the presence of aPL, which is probably an additional prothrombotic factor[7].

Antiphospholipid antibodies abnormally target phospholipid proteins, and the presence of these antibodies is central to the diagnosis of the antiphospholipid syndrome[8,9]. However, these anti-bodies can also arise transiently in patients with critical illness and various infections. The presence of these antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy[10]. In fact, the possible relationship between LA and the patient's procoagulant status is controversial and no study has specifically evaluated the impact of LA on NIMV.

The aim of our study was to analyze the association between lupus anticoagulant, von Willebrand factor and interleukin-6 and the need for noninvasive mechanical ventilation in 44 consecutive patients hospitalized for severe SARS-CoV-2 pneumonia.

## MATERIALS AND METHODS

### Design

This is a prospective, multicenter, observational study conducted between January 1 and March 31, 2022, in which the Internal Medicine Services of the Public Hospital of Monforte de Lemos, the Complexo Hospitalario Universitario de Ourense and the Complexo Hospitalario Universitario de Santiago de Compostela located in northwestern Spain participated. A total of 44 consecutive patients who met the inclusion criteria of being over 18 years of age and having a hospitalization for severe infection secondary to SARS-CoV-2 were included.

### Variables

A patient with COVID-19 was defined as a patient with a positive PCR determination for SARS-CoV-2 virus. The following variables were analyzed at the time of hospital admission: age, gender, blood group and Rh, IL-6 values, presence of venous thromboembolic disease, need for NIMV, admission to the intensive care unit, IL-6 values, vWF and circulating LA levels. Non-invasive mechanical ventilation (NIMV) is defined as a respiratory support approach that provides assistance to the patient without the need for invasive intervention, such as the insertion of an endotracheal tube into the trachea. Instead, NIMV utilizes non-invasive interfaces, such as facial or nasal masks, to administer airflow and aid in ventilation. Severe illness due to SARS-CoV2 pneumonia was defined as that requiring mechanical ventilation.

The analytical parameters were determined by an analytical study at the time of admission. A 20 mL blood sample was obtained from an antecubital vein and analyzed at the time of blood collection. The determination of vWF was performed by the multimeric analysis technique. It consists of diluting the plasma samples in a loading buffer according to the amount of vWF antigen, they are subjected to non-reducing electrophoresis in the presence of the denaturing agent sodium dodecylsulfate (SDS, Sigma-Aldrich S.A., Madrid, Spain), on 1% low resolution gels (Agarose Seakem HGT (P), Iberlabo S.A., Madrid, Spain) and 2% high resolution gels (Agarose Type VII, Sigma-Aldrich S.A., Madrid, Spain). The proteins are then transferred by electrical transfer (Hoeffer TE65, Amersham Bioscience, Piscataway, USA) to a polyvinylidene vinylidene fluoride (PVDF) immobilon membrane (Millipore Corporation, Bedford, MA, USA), pretreated with methanol and distilled water.

Visualization of the multimers is achieved by incubating the membrane first with a rabbit anti-human VWF antibody (Ac) (Dako, Glostrup, Denmark), then with a goat anti-IgG rabbit Ac (Dako, Glostrup, Denmark) and finally with a goat anti-IgG Ac containing alkaline phosphatase (Sigma-Aldrich S.A., Madrid, Spain), which develops color using a histological stain for this enzyme and chromogenic substrates (Fast Blue RR SALT, Sigma). Normal vWF range is 45% to 150% in our laboratory (IU/dL). LA was determined by the diluted Russell's viper venom test (screening and confirmatory). In the screening test a ratio was established between the clotting time of the sample and the reference time obtained with normal plasmas. If this ratio was higher than 1.2 the screening was considered positive. In the confirmatory test a ratio was established in a similar way, but the test result was given by the normalized ratio (NR): ratio screen/ratio confirm. If this NR

was higher than 1.2 the lupus anticoagulant was considered positive. Thromboembolic disease was studied by means of three variables: symptomatology, venous echo-Doppler study of the lower extremities and computed tomography angiography study when there was a high clinical suspicion of pulmonary embolism.

### Ethical issues

The investigators declare that the development of the project was carried out respecting the Standards of Good Clinical Practice, the fundamental ethical principles established in the Declaration of Helsinki and the Oviedo Convention, as well as the requirements established in Spanish legislation on research. All participants gave their informed consent, and the study has been conducted under the auspices of the "Registry SEMI-COVID.19" approved by the CEIC of Andalusia (SPAIN) on March 27, 2020.

### Statistical analysis

A descriptive analysis of the data was performed where continuous variables were expressed as mean and standard deviation and categorical variables as frequencies and percentages (%). The normal distribution of quantitative variables was tested using the Shapiro-Wilks test. In the case that the quantitative variables had normal distribution, the relationship between the need for NIMV and vWF and LA levels were analyzed by T-student and its cut-off point was defined by ROC curve. Multivariate analysis was performed to establish poor prognostic factors. A decision tree was performed to prognostically categorize patients. SPSS 27.0 statistical software was used, and an alpha error of 0.05 was established as a threshold for statistical significance.

## RESULTS

In our series of 44 patients hospitalized with severe SARS-CoV-2 pneumonia there were 25 males (56.8%). The mean age of the patients was 68.5 (±17.9) years. None of the patients studied developed venous thromboembolic disease. All patients received low-molecular-weight heparin at prophylactic doses as part of the treatment protocol in our hospital and in-hospital mortalitiy was 11.36%.

At the time of admission, plasma vWF levels were determined, being in 39 patients (88.6%) higher than 200%. LA levels were determined, the mean values being 1.32±0.27 in patients who required NIMV versus 1.12±0.17 in those who only required conventional oxygen therapy (p=0.011) (Figure 1).

In 21 patients (47.7%) the LA values were higher than 1.1 IU and 8 of these patients required NIMV. No patient with LA <1.1 required NIMV, being the difference statistically significant (p=0.003) (Figure 2).

A ROC curve was performed to determine the optimal cut-off point for plasma LA levels with a discriminatory point to predict the need for NIMV. The estimated cut-off point was 1.11 with an AUB of 0.79 (0.64-0.93) (Figure 3).

Plasma IL-6 levels were analyzed. Patients with plasma IL-6 levels >78 pg/mL showed a higher probability of ICU admission (p=0.01) (Figure 4).

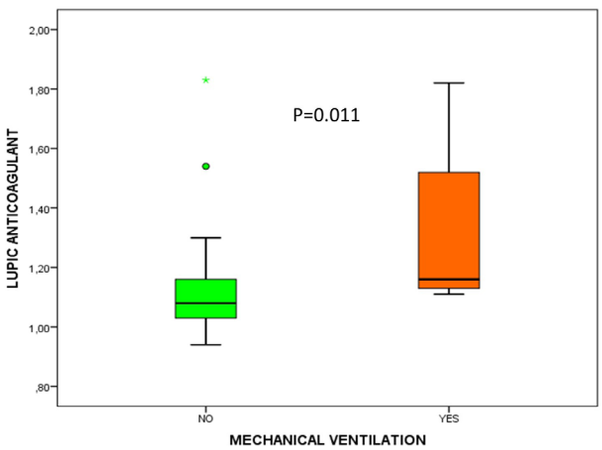



Figure 1. Box plot of lupus anticoagulant levels as a function of the need for noninvasive mechanical ventilation (NIMV).

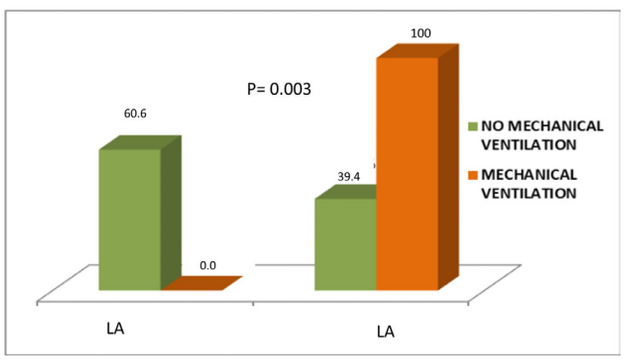



Figure 2. Cut-off point of lupus anticoagulant levels for prediction of for noninvasive mechanical ventilation (NIMV).

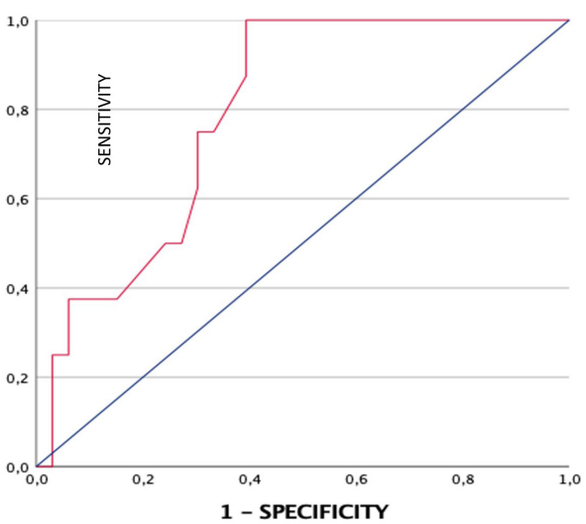
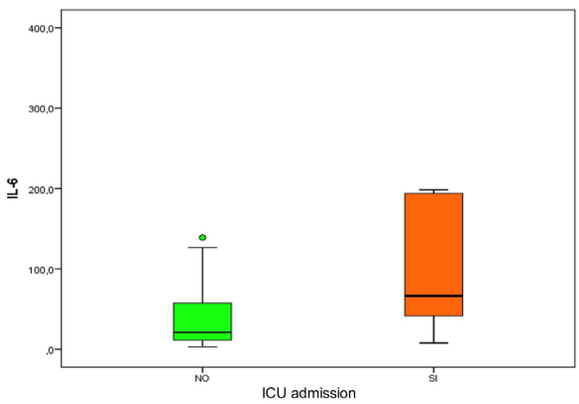



Figure 3. Determination of the cut-off point for lupus anticoagulant levels for prediction of noninvasive mechanical ventilation (NIMV).

Figure 4. Plasma levels of IL-6 as a function of the need for admission to the critical care unit.




There were no significant differences in clinical outcome according to blood group or Rh factor. A multivariate analysis was performed to determine the worst prognostic factors in relation to NIMV. The following covariables were included: age, gender, and admission to the ICU. Of these, only ICU admission was statistically significant in the multivariate analysis (p=0.02) (OR 0.055 [0.009-0.35]). For NIMV risk, LA has a sensitivity of 1, specificity of 0.62 and a NPV (negative predictive value) of 1 being the most discriminative parameter with a positive likelihood ratio of 2.63. Although the NPV of vWF is 1 and that of IL-6 is 0.94, their specificities are much lower (0.11 and 0. 48 respectively). A predictive analysis was performed by means of a decision tree in which the dependent variable was the need for mechanical or NIMV and the independent variables were plasma levels of LA, IL-6, age, blood group and Rh. CRT was introduced as a growth method, which allows the data to be divided into segments to make them as homogeneous as possible with respect to the dependent variable. In this classification the most important group of patients requiring NIMV were patients with plasma levels of LA >1.105 and an age >57.5 years (38.6% of the total). This method had a predictive capacity of 81.8%.

## DISCUSSION

Patients with elevated plasma levels of vWF and LA are more likely to be admitted to a critical care unit and receive NIMV, reflecting a situation of disseminated microthrombosis that aggravates the clinical situation of patients with severe SARS-CoV2 pneumonia.

It is currently accepted that this entity causes a chronic reactive endothelitis mediated by a chronic oxidative stress mechanism[3]. This situation triggers a release of vWF multimers[4] and generates hypercoagulability, despite the thrombopenia caused by SARS-CoV-2. An imbalance occurs that resolves in favor of prothrombotic situation, whereby thrombin and D-dimer levels are elevated. D-dimer levels have been shown to be a prognostic factor for disease severity, especially in the older population[11]. Sieiro-Santos *et al.* demonstrated that LA, in addition to vWF, fibrinogen, thrombin and Beta-2 glycoprotein (B2Gp), have an important influence on the development of thrombogenesis mediated by SARS-CoV-2.[6,12,13]

In our study, no patient developed venous thromboembolic disease, perhaps due to the correct prophylaxis with low-molecular-weight heparin from the time of admission.

On the other hand, our group has already demonstrated that cytokine storm also amplifies platelet production, leading to increased formation of disseminated microthrombi in various vascular territories[7]. Helms *et al.* observed that 87.7% of 57 ICU patients had elevated LA and that this correlated with major thrombotic problems, mainly pulmonary thromboembolism[16]. Other authors found elevated LA in 20-50% of the sample but did not find significant differences either in the use of NIMVM or in mortality[17,18] probably because the sample sizes were small. Devreese *et al.* state that the elevation of LA plasma levels is transient and should be studied in greater depth in view of the existing controversy[19]. What seems clear is that the thrombogenicity of SARS-CoV-2 directly influences the clinical deterioration of patients and that elevated LA levels could contribute to the selection of a subgroup of patients at greater risk of thrombosis and admission to the ICU[20]. Cases have recently been published following vaccination against COVID19.[21]

To confirm this finding, studies with a larger sample size and longer follow-up time should be performed. Our study has limitations. Although it is a multicenter study, the sample size is small, and this limits the generalizability of our conclusions. However, statistically significant differences are shown, which support the hypothesis of this work. Another limitation is the non-applicability of the results to pediatric patients, since one of the inclusion criteria was being older than 18 years, although, fortunately, children rarely require NIMV for severe COVID-19 pneumonia. The study only evaluated patients during their hospital stay, and no subsequent follow-up was performed to assess their short- to medium-term prognosis. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

In Conclusion, Plasma levels of von Willebrand factor, lupus anticoagulant and IL-6 can be a very useful prognostic tool for assessing the need for hospital admission to the critical care unit and the need for noninvasive mechanical ventilation. It would be interesting to include these determinations as routine assessments in patients with severe SARV-CoV2 pneumonia.

**FUNDING**
No funding has been received for this project.

**INSTITUTIONAL REVIEW BOARD STATEMENT**
The investigators declare that the development of the project was carried out respecting the Standards of Good Clinical Practice, the fundamental ethical principles established in the Declaration of Helsinki and the Oviedo Convention, as well as the requirements established in Spanish legislation on research.

**INFORMED CONSENT STATEMENT**
All participants gave their informed consent, and the study has been conducted under the auspices of the "Registro SEMI-COVID.19" approved by the CEIC of Andalusia- SPAIN on March 27, 2020.

**CONFLICTS OF INTEREST**
None declared.

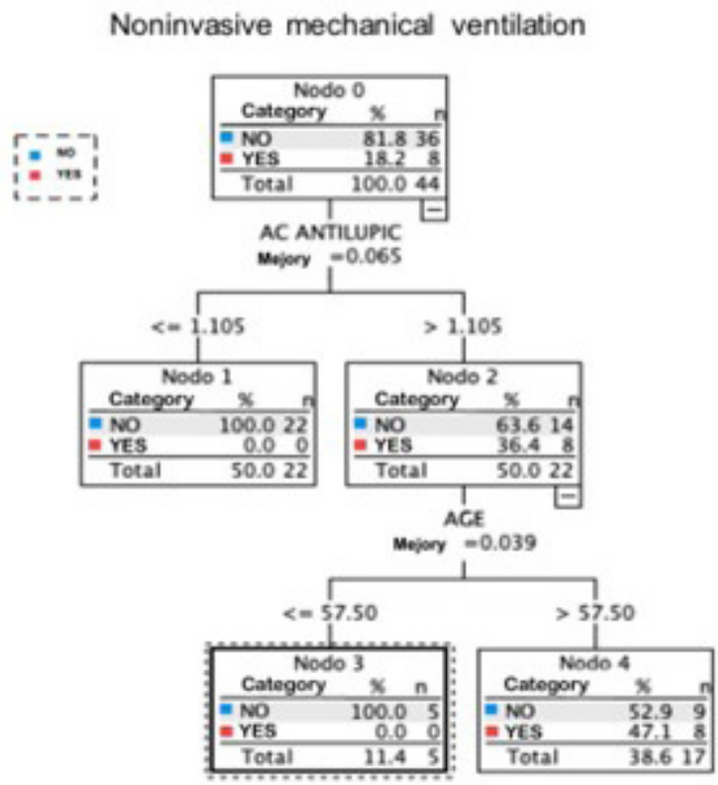



Figure 5. Decision tree for classification of patients who required noninvasive mechanical ventilation (NIMV) according to age, plasma levels of lupus anticoagulant, Rh and blood group.

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# Efectividad del entrenamiento de la marcha mejorado por estimulación auditiva rítmica y ejercicios de Frenkel para mejorar la movilidad entre la población geriátrica

## *Effectiveness of rhythmic auditory stimulation enhanced gait training and Frenkel exercises in improving mobility among geriatric population*

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## ABSTRACT

Age-related changes in mobility demand interventions.One of the difficult faced by older patients are decreased walking speed and increased risk of falling. Rhythmic auditory stimulation and enhanced gait training may be a successful intervention technique, on the other hand Frenkel exercise shows improvement in dynamic balance. In order to determine the best between these two the study protocol has been designed.

**Aim:** To find any significant differences between the effect of rhythmic auditory stimulation, enhanced gait training and Frenkel exercises in improving mobility among the geriatric population.

**Method:** A total of 40 participants were selected using convinent sampling method based on inclusion and exclusion criteria, then the subjects were divided into two groups. In Group A (n=20) patients received RAS enhanced gait training. In Group B (n=20) patients received Frenkel exercise , one session per day, six days per week, for a duration of 25 mins of 4 week.

**Result:** The paired and unpaired t-test were used to statistically analyze. According to the post-test mean value of the 10 m walk test and time up and go test yielded a p-value of less than 0.05. This demonstrates that RAS have a significant impact on mobility for geriatic population.

**Conclusion:** From the data analysis obtained in the study, it concluded that rhythmic auditory stimulation group have better improvement than the Frenkel exercise group.

**Keywords:** Walking, exercise, gait, aging.

## RESUMEN

Una de las dificultades que enfrentan los pacientes mayores es la disminución de la velocidad al caminar y el mayor riesgo de caídas. Los cambios relacionados con la edad en la movilidad exigen intervenciones. La estimulación auditiva rítmica y el entrenamiento de la marcha mejorado pueden ser una técnica de intervención exitosa; por otro lado, el ejercicio Frenkel muestra una mejora en el equilibrio dinámico. Para determinar lo mejor entre estos dos, se ha diseñado el protocolo de estudio.

**Objetivo:** Encontrar diferencias significativas entre el efecto de la estimulación auditiva rítmica, el entrenamiento de la marcha mejorado y los ejercicios de Frenkel para mejorar la movilidad entre la población geriátrica.

**Método:** Se seleccionó un total de 40 participantes utilizando un método de muestreo conveniente basado en criterios de inclusión y exclusión, luego los sujetos se dividieron en dos grupos. En el Grupo A (n =20), los pacientes recibieron entrenamiento de la marcha mejorado con estimulación auditiva rítmica. En el Grupo B (n=20), los pacientes recibieron ejercicio Frenkel, una sesión por día, seis días por semana, con una duración de 25 minutos durante 4 semanas.

**Resultado:** Para el análisis estadístico se utilizó la prueba t pareada y no pareada. Según el valor medio del test posterior a la prueba de marcha de 10 m y a la prueba de levantarse y caminar arrojó un valor de p inferior a 0,05. Esto demuestra que la estimulación auditiva rítmica tiene un impacto significativo en la movilidad de la población geriátrica.

**Conclusión:** Del análisis de los datos obtenidos en el estudio, se concluyó que el grupo de estimulación auditiva rítmica tiene una mayor mejoría que el grupo de ejercicio Frenkel.

**Palabras clave:** Caminar, ejercicio, marcha, envejecimiento.

## INTRODUCTION

Walking is a foundation for optimal mobility and independence while aging, a natural phenomena impact gait . The aging process needs to be examined as a unique physiological bodily mechanism with a specific evolutionary purpose. Ageing is characterized by a decrease in the body's capacity for adaptation, which is brought on by a symptomatic deterioration in organ, system, and cell capabilities.[1]

Walking is an ordinary part of everyday life where it involves the cardio-respiratory system, musculoskeletal components, and all levels of the neurological system. The prevalence of balance and gait abnormalities are noticeable, rising with age, from around 10% in those between 60 and 69 years old to over 60% in people over 80 years old. Furthermore, the most frequent cause of serious injuries among the elderly may be preceded by issues with balance and gait. Walking speed at which they walk has a strong correlation with life expectancy. Significantly, sluggish gait in older adults without dementia is associated with a risk of dementia develop later in life than subjective cognitive impairment.[2]

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According to research, the older people who are at high risk of falling, move more slowly (to avoid risk of fall).[3]

There are several ways to increase gait speed, including practicing on a treadmill, using a robot to aid with walking, and applying rhythmic auditory stimulation (RAS). It is difficult to implement, due to the high expense of the necessary tools and labor as well as the challenges associated with moving the equipment.[4]

The objective of locomotor training is to force the use of unmasked routes by powerful sensory cues from many sources. It is a functional activity, and early attention should be placed on tasks linked to walking.[5]

Individuals who undergone treadmill training after a stroke, with or without body weight support, have a higher chance of improving their ability to walk on their own. However, those who do not receive treadmill training may experience decrease in walking speed and capacity.[6,7]

For chronic stroke patients, treadmill walking may be a helpful strategy to enhance their walking capacity and speed. It has been linked to increase in power, decrease in energy use, as well as improvement in the quality and pace of walking.[8]

Rhythmic auditory stimulation (RAS) is a technique of practicing gait while playing the sound of metronome or other songs at general intervals, which enhances stride length and gait speed.[9]

There seems to be a carryover effect while walking with RAS, which supports the idea that increase mobility and lower the risk of falls.[10]

Several physical therapy intervention techniques have been developed to enhance parkinsonian repetitive movements as a result of the condition's reliance on outside stimuli to produce repetitive, rhythmic movements. Effective example include metronome therapy, rhythmic auditory stimulation (RAS), and physical rehabilitation programs (PRPs) that involve a range of motor exercises carried out in combination with rhythmic sound in various cadences.[11,12]

Frenkel's exercises included turning, sitting, and standing up using ordinary objects such as beds, chairs, and lines drawn on the floor, as well as acquiring walking skills using one's upper extremities.[13]

Frenkel's exercise depends on the principles of focus, accuracy, and repetition of motions. The term "rhythmic-auditory stimulation" (RAS) refers to the therapeutic use of pulsed rhythmic or musical stimulation to enhance gait or movement characteristics associated to gait. Balance is adversely impacted by the loss of gray matter in the brain regions that control motor processes, the basal and thalamic nuclei. Similar findings were reached when analyzing the parietal lobe's gray matter volume, which showed that decreasing this amount affects balance.

Frenkel's exercise is a training program made up of a group of precisely designed exercises which helps to force the patient to use the residual muscular sense that has effort to stop further deterioration of the sense or even to produce an improvement. Frenkel's workout regimen, which is mainly utilized for movement correction and coordination, is now widely employed by therapists.[14,15]

In comparison to younger adults, elderly people exhibit much lower foot position awareness, which is probably caused by a decline in plantar mechanoreceptive sensitivity. Shoes contribute to this reduction by reducing tactile feedback, which reduces awareness of foot position. The mechanoreceptive sensation in the toes and heels also decreases with age. In addition to inclining with age, vestibular function also starts to decrease significantly hence balance was affected.[16]

## MATERIALS AND METHODS

A comparative study was done with the subjects meeting the inclusion criteria and pre-evaluation of mobility of the group. RAS enhanced gait training group and frenkel exercise group was recruited from physiotherapy op at primary hospital Chennai Tamil nadu. This study was approved by institutional scientific review board (ISRB 01/005/2023/ISRB/SR/SCPT). Trough convinent sampling technique, 40 individuals were selected for study. 40 subjects diagnosed with age-related gait impairement were screened for inclusion and exclusion criteria. This study involved both men and women aged above 60 years and who have ability to walk at least 10m with the confirmation of aging gait impairment. This study excludes the subject with persons with visual impairment that interferes with daily living, history of chronic illness. All participant were asked to sign their consent form. Before providing their consent form every participants were briefed experimental methodology and techniques. The subjects are split up into two groups, A and B. Each group has twenty participants, and after being informed about the intervention and the study, their informed agreement was obtained.

In addition to the timed up and go test and the 10-meter walk test, demographic data were collected. The patients in Group A (n=20) received the rhythmic auditory stimulation enhanced gait training method. Group B (n=20) received the Frenkel exercise treatment once a day, six days a week, for four weeks, for a total of 25 minutes. The collected data and outcome will be analyzed and evaluated. A statistical comparison and evaluation are made between the test pre and after values. The Frenkel exercises, Rythmic auditory stimulation enhanced gait training exercise were given to the respective groups. They are documented by using the outcome tools such as time up and go test and ten meter walk test to assess the mobility.

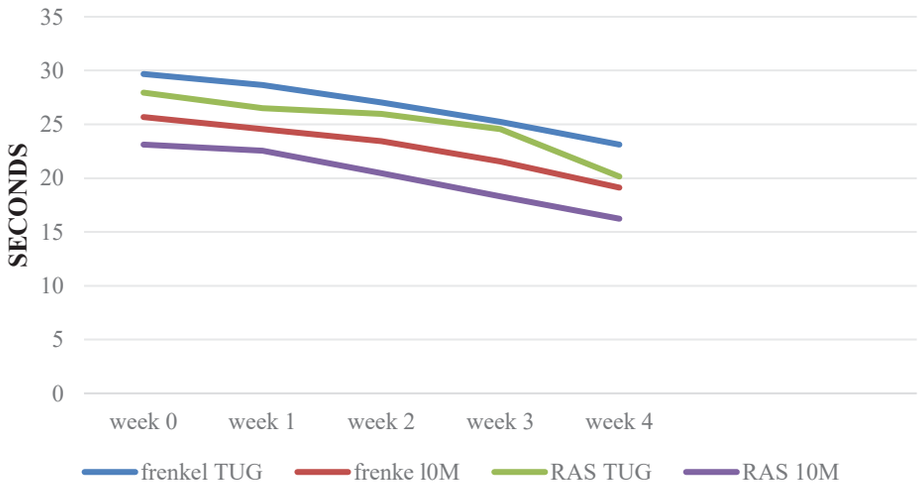
### 10-meter walk test

The 10-meter walk test is a clinical assessment used to assesses an individual's mobility and gait speed by measuring time it takes to cover the distance of ten meters. It is widely utilized in healthcare to asses mobility, gait speed, and overall physical performance. Every participant was told to walk for 10 meters at a comfortable, regular pace. The middle 6 m was timed, the 2m front for acceleration and back 2 m were excluded. The leading foot's toes crossed the 2- and 8-meter marks. Using these measurements, the speed was computed by dividing the walking distance in seconds (the middle 6 m) by the walking duration .

### Timed up and go test

Timed up and go test is widely used to assess mobility and balance. Patients can wear their usual shoes and, if needed, a walking aid. At first, the patient is seated. The patient gets up, moves three meters, turns around, and returns to the chair to sit down. Time stops when the patient is seated.

Image 1. Pre to post Frenkel group and RAS (10m walk test, time up and go test)




Note: RAS = rhythmic auditory stimulation; TUG = timed up and go test; 10M = 10M walk test.

The Frenkel exercises comprise

- hip flexion, extension, abduction, and adduction (10 rep, 2 set)
- knee flexion and extension (10 set, 2 rep)
- bring the heel to the patella, midpoint of the tibia, and the opposing leg's ankle joint (10 rep, 3 set)
- standing up with both feet fully on the floor (10 rep, 2 set)
- walking heel to toe (10 rep, 2 set)
- walking forward (2 mins, 3 times)
- walking sideways and back to the starting position (1 min, 3 times)
- walking backwards (1 min, 3 times)
- walking and turning around 90 to 180 degrees (1 min, 3 times)
- walking in a zigzag pattern (1 min, 3 mins)

### Rythmic auditory stimulation

Rhythmic auditory stimulation should be carried on a smooth, plain, flat walking path free from sound or musical influences. The patient is asked to walk and the time taken before receiving rhthymic auditory stimulation was noted. The pace at which the RAS is administered will vary from person to another and be 110 percent more than the person before walking rate. With a metronome, beats where used to provide the RAS while performing enhanced gait training lower the risk of falling, the therapist is always close by. Rest periods are timed and lengthened at the therapist's discreation

Materials required: meter tape, stopwatch, chair, neckband, mobile.

## RESULT

The gathered information was analyzed and examined For each parameter, the mean and SD were utilized. The statistically significant differences between pre-test and post-test measures were examined using the Paired t-test. The difference between the post-test values was determined using unpaired t-test (Image 1).

When compared to the pre-assesment and the post-assessment shows that there is a significant increase in mobility (walking speed) using 10 m walk test and time up and go test scales. The statistical mean value for 10 m Group A pre-intervention was 23.12± and standard deviation was 4.85, post-intervention value was 16.23±3.28. Hence the post-intervention mean value shows more significant value than the pre-intervention. The statistical mean value for 10 m of group B pre-intervention was 25.68± and standard deviation was 4.12, and post-intervention value was 19.12±3.49. Hence the post-intervention mean value shows more significant value than the pre-intervention (Table 1).

The statistical mean value for time up and go of Group A pre-intervention was 27.95± and standard deviation was 4.97±, post-intervention value was 20.15± and 3.94±. Hence the post-intervention mean value shows more significant value than the pre-intervention. The statistical mean value for time up and go test of Group B pre-intervention was 29.68± and standard deviation was 4.97±, post-intervention value was 23.12± and 4.73±. Hence the post-intervention mean value shows more significant value than the pre-intervention (Table 2).

The paired t-test and unpaired t-test was used to statistically analyze the values. A statistically significant difference was found between Group A (RAS) and Group B (Frenkel exercise) as well as within the group,according to the statistical analysis performed on the quantitative data. In Group A the post mean and sd value of 10 m and time up and go test is 16.23±3.28 and 20.15± 3.94, whereas in Group B it is 19.12 ±3.49 and 23.12±4.73 (Table 3).

This demonstrates that the rhythmic auditory stimulation enhanced gait training group final results show a significant improvement in mobility.

## DISCUSSION

The goal of the study is to determine if rhythmic auditory stimulation enhanced gait training and Frenkel exercises are useful for treating geriatric population with gait impairement especially gait speed.

This research extends the application of RAS to the geriatric context, aiming to contribute insights into its potential advantages for mobil-

Table 1. Pre and post-test values for RAS group A and Frenkel exercise (10 m walk test)

| GROUP | | MEAN ± SD | T-TEST | P-VALUE |
|---|---|---|---|---|
| RAS | PRE-TEST | 23.12 ±4.85 | 5.2627 | <0.0001 |
| | POST-TEST | 16.23± 3.28 | | |
| Frenkel | PRE-TEST | 25.68±4.12 | 5.4333 | <0.0001 |
| | POST-TEST | 19.12± 3.49 | | |

Table 2. Comparison pre-test and post-test value of RAS group and Frenkel group (time up and go test)

| GROUP | | MEAN ± SD | T-TEST | P-VALUE |
|---|---|---|---|---|
| RAS | PRE-TEST | 27.95±4.97 | 5.500 | <0.0001 |
| | POST-TEST | 20.15± 3.94 | | |
| Frenkel | PRE-TEST | 29.68±4.97 | 4.2759 | <0.0001 |
| | POST-TEST | 23.12± 4.73 | | |

Table 3. Comparison post-test value of Frenkel group and RAS (10m walk test, time up and go test)

| POST TEST | | MEAN ± SD | T-TEST | | P-VALUE |
|---|---|---|---|---|---|
| 10m walk test | RAS | 16.23±3.28 | 5.2627 | 2.6985 | 0.0103 |
| | Frenkel | 19.12±3.49 | 5.4333 | | |
| Time up and go test | RAS | 20.15±3.94 | 5.500 | 2.1576 | 0.0373 |
| | Frenkel | 23.12±4.73 | 4.2759 | | |

ity improvement in the elderly. The involvement of either rhythmic stimuli or Frenkel training is considered in our study and findings on RAS also aligns with MH Thaut *et al*. (1997), where comparison to gait training without rhythmic facilitation, gait training with rhythmic facilitation shows greatly increased stride length and gait velocity. In comparison to the control group, rhythmic facilitation also resulted in a discernible improvement in stride symmetry.[17]

This study, the utilization of rhythmic auditory stimulation (RAS) for gait training enhancement in the geriatric population is being investigated so the effectiveness of RAS in improving mobility is being explored, while Soo Ji Kim *et al*. (2011) highlighted the benefits of RAS for addressing motor coordination challenges in individuals with cerebral palsy (CP), the causation of RAS is attributed to repetitive rhythmic sound patterns that increase the excitability of spinal motor neurons via the reticulospinal pathway, enabling the entrainment of axial and proximal movement in response to a specific motor command.[18]

Conklyn D *et al*. (2010): The frequency of the rhythmic auditory signal in the aforementioned investigations was chosen based on the subjects' desired gait cadence. Nonetheless, it seemed that a noteworthy rise in the rhythmic auditory cue frequency cadence in this investigation was 10% greater than the individuals' favored tempo. The study's findings corroborated those showing that MS patients' stride length, cadence, and gait speed significantly improved.[19]

As per a study by Roerdink *et al*. (2009) in stroke rehabilitation, auditory stimulation is used to increase the reticulospinal pathway's ability to excitably sense spinal motor neurons, hence lowering the time it takes for a tissue to respond to a nerve signal. When sensory stimulation is applied rhythmically, in sync with the motor response, and in harmony with walking performance, it can be a useful tool for improving functional movement.[20]

The 10-Meter Walk Test (10MWT) is widely used to assess gait speed, a key indicator of functional mobility and rehabilitation outcomes. However, there are inconsistencies in the literature regarding whether the entire 10 meters or only the middle 6 meters should be timed. This discrepancy is due to variations in protocol design, study objectives, and historical methodologies.

The most widely accepted approach, supported by Fritz & Lusardi (2009) and Bohannon (1997), recommends timing only the middle 6 meters, excluding the first 2 meters for acceleration and the last 2 meters for deceleration. This ensures that gait speed is measured at a steady-state pace, reducing variability introduced by changes in walking momentum. Studies have demonstrated that using the 6-meter timing approach provides higher test-retest reliability and better clinical applicability in stroke rehabilitation, Parkinson's disease, and older adult populations. Given these considerations, the 6-meter timing method remains the preferred protocol for assessing functional gait speed while whole 10 meter timing method best in endurance.[21,22]

## CONCLUSION

Rhythmic auditory stimulation and Frenkel exercise are the better interventions to treat and improve the gait and mobility in the geriatric

population. From the data analysis and results obtained in the study, it concluded that rhythmic auditory stimulation group have better improvement than the Frenkel exercise group.

**CONFLICT OF INTEREST**
The authors have no conflict of interest.

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**ETHICAL ASPECTS**
All participants submitted a consent form to be included in this study.

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# Polineuropatía amiloide familiar: Desafíos diagnósticos en un hombre de 78 años con polineuropatía e insuficiencia cardíaca

## *Familial Amyloid Polyneuropathy: Diagnostic challenges in a 78-year-old male with polyneuropathy and heart failure*

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## ABSTRACT

Transthyretin amyloidosis (ATTR) is a rare, progressive disorder caused by the accumulation of misfolded transthyretin (TTR) proteins in various tissues and organs, leading to the formation of amyloid deposits.

In ATTR, genetic mutations (hereditary form) or age-related changes (wild-type form), cause the TTR proteins to become unstable, misfold, and aggregate into amyloid fibrils. These amyloid deposits can affect multiple organs, most commonly the peripheral nerves and the heart.

Symptoms vary depending on the organs involved, being heart failure and/or polyneuropathy the predominant. The treatment aims at stabilizing the TTR, reduce amyloid production, or remove amyloid deposits.

The authors present a case of a 78-year-old man, with a recent onset of polyneuropathy and recurrent episodes of decompensated heart failure, in whom, the diagnosis of Familial Amyloid Polyneuropathy, a subtype of hereditary ATTR was made.

**Keywords:** Hereditary transthyretin amyloidosis, heart failure, familial amyloid polyneuropath.

## RESUMEN

La amiloidosis por transtiretina (ATTR) es un trastorno raro y progresivo causado por la acumulación de proteínas transtiretina (TTR) mal plegadas en diversos tejidos y órganos, lo que conduce a la formación de depósitos amiloides.

En la ATTR, las mutaciones genéticas (forma hereditaria) o los cambios relacionados con la edad (forma de tipo salvaje) provocan que las proteínas TTR se vuelvan inestables, se plieguen incorrectamente y se agrupen en fibrillas amiloides. Estos depósitos amiloides pueden afectar a múltiples órganos, siendo los más comunes los nervios periféricos y el corazón.

Los síntomas varían en función de los órganos afectados, siendo la insuficiencia cardíaca y/o la polineuropatía los más predominantes. El tratamiento tiene como objetivo estabilizar la TTR, reducir la producción de amiloide o eliminar los depósitos amiloides.

Los autores presentan el caso de un varón de 78 años, con un inicio reciente de polineuropatía y episodios recurrentes de insuficiencia cardíaca descompensada, en el que se diagnosticó polineuropatía amiloide familiar, un subtipo de ATTR hereditaria.

**Palabras clave:** Amiloidosis transtiretina hereditaria, insuficiencia cardíaca, polineuropatía amiloide familiar.

## INTRODUCTION

Amyloidosis is a heterogeneous disease, and results from the extracellular tissue deposition of fibrils composed of subunits of a variety of proteins. It can be either acquired or hereditary and may present as either a localized or systemic disease.

Hereditary transthyretin amyloidosis is an adult-onset, autosomal dominant disease produced by mutations in the *TTR* gene, which encodes the transthyretin (TTR) protein[1]. The TTR protein, which is normally produced by the liver, pathologically misfolds, aggregates into amyloid fibrils, and deposits in various tissues causing irreversible damage.[2]

The range of clinical symptoms vary extensively from neurological to cardiac. The phenotypic heterogeneity depends on many factors, such as specific TTR mutation site, geographical distribution, inheritance pattern, timing of onset, and epidemic/non-epidemic aggregation.

A few countries are endemic to the disease, with Portugal being one of them. In fact, Portugal has one of the highest prevalence rates of transthyretin amyloidosis in Europe. The condition is particularly widespread in northern regions such as Vila do Conde, Póvoa de Varzim, Serra da Estrela, and Figueira da Foz. The Val30Met variant, known as transthyretin familial amyloid polyneuropathy (ATTR-FAP), is the most frequent form of TTR amyloid and in 2016, the prevalence of TTR-FAP was 22.93 per 100,000 adult inhabitants.[3]

Lack of recognition of the disease, non-specific symptoms, and co-morbidities often leads to delayed diagnosis, which can be fatal, if untreated.

## CLINICAL CASE

A 78-year-old male patient with an ECOG of 3, presented to the Emergency Department with a history of shortness of breath and peripheral oedema. The patient had a known history of heart failure with preserved ejection fraction, with prior hospitalizations.

On physical examination, his vitals were: blood pressure of 85/45 mmHg, a heart rate of 62 bpm, and an oxygen saturation of 95%.

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He presented with anasarca. Laboratory tests showed mild inflammation, with a C-reactive protein level of 6 mg/dL. There was also evidence of acute-on-chronic kidney disease, indicated by a creatinine level of 1.65 mg/dL, compared to a baseline creatinine of 1-1.1 mg/dL. The urine culture revealed *Klebsiella pneumoniae* ESBL+ (Extended-Spectrum Beta-Lactamase positive), and meropenem was administered for seven days. The patient was admitted to the Internal Medicine Ward for heart failure management.

During his stay, the patient reported progressive loss of strength in both upper and lower limbs, along with recurrent episodes of urinary retention at home. Tetraparesis with gait apraxia was observed. Given the decompensated heart failure and neurological findings, an extensive workup was initiated.

Transthoracic echocardiography revealed heart failure with preserved ejection fraction (LVEF 68%), severe concentric hypertrophy of the left ventricular walls, and images suggestive of myocardial infiltration in the interventricular septum, along with type III diastolic dysfunction. Blood tests, including blood and urine electrophoresis and immunofixation, as well as the serum free light chain assay, were normal. A biopsy of the minor salivary glands showed amyloid deposits. Electromyography of the lower limbs indicated axonal sensorimotor polyneuropathy.

Due to suspicion of ATTR, $^{99m}$Tc-DPD scintigraphy and genetic testing were conducted. The scintigraphy revealed abnormal and increased uptake of the tracer in the myocardium (Figures 1 and 2), and the genetic testing identified the p.Val30Met variant in the TTR gene in a heterozygous state. With a diagnosis of Familial Amyloid Polyneuropathy (FAP), the patient was referred to a specialized center, however given the advanced stage of the disease, best supportive care was offered.

## DISCUSSION

Familial Amyloid Polyneuropathy remains a challenging diagnosis due its diverse clinical presentations.

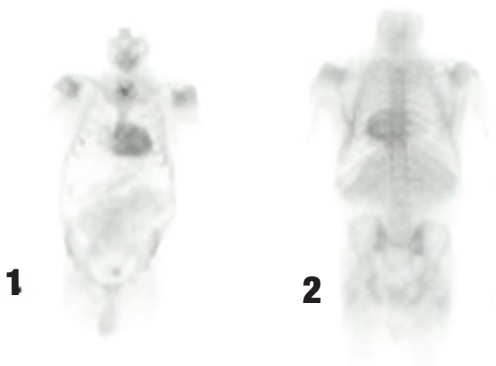
In the last few decades, new mutation types were identified, and to this day, more than 120 TTR gene mutations were described, with the Val30Met being the most common[5]. With the identification of new mutation types, we were able to understand that the presenting symptom, age at onset, type of the neuropathy and additional systemic involvement can be highly variable.

Age at onset is also affected by the geographic area. It is remarkably earlier in patients from endemic regions such as Portugal and Japan, compared to Sweden where late-onset disease predominates.[7]

Length dependent sensory-motor neuropathy with autonomic involvement is the hallmark of the disease. Amyloid typically first affects small nerve fibers altering pain and temperature sensation. Motor deficit appears in the distal lower limbs, and walking becomes increasingly difficult with loss of balance and steppage gait.[6]

In patients with early-onset disease, is not uncommon, for quick deterioration due to autonomic dysfunction and rapid progression of the

Figures 1 (anterior) and 2 (posterior) body views, showing the increased uptake of the tracer ($^{99m}$Tc-DPD) in the myocardium.




sensory-motor deficit. On the other hand, older patients, the polyneuropathy progresses slowly, often with a cardiac involvement but with less autonomic dysfunction.[7]

Cardiac involvement is the most common extra-neurological manifestation. Heart failure induced by restrictive cardiomyopathy is frequently observed in these patients, together with electrical disturbances. Commonly, findings such as low voltage in electrocardiogram, aortic stenosis and increased ventricular wall thickness in echocardiogram are common.

For its diagnosis genetic testing for TTR is essential. The absence of a pathologic mutation excludes TTR-FAP. The presence of symptoms and documentation of amyloid deposits in tissue, is also important to distinguish symptomatic patients from carriers.

By publishing this clinical case, the authors intend to emphasize the complex presentation with decompensated heart failure, and progressive tetraparesis, coupled with imagiologic and histological findings, that initially pointed to multiple possible diagnoses.

The case highlights several key aspects of FAP, particularly how it mimics more prevalent conditions in older adults. The patient's echocardiogram findings were indicative of restrictive cardiomyopathy, which can be easily mistaken for age-related hypertensive heart disease or hypertrophic cardiomyopathy. This underscores the importance of maintaining a high index of suspicion for systemic amyloidosis in elderly patients with unexplained cardiac or neurological symptoms.

Furthermore, the onset and progression of FAP can vary widely depending on the specific TTR mutation and patient demographics. The p.Val30Met mutation, as seen in this patient, is the most common mutation associated with FAP. It typically presents earlier in endemic regions, but in this case, the late onset of disease and the severe systemic involvement reflects the variability seen in non-endemic areas. The patient's advanced age and the late-stage diagnosis (stage 3) are consistent with the slower disease progression often seen in older patients.

## CONCLUSION

In conclusion, this case highlights the importance of considering hereditary ATTR as a potential diagnosis in elderly patients presenting with unexplained polyneuropathy and heart failure. Early recognition and diagnosis are crucial for appropriate management and treatment, as timely intervention can help stabilize the condition and potentially improve patient outcomes.

**CONFLICT OF INTEREST**
The authors declare that they have no conflict of interests.

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**ETHICAL ASPECTS**
All participants submitted a consent form to be included in this study.

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# Poliserositis: un desafío diagnóstico

## *Polyserositis: a diagnostic challenge*

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## ABSTRACT

Polyserositis, the inflammation of multiple serous membranes, presents a diagnostic challenge with etiologies ranging from neoplasms and autoimmune diseases to infections. Many cases remain idiopathic.

We describe a 72-year-old woman presenting with cardiac tamponade and bilateral pleural effusion, confirmed as exudative. Extensive workup excluded neoplastic, infectious, and autoimmune causes, leaving a recent SARS-CoV-2 mRNA vaccination as the only significant factor. A vaccine-induced systemic inflammatory response was hypothesized, with full recovery achieved using anti-inflammatory therapy.

This case highlights diagnostic complexity in polyserositis and suggests a rare potential adverse effect of mRNA vaccination.

**Keywords:** Systemic inflammatory response, mRNA vaccine, polyserositis.

## RESUMEN

La poliserositis, inflamación de múltiples membranas serosas, representa un desafío diagnóstico con etiologías que van desde neoplasias y enfermedades autoinmunes hasta infecciones. Muchos casos permanecen como idiopáticos.

Describimos el caso de una mujer de 72 años que presentó taponamiento cardíaco y derrame pleural bilateral, confirmado como exudativo. Un exhaustivo estudio diagnóstico excluyó causas neoplásicas, infecciosas y autoinmunes, dejando como único factor significativo una reciente vacunación con ARNm contra el SARS-CoV-2. Se hipotetizó una respuesta inflamatoria sistémica inducida por la vacuna, con recuperación total mediante tratamiento antiinflamatorio.

Este caso resalta la complejidad diagnóstica de la poliserositis y sugiere un raro efecto adverso potencial de la vacunación con ARNm.

**Palabras clave:** Respuesta inflamatoria sistémica, vacuna de ARNm, poliserositis.

## INTRODUCTION

Polyserositis, defined as the concurrent inflammation of multiple serous membranes (pleura, pericardium, peritoneum), is a rare condition often presenting with exudative effusions[1,2]. Its diagnosis is challenging due to nonspecific clinical manifestations and diverse etiologies, including neoplasms, autoimmune disorders, and infections. In some cases, no cause is identified, leading to an idiopathic classification[1,2]. Recent reports suggest that vaccines, including mRNA-based COVID-19 vaccines, may trigger systemic inflammatory responses resembling autoinflammatory or autoimmune conditions[3-7]. This report aims to contribute to this emerging body of knowledge by detailing a rare case of vaccine-associated polyserositis.

## CLINICAL CASE

We present the case of a 72-year-old woman with no significant past medical history, who presented to the emergency department with a 3-day history of left pleuritic chest pain radiating to the shoulder, along with dyspnea on minimal exertion. She reported a 5 kg weight loss in the past month but denied fever, night sweats, gastrointestinal symptoms, or signs and symptoms of infection. Physical examination revealed dehydration, no fever, low blood pressure (99/55 mmHg), and diminished heart and breath sounds.

Initial laboratory tests show mild anemia, normal leukocyte count and low grade of inflammation. The complete initial laboratory tests, including autoimmunity and virology, showed no other specific changes and they are summarized in Table 1. Electrocardiogram (ECG) revealed low voltage QRS complexes without electrical alternans. A chest X-ray showed an enlarged cardiothoracic ratio and bilateral pleural effusions (Figure 1). An echocardiogram demonstrated a severe circumferential pericardial effusion causing right heart chamber collapse, consistent with cardiac tamponade. An emergent pericardiocentesis was been done, draining 110 mL of serohematic fluid. Post-procedure echocardiogram confirmed residual pericardial effusion.

In acute phase, a treatment with colchicine at 0.5 mg three times daily, ibuprofen 600 mg twice and prednisolone 40 mg once daily were initiated. Given the absence of evidence of an ative infection, it was decided not initiate empirical antibiotic therapy. The patient was hospitalized for further diagnostic workup, which included:

- SARS-CoV-2 RT-PCR: Negative.
- Serial blood cultures: Negative.
- Mycobacterial cultures (blood and pleural and pericardial fluids): Negative.
- Urine: Negative urine culture; BK-direct and BK-PCR negative.
- Fecal analysis: Negative coproculture. Negative fecal calprotectin. Negative parasitological analysis.
- Body CT scan: Pericardial and bilateral pleural effusion without other notable findings (Figure 2).
- Upper digestive endoscopy and colonoscopy: Normal.
- Mammography, breast ultrasound, and thyroid ultrasound: Normal.
- FDG-PET scan: No hyperfixation detected.
- Bronchoscopy: Normal findings.
- Bone marrow biopsy and myelogram: Normocellular marrow, with no changes in lineages and no signs of involvement by lymphocyte or plasma cell neoplasia. Negative myeloculture.

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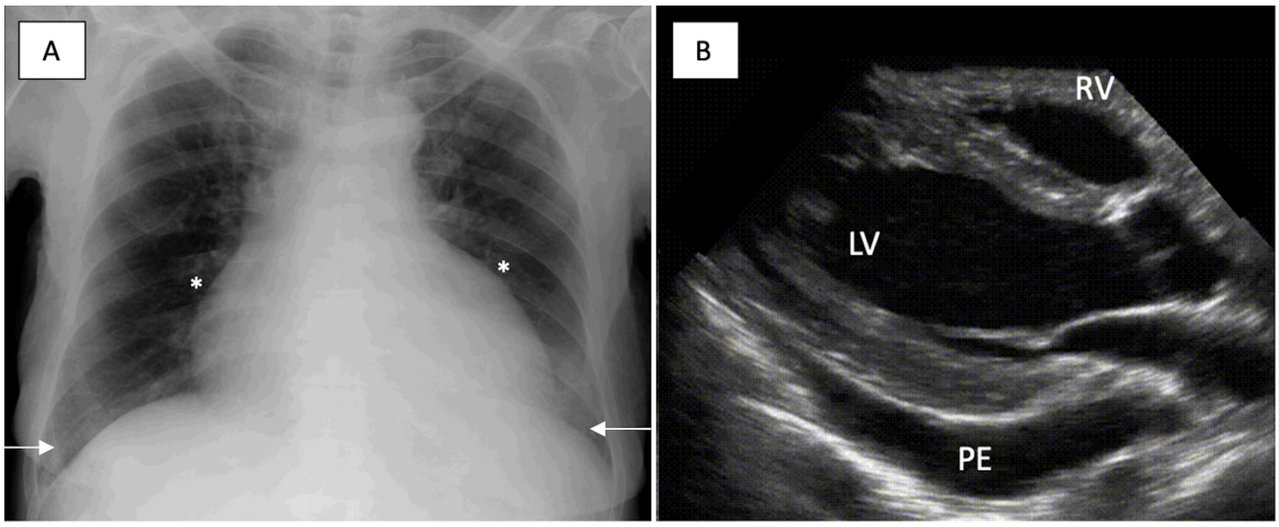



Figure 1. A. Chest X-ray at admission. Increased cardiothoracic ratio (asterisks) and bilateral pleural effusion (white arrows). B. Transthoracic echocardiogram at admission. PE – Pericardial effusion. LV – Left ventricle. RV – Right ventricle.

- Pericardial fluid analysis: 3000 cells with 60% neutrophils and 40% lymphocytes. Negative culture. ADA negative, with BK-direct and BK-PCR negative. Cytological with inflammatory aspects, predominance of neutrophils. Absence of neoplastic cells.
- Pleural fluid analysis: 238 cells with 14% neutrophils and 3% lymphocytes. Negative culture. ADA negative. BK-direct and BK-PCR negative. Cytological with reactive mesothelial cells, aspects suggestive of a reactive inflammatory process, with histiocytes and lymphocytes. Absence of neoplastic cells.
- Bronchoalveolar lavage and respiratory panel (*Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Bordetella pertussis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*): Negative for infections and neoplastic cells.

Both effusions were classified as exudates by Light's criteria, with inflammatory profiles. Cytological examination confirmed reactive mesothelial cells without neoplastic features. After ruling out neoplastic, autoimmune, and infectious causes, the recent administration of an mRNA SARS-CoV-2 vaccine 28 days prior was the only significant finding in the patient's history. It was hypothesized that the patient's polyserositis was triggered by a systemic inflammatory response to this mRNA vaccine, due this temporal association.

Inflammatory markers improved within a few days of anti-inflammatory treatment that included colchicine at 0.5 mg three times daily, ibuprofen 600 mg twice daily during two weeks and prednisolone 40 mg once a day during first 10 days, follow by three weeks of tapering regime. She was discharged after 30 days of hospitalization. An echocardiogram at discharge showed no significant pericardial effusion, and chest ultrasound confirmed resolution of pleural effusions. Laboratory tests at discharge are discriminated in Table 1.

The patient was discharged on a regimen of colchicine 0.5 mg twice daily during three months, with folic acid and vitamin D supplements. Six months later, she remained asymptomatic, with weight gain and no recurrence of symptoms or sequelae. Follow-up echocardiogram and chest X-ray were normal (Figure 3), and laboratory tests remained stable (Table 1).

## DISCUSSION

Polyserositis remains an underdiagnosed condition, likely due to its nonspecific symptoms and overlapping features with other diseases. This case emphasizes the need for clear diagnostic criteria and further prospective studies to better understand its etiology and prevalence, as many cases are ultimately labeled idiopathic.[1,2]

Serositis might be attributed to numerous etiologies including infection, malignancy, uremia, or autoimmune disease[1]. In this patient, an exhaustive diagnostic workup excluded common causes such as neoplasia, infections, and autoimmune diseases. Pericardial effusion and pleural effusion were lymphocytes-predominant exudates and polymorphonuclear leukocytes could be yielded from them, serving as evidence of local inflammation of the pericardium and the pleura.

Neoplastic processes are a frequent cause of polyserositis, particularly lymphomas and metastatic tumors, which can invade serous membranes or induce secondary inflammatory effusions[1,2]. This was ruled out based on imaging, PET scan, and cytological analyses of all effusions, that didn't yield any malignant cell.

Infectious diseases (such as viral or bacterial infections) were also excluded. Viral infections, such as SARS-CoV-2, Epstein-Barr virus, and cytomegalovirus, can induce inflammation of serous membranes[1,2,5]. The normal white blood cell count, low level of C-reactive protein, negative procalcitonin value and all relevant cultures and serologies were all negative, made a primary infectious etiology less likely. High adenosine deaminase (ADA) levels in pleural or pericardial fluid are highly suggestive of tuberculous serositis. In this case, ADA levels were normal, and tuberculosis was excluded by negative PCR and culture results, further narrowing the differential diagnosis.

Autoimmune diseases, another key etiology, are commonly linked to systemic serositis, as seen in conditions like systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. The patient had no family history or past history of an autoimmune disease, and lacked clinical and laboratory evidence of autoimmune diseases. Autoimmune polyserositis is often associated with elevated markers such as antinuclear antibodies, anti-double stranded DNA antibodies,

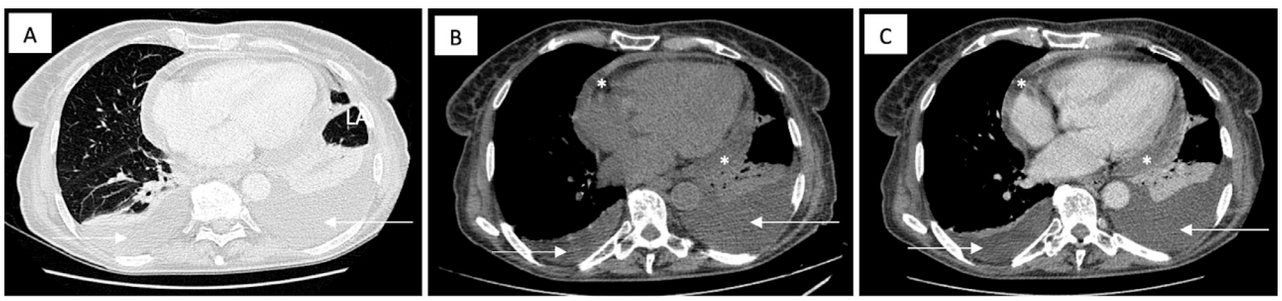



Figure 2. Body CT-Scan (A – Lung window. B – Without contrast. C – With contrast).
Asterisks - Circular pericardial effusion. White arrows - Bilateral pleural effusion.

or anti-SSA/SSB antibodies, none of which were present in this case. Finally, she had no typical presentation of any autoimmune diseases such as skin rash, muscle weakness, skin thickening, telangiectasia, oral ulcer, arthralgia, or Raynaud's phenomenon, so anyone autoimmune condition could be diagnosed with current criteria.

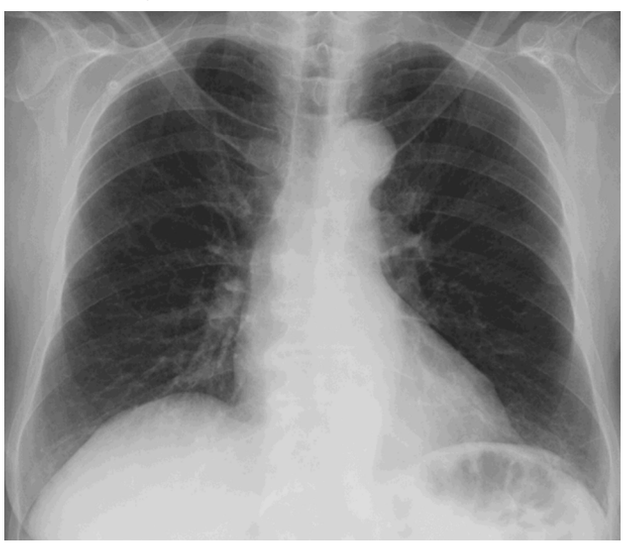
Thyroid function was normal, ruling out hypothyroidism. N-Terminal Pro–B-Type Natriuretic Peptide values are normal and congestive heart failure effusion usually is classified as a transudate, making the heart failure related serositis improbable. Finally, urea values are normal, so uremic serositis don't explained the clinical findings.

Idiopathic cases of serositis are common but reflect limitations in understanding its underlying mechanisms. The temporal association between symptom onset and mRNA SARS-CoV-2 vaccination strongly suggests a vaccine-induced inflammatory response. While these vaccines have shown high efficacy and safety profiles, some individuals develop autoimmune or autoinflammatory reactions post-vaccination. Several mechanisms have been proposed to explain post-vaccination inflammation of serous membranes, though none are fully understood. Proposed mechanisms include:

The temporal association between symptom onset and the recent administration of the SARS-CoV-2 mRNA vaccine strongly suggests a vaccine-induced inflammatory response as the most plausible explanation. Vaccines, including those for SARS-CoV-2, are known to trigger immune responses, and proposed mechanisms for this include hyperactivation of the immune system, cytokine overexpression, and molecular mimicry[5]. The robust immune response elicited by mRNA vaccines may cross-react with host proteins, leading to localized or systemic inflammation[3,5]. Additionally, lipid nanoparticles used in the formulation may activate the NLRP3 inflammasome, promoting the overproduction of pro-inflammatory cytokines like IL-1β[3,5]. Molecular mimicry may also play a role, with vaccine-induced antibodies targeting host antigens and triggering serosal inflammation[3,5]. Although these mechanisms remain hypothetical, similar inflammatory responses have been documented in isolated cases of polyserositis associated with vaccines, including those for SARS-CoV-2[3-5]. Although rare, vaccine-associated polyserositis has been described in isolated cases, supporting the hypothesis of immune dysregulation.[5]

Treatment in this case followed standard protocols and involves anti-inflammatory agents, such as colchicine, nonsteroidal anti-inflammatory drugs, and corticosteroids, which were effective in this case[8]. As proposed mechanisms for serositis induced by mRNA vaccine involves a disproportionate and uncontrolled activation of the inflammasome, with IL-1β-driven inflammation, some patients can develop

Figure 3. Chest X-ray at six months follow-up.
Absence of pleural effusion and normal cardiothoracic ratio.



recurrent polyserositis similar to those observed in some auto-inflammatory diseases, like Familiar Mediterranean Fever. In that cases, conventional anti-inflammatory therapies could be not able to control the disease and prevent relapses, so is important to consider optimized therapeutics like IL-1 inhibitors (anankira or canakinumab) that are effective agents in cases of persistent or severe polyserositis. Immunosuppressants can also be considered if autoimmune manifestations occur, like azathioprine or human immunoglobulin.[8]

It is important to say that there may be an association between COVID-19 vaccination and autoimmune and inflammatory diseases. Some autoimmune disorders seem to be more common than others and vaccines and SARS-CoV-2 may induce autoimmunity through similar mechanisms[6,9]. The most common diseases associated with new onset events following vaccination were immune thrombocytopenia, myocarditis, and Guillain-Barré syndrome. In contrast, immune thrombocytopenia, psoriasis, IgA nephropathy, and systemic lupus erythematosus were the most common illnesses associated with relapsing episodes.[5]

Polyserositis has also been linked to other vaccines, including pneumococcal and influenza vaccines. With the rollout of COVID-19 vaccination, various adverse effects have been reported, including myocarditis and pericarditis. These, while rare, are more commonly observed in younger males shortly after vaccination. Our literature search revealed only two cases of polyserositis associated with SARS-

Table 1. Analytical study at hospital admission, at discharge date and at 6 month-follow up after hospital discharge

| | At admission | At discharge | At 6 month-follow up |
|---|---|---|---|
| Hemoglobin (g/dL) | 11,4 | 11,0 | 12,9 |
| Mean corpuscular volume (fL) | 94,7 | 92,4 | 93,7 |
| Mean corpuscular hemoglobin concentration (g/dL) | 34,3 | 33,4 | 34,2 |
| Leucogram | Normal | Normal | Normal |
| Platelets (x10^9/L) | 392 | 342 | 301 |
| Sedimentation rate (mm) | 102 | 42 | 6 |
| International Normalized Ratio | 1,2 | 1,1 | 1,0 |
| Urea (mg/dL) | 18,9 | 41,1 | 51,4 |
| Creatinine (mg/dL) | 0,75 | 0,82 | 0,56 |
| Ionogram | Normal | Normal | Normal |
| High-sensitivity troponin | Negative | - | - |
| Angiotensin converting enzyme (U/L) | 59,3 | - | - |
| Aspartate/Alanine aminotransferases | 16/14 | 23/20 | 37/22 |
| Bilirrubin levels | Normal | Normal | Normal |
| Alkaline phosphatase | 66 | 70 | 56 |
| Gamma-glutamyl Transferase | 13 | 12 | 10 |
| C-reactive protein (mg/dL) | 6,7 | 1,9 | 0,23 |
| Thyroid stimulating hormone (mU/L) | 1,85 | - | 1,87 |
| Albumine | 3,7 | 3,5 | 3,9 |
| Protein electrophoresis | Policlonality | - | Normal |
| N-terminal pro B-type natriuretic peptide (pg/mL) | 931 | 123 | 89 |
| Ferritin (ng/mL) | 441 | - | 67 |
| Folic acid (ng/ml) | 2,09 | - | 5,4 |
| Cianocobalamin (pg/mL) | 416 | - | 567 |
| Immunoglobulin A (mg/dL) | 166 | - | - |
| Immunoglobulin G (mg/dL) | 822 | - | - |
| Immunoglobulin M (mg/dL) | 89 | - | - |
| Complement levels (C3, C4) | Normal | - | Normal |
| Beta-2 Microglobulin (ng/mL) | 2410 | - | - |
| Alpha-1 Antitrypsin (mg/dL) | 298 | - | - |
| Rheumatoid factor | Negative | - | Negative |
| Anti-cyclic citrullinated peptide | Negative | - | Negative |
| Anti-double stranded DNA antibodies - IFI | Negative | - | Negative |
| Anti-nuclear and anti-cytoplasmatic antibodies - IFI | Negative | - | Negative |
| Toxoplasmosis IgG e IgM | Negative/Negative | - | - |
| Rubella IgG/IgM | Positive/Negative | - | - |
| Cytomegalovirus IgG/IgM | Positive/Negative | - | - |
| Epstein Barr IgG/IgM | Positive/Negative | - | - |
| Herpes Simplex 1 IgG/IgM | Positive/Negative | - | - |
| Herpes Simplex 2 IgG/IgM | Negative/Negative | - | - |
| Parvovirus IgG/IgM | Negative/Negative | - | - |
| Venereal Disease Research Laboratory (VDRL)/ Rapid Plasma Reagin (RPR) | Non reative | - | - |
| Human immunodeficiency virus | Negative | - | Negative |

| | | | |
|---|---|---|---|
| Hepatitis B virus antigen HBs | Negative | - | - |
| Hepatitis B virus antibody HBc | Negative | - | - |
| Hepatitis B virus antibody HBs | Positive | - | - |
| Hepatitis C virus Antibody | Negative | - | - |
| Hepatitrs A vírus IgG/IgM | Positive/Negative | - | - |
| Interferon Gama Release Assay | Negative | - | - |
| Urinalysis | Normal | - | Normal |

CoV-2 mRNA vaccination: one, in a 65-year-old man; and another, in a 94-year-old-man[3,6,7]. However, we believe that this condition may be underreported or misdiagnosed, given its complexity and the difficulty in establishing a definitive etiology in many cases.

With this report, we illustrated the diagnostic challenges posed by polyserositis in clinical practice. The patient's age and clinical presentation would typically suggest more common causes such as neoplastic or autoimmune conditions, like lupus or rheumatoid arthritis, yet thorough investigation led to the exclusion of these. The temporal association between the onset of symptoms and vaccination, coupled with the exclusion of other causes, strongly supports vaccine-induced polyserositis as the most plausible diagnosis.

This case underscores the importance of considering recent vaccination in patients presenting with polyserositis, particularly when other causes have been excluded. While the association between vaccination and inflammatory responses is rare, its recognition is critical to guiding management. Further research is needed to elucidate the pathophysiological mechanisms of vaccine-induced inflammation, to establish treatment algorithms and to identify individuals predisposed to such events. Despite this extremely rare adverse effect, the benefits of SARS-CoV-2 vaccination far outweigh the risks, given its proven efficacy in preventing severe COVID-19 disease.

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**CONFLICT OF INTEREST**
All authors declare that there are no conflicts of interest in carrying out this work.

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**ETHICAL ASPECTS**
The patient's written consent was obtained for publication of this case.

# Enfermedad de Darier con afectación esofágica, un caso clínico

## *Darier disease with esophageal involvement, a case report*

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## ABSTRACT

Darier's disease (DD) is an autosomal dominant dermatosis caused by a mutation in the ATP2A2 gene at 12q23-24, characterized histologically by acantholysis and dyskeratosis. It is a rare disease, distinguished by the presence of red-brown keratotic papules, typically distributed follicularly, palm-plantar, on nails, and less frequently in the oral mucosa.

We report the case of a 70-year-old woman with a medical history of neuropsychiatric disorders, chronic kidney disease (CKD), anemia of CKD, diabetes mellitus type 2, and hypertensive heart disease. Upon admission, she presented with widespread hyperkeratotic skin lesions and erythronychia. A skin biopsy confirmed the diagnosis of DD. An upper gastrointestinal endoscopy revealed extensive esophagitis, histologically suggestive of an association with DD.

Some extracutaneous manifestations have been described, mostly neuropsychiatric disorders, with only a few cases of esophageal mucous membrane involvement. This appears to be due to the pleiotropic effect of mutations in ATP2A2 in other cells.

**Keywords:** Darier's disease, acantholysis, dyskeratosis, esophageal involvement.

## RESUMEN

La enfermedad de Darier (ED) es una dermatosis autosómica dominante causada por la mutación del gen ATP2A2 en 12q23-24, caracterizada histológicamente por acantólisis y disqueratosis. Es una enfermedad rara, caracterizada por la presencia de pápulas queratósicas marrón rojizo de distribución folicular, palmo-plantar, ungueal y menos frecuentemente en la mucosa oral.

Presentamos el caso de una mujer de 70 años con antecedentes de trastornos neuropsiquiátricos, enfermedad renal crónica, anemia de CKD, diabetes mellitus tipo 2 y cardiopatía hipertensiva. A su ingreso presentó lesiones cutáneas hiperqueratósicas diseminadas y eritroniquia. La biopsia cutánea confirmó el diagnóstico de ED. La endoscopia digestiva alta reveló una esofagitis extensa, histológicamente a favor de una asociación con ED.

Se han descrito algunas manifestaciones extracutáneas en la ED, la mayoría trastornos neuropsiquiátricos, y en pocos casos se ha reportado afectación de la mucosa esofágica. Esto parece ser debido al efecto pleiotrópico de las mutaciones en ATP2A2 en otras células.

**Palabras clave:** Enfermedad de Darier, acantólisis, disqueratosis, afectación esofágica.

## INTRODUCTION

Darier's disease (DD) is an autosomal dominant dermatosis caused by a mutation in the ATP2A2 gene at 12q23-24, characterized histologically by acantholysis and dyskeratosis. It is a rare disease, distinguished by the presence of red-brown keratotic papules, typically distributed follicularly, palm-plantar, on nails, and less frequently in the oral mucosa.

## CASE REPORT

A 70-year-old Portuguese woman with a significant medical history of neuropsychiatric disorders (schizophrenia and bipolar disorder), chronic kidney disease (CKD) stage 3b, anemia of CKD, diabetes mellitus type 2, arterial hypertension, hypertensive heart disease, and a family history of skin disorders since childhood. Since DD is an autosomal dominant genetic disease, we investigated the family history and found that the patient's father, aunt, both daughters, and a grandson had similar skin lesions. Extracutaneous manifestations were unknown in these family members.

She was admitted to our hospital's emergency department following a lumbar trauma after a fall. After clinical evaluation and laboratory workup, she was transferred to the Internal Medicine department with the following diagnoses: iron deficiency anemia, acute on chronic renal disease, hyperkalemia, acute on chronic heart failure, and exacerbating skin lesions characterized by keratotic, crusted papules with a greasy, warty texture, predominantly on the body, upper and lower limbs, along with V-shaped nails and papules with a central depression on the lips and oral mucosa.

After addressing the acute issues, we performed a lesional skin biopsy, which showed the following histological findings: epidermis with mild acantholysis, foci of acantholysis with suprabasal clefts, and dermis with a lymphocytic infiltrate (Figure 1), confirming the diagnosis of DD.

For further evaluation of iron deficiency anemia and the extent of oral mucosal lesions, an upper gastrointestinal endoscopy was performed. This revealed grade D peptic esophagitis with areas of hyperkeratotic lesions. Biopsy specimens were taken from the upper esophagus and gastroesophageal junction. The histological findings in the upper esophagus mucosa were similar to the skin biopsy, with acanthosis and papillomatosis, small areas of acantholysis, suprabasal clefts, and fibrino-leukocytic and necrotic exudates.

Histological findings in the gastroesophageal junction were more nonspecific, showing slight acanthosis and chronic inflammatory infiltrates without active dysplasia but with areas of metaplasia (Figure 2).

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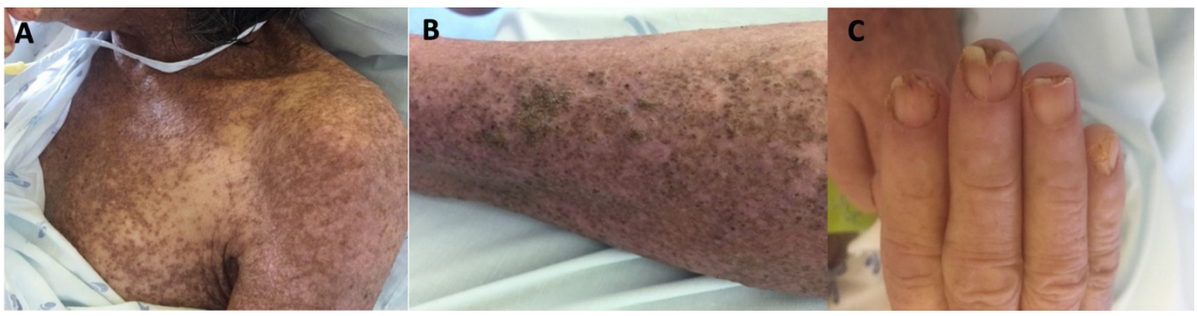


Figure 1. Extended confluent papular, hyperkeratotic lesions and crusted plaques on the body (A) and lower limbs (B). Notching of the free nail border: V-shaped nails (C).

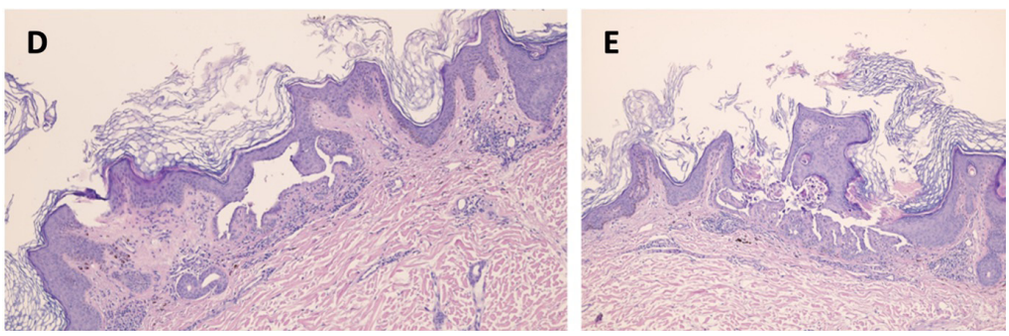


Figure 2. Histological examination of the lesional skin showing mild acantholysis, foci of acantholysis with suprabasal clefts, and dermis with a lymphocytic infiltrate (D, E).

The patient and her family were referred to the dermatology and gastroenterology departments for further management and genetic counseling.

## DISCUSSION

Some extracutaneous manifestations of Darier's disease have been described, with neuropsychiatric disorders being the most common. However, only a few cases have documented esophageal mucous membrane involvement. This could be due to the pleiotropic effect of ATP2A2 mutations in other cells. The ATP2A2 gene encodes the calcium ATPase pump (SERCA2b) in the endoplasmic reticulum, which is present in all body cells, suggesting that this genetic disorder could potentially induce extracutaneous manifestations.

We present the case of a woman with a delayed diagnosis of her skin condition, which also involved the esophagus and revealed areas of metaplasia. Some studies have suggested an association between mutations in the ATP2A2 gene and the development of squamous cell carcinoma in patients with esophageal involvement. In this patient, the findings of metaplasia prompted closer monitoring due to a higher risk of esophageal cancer. Unfortunately, the patient passed away, and we were unable to extend the genetic study to all family members.

This case is one of the few published instances of Darier disease (DD) with documented extracutaneous involvement, highlighting that DD is not solely a dermatological condition. Further investigation of other DD cases is necessary to elucidate the underlying pathological mechanisms of the disease, improve our understanding of its implications, and explore new therapeutic approaches.

**CONFLICT OF INTEREST**
The authors declare no conflicts of interest.

**SOURCE OF FUNDING**
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**ETHICAL ASPECTS**
The ethical standards of the Research Committee and the Declaration of Helsinki (1975) were followed during the conduct of this study.

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# Insuficiencia respiratoria aguda y bleomicina: un caso de neumonitis inducida por bleomicina

## *Acute Respiratory Failure and Bleomycin: A Case of Bleomycin-Induced Pneumonitis*

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## ABSTRACT

Bleomycin-induced pneumonitis (BIP) is a potentially life-threatening complication of bleomycin chemotherapy, particularly in older patients. We report a case of a 70-year-old female admitted to the hospital with acute respiratory failure, later diagnosed with bleomycin-induced pneumonitis. This case highlights the importance of early recognition and management of BIP, as well as the role of minimizing bleomycin exposure in high-risk populations.

**Keywords:** Respiratory failure, bleomycin, pulmonary toxicity.

## RESUMEN

La neumonitis inducida por bleomicina (NIB) es una complicación potencialmente mortal de la quimioterapia con bleomicina, particularmente en pacientes de edad avanzada. Presentamos el caso de una mujer de 70 años ingresada en el hospital con insuficiencia respiratoria aguda, que posteriormente fue diagnosticada con neumonitis inducida por bleomicina. Este caso destaca la importancia del reconocimiento y manejo precoz de la NIB, así como la necesidad de minimizar la exposición a bleomicina en poblaciones de alto riesgo.

**Palabras clave:** Insuficiencia respiratoria aguda, bleomicina, toxicidad pulmonar.

## INTRODUCTION

Bleomycin is a chemotherapeutic agent used primarily in the treatment of Hodgkin's lymphoma, testicular cancer, and other malignancies. Its cytotoxic effects are exerted through the induction of DNA strand breaks. While effective, bleomycin is known for its dose-limiting pulmonary toxicity, which occurs in approximately 10-20% of patients receiving the drug, with the risk increasing in the elderly population, those with pre-existing lung disease, or patients receiving higher cumulative doses[1,2]. This case discusses a 70-year-old woman undergoing bleomycin-based chemotherapy who presented with acute respiratory failure secondary to bleomycin-induced pneumonitis (BIP).

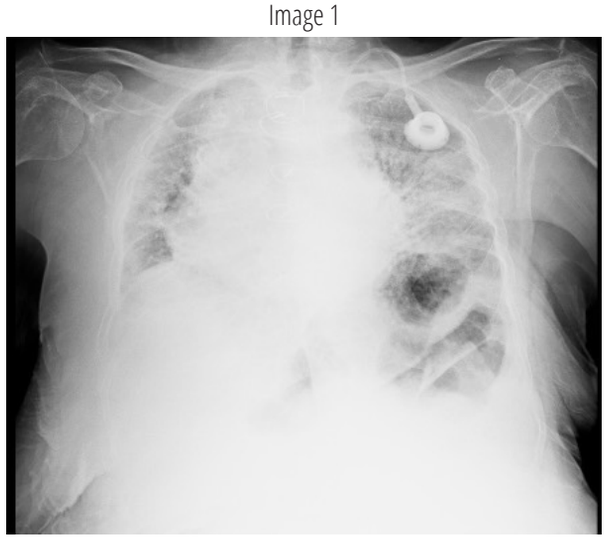
## CASE REPORT

A 70-year-old female with a history of stage IIIB Hodgkin's lymphoma was admitted to our hospital with acute onset of shortness of breath, orthopnea and hypoxemia. She had completed three cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine), with a cumulative bleomycin dose of 180 mg/m².

Her past medical history included hypertension and coronary artery bypass surgery, but no known history of lung disease or smoking. The patient reported a gradual increase in dyspnea over the preceding two weeks, which worsened acutely in the 24 hours prior to admission. She denied fever, chest pain, or hemoptysis.

On examination, she was tachypneic and she has an oxygen saturation of 88% on room air. Auscultation of the lungs revealed bilateral fine crackles, and there was no peripheral edema. Laboratory investigations showed no evidence of infection, with a normal white blood cell count and no bacterial growth in blood cultures. Arterial blood gases indicated Type 1 respiratory failure (PaO2 of 55 mmHg on 60% oxygen).

Image 1



A chest X-ray showed bilateral interstitial infiltrates (Image 1). Initially, these alterations were interpreted in context of acute heart failure and oriented with noninvasive mechanical ventilation, diuretic bolus and diuresis monitoring. Despite negative balance, and a positive response to diuretic therapy (given by urinary sodium and urine output at 6 hours), the patient presents a deterioration in her pulmonary function. In this context, a high-resolution computed tomography scan of the chest revealed diffuse ground-glass opacities with areas of consolidation, without evidence of pulmonary embolism or malignancy recurrence (Image 2). Given her recent chemotherapy and imaging findings, the diagnosis of bleomycin-induced pneumonitis was suspected. Bleomycin was immediately discontinued, and the patient was started on high-dose corticosteroids (methylprednisolone 1 mg/kg/day). Broad-spectrum antibiotics were initiated empirically but discontinued after a complete two sets of negative microbiologi-

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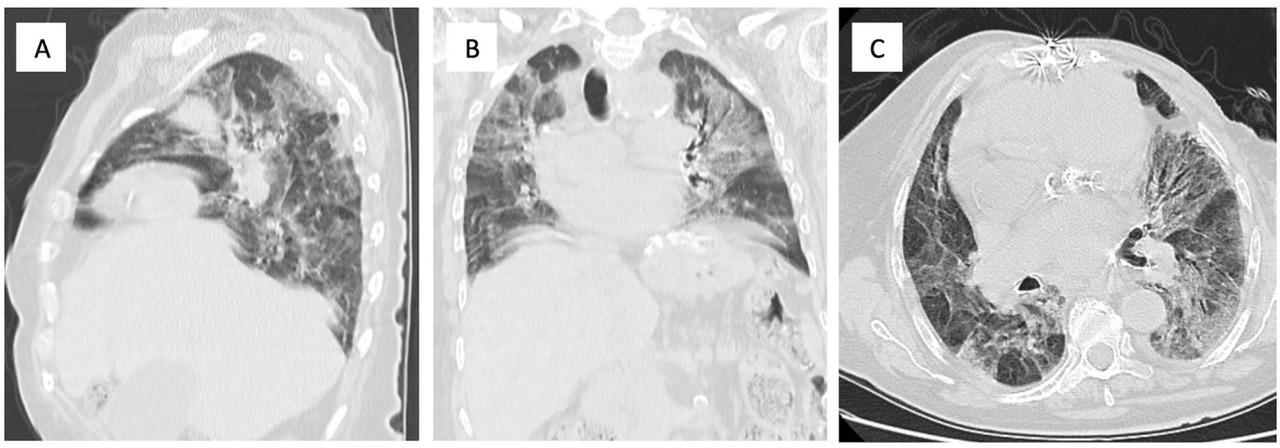


Image 2

cal tests. After two weeks with continued corticosteroid therapy, her respiratory function gradually improved. The corticosteroid dose was tapered over eight weeks, and the patient was discharged after twenty-eight days of hospitalization, with an ambulatory monitoring planning. At three months after discharge, a chest X-ray (Image 3) showed the resolution of practically all documented changes, without recurrence of symptoms.

## DISCUSSION

Bleomycin-induced pneumonitis (BIP) is an established complication of bleomycin therapy, with a reported incidence of 10-20%. The risk of BIP is influenced by cumulative dose, patient age, renal function, and concurrent oxygen therapy[3]. In this case, the patient received a total dose of 180 mg/m², which is within the range associated with higher risk for pulmonary toxicity, particularly in elderly patients.

The pathophysiology of BIP is not fully understood, but it is thought to involve direct cytotoxic effects on pulmonary endothelial cells and the generation of reactive oxygen species, leading to oxidative stress and inflammation.[4] The disease typically presents with progressive dyspnea, non-productive cough, and hypoxemia. Radiological findings include bilateral interstitial infiltrates and ground-glass opacities, as seen in our patient.[4]

The differential diagnosis of acute respiratory failure in cancer patients is broad and includes infection, pulmonary embolism, cardiogenic edema, and progression of the underlying malignancy. However, the absence of infection, malignancy recurrence, and the presence of characteristic imaging findings supported the diagnosis of BIP in this patient.

The management of BIP involves the immediate cessation of bleomycin and the administration of corticosteroids, which can reverse the inflammatory process. In severe cases, mechanical ventilation may be required, as was necessary for our patient. The role of corticosteroids is well established, though the optimal dose and duration remain debated[5]. In this case, prolonged steroid therapy with gradual tapering was effective. Given the significant morbidity and mortality associated with BIP, it is crucial to identify patients at risk and minimize bleomycin exposure when possible. Alternative chemotherapy regimens without bleomycin should be considered in elderly patients or those with predisposing factors for pulmonary toxicity.[6]

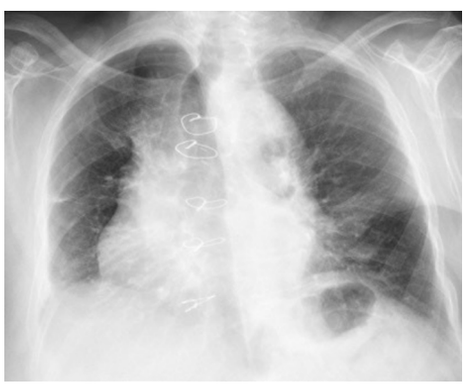

Image 3

This case highlights the potentially life-threatening pulmonary toxicity of bleomycin, especially in older patients. Prompt recognition and treatment with corticosteroids can improve outcomes, but BIP remains a challenging complication that requires close monitoring. In patients at high risk, such as the elderly or those with underlying pulmonary disease, bleomycin-sparing regimens should be strongly considered to reduce the likelihood of this serious adverse event.

**CONFLICT OF INTEREST**
All authors declare that there are no conflicts of interest in carrying out this work.

**SOURCE OF FUNDING**
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**ETHICAL ASPECTS**
The patient's written consent was obtained for publication of this case.

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# Toxicidad aguda por nitrofurantoina – Descripción de caso

## *Acute nitrofurantoin toxicity - Case description*

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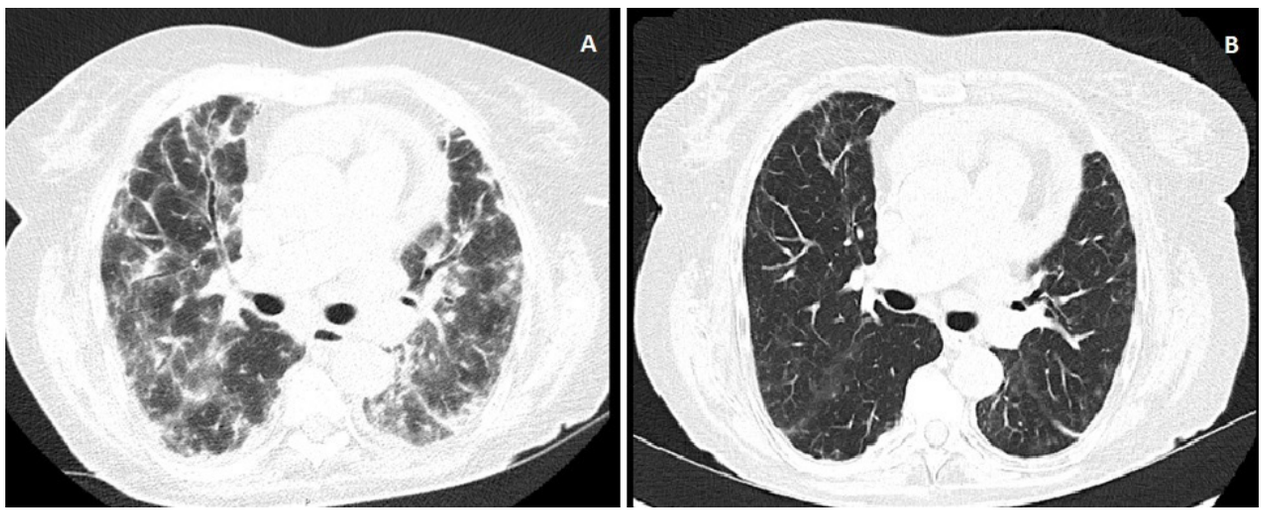


Figura 1. Imagen de tomografía computarizada de tórax realizada durante el ingreso (Figura 1A), que muestra opacidades en vidrio esmerilado asociadas con engrosamiento intersticial, afectando los tabiques interlobulillares y las paredes bronquiales, así como algunas zonas de consolidación en un patrón alveolar. Imagen de tomografía computarizada de tórax tomada dos meses después de haber suspendido la nitrofurantoína (Figura 1B), en la que se observan pequeñas áreas con patrón de "vidrio esmerilado", dispersas y predominantemente periféricas. Persisten discretas ectasias bronquiales. Estos hallazgos están relacionados con la neumonía organizada en fase de resolución.

Mujer, 82 años, sin antecedentes de enfermedad pulmonar u otras enfermedades, consulta en urgencias por tos seca, fiebre y disnea de 2 días de evolución. Recibía tratamiento profiláctico con nitrofurantoína desde hacía 6 meses debido a infecciones urinarias recurrentes. Destacaba insuficiencia respiratoria grave, y la tomografía computarizada torácica (TC) mostró un patrón de neumonía organizada (Figura 1A).

Se completó el estudio con broncofibroscopía, aspirado y lavado broncoalveolar, sin crecimiento de agentes microbiológicos ni hallazgos citológicos de células neoplásicas. Los cultivos de esputo también fueron negativos, al igual que los estudios autoinmunes, reumatológicos y de serología viral. Se diagnosticó neumonía organizada inducida por nitrofurantoína. Se suspendió el tratamiento con el fármaco y se inició terapia con prednisolona 1 mg/kg, con una evolución clínica favorable y mejoría de las alteraciones previamente identificadas, como se evidenció en la TC de control (Figura 1B). Dada la gravedad del caso, se notificó a las autoridades sanitarias y al laboratorio fabricante.

La nitrofurantoína es una de las opciones recomendadas por la Sociedad Europea de Urología para la profilaxis de infecciones urinarias recurrentes y ampliamente utilizada[1]. Sin embargo, su uso prolongado puede asociarse con reacciones adversas pulmonares graves - fibrosis pulmonar, neumonitis intersticial e hipersensibilidad severa[2,3]. Este riesgo es mayor en personas de edad avanzada, especialmente con enfermedades pulmonares subyacentes o deterioro de la función renal.[2,3]

Los síntomas de toxicidad pulmonar incluyen disnea, tos seca y fatiga[3]. La ficha técnica del medicamento y las recomendaciones médicas destacan que el uso prolongado o intermitente de nitrofurantoína no debe indicarse de forma indiscriminada, siendo esencial un seguimiento estrecho de los riesgos asociados con efectos secundarios graves. En casos de toxicidad, el diagnóstico precoz y la suspensión del fármaco suelen asociarse a un buen pronóstico[2,3]. La terapia con corticosteroides constituye la piedra angular del tratamiento, junto con la suspensión del fármaco.[3]

**CONFLICTO DE INTERESES**
Los autores declaramos que no existe ningún conflicto de intereses.

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**CONSIDERACIONES ÉTICAS**
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# Desde la tuberculosis pulmonar a la meningitis: un caso clínico revelador

## *From pulmonary tuberculosis to meningitis: a revealing clinical case*

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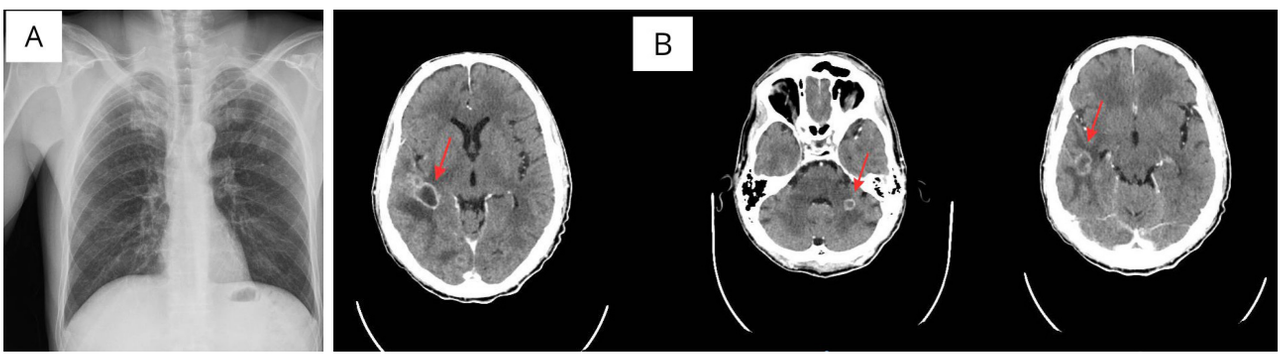


Presentamos el caso de un varón de 58 años, originario de Pakistán, sin antecedentes médicos relevantes, con adecuado estado vacunal y nutricional, con pruebas de *screening* de VIH negativas y sin otros datos de inmunosupresión que acude a urgencias con un cuadro de una semana de evolución caracterizado por fiebre persistente, cefalea intensa, vómitos y alteración en la orientación temporal y espacial. Además, el paciente reportó una pérdida de peso no cuantificada durante los últimos 2-3 meses.

La radiografía de tórax (Fig. A) reveló un infiltrado reticulonodular en los lóbulos superiores de ambos pulmones, un hallazgo compatible con tuberculosis pulmonar activa.

Una tomografía computarizada (TC) de cráneo (Fig. B) mostró múltiples lesiones intraaxiales hipodensas con realce periférico tras la administración de contraste, localizadas en regiones supratentoriales y periventriculares, con características sugestivas de un proceso expansivo. Ante la alta probabilidad de tuberculosis diseminada, se procedió a realizar una punción lumbar para el análisis del líquido cefalorraquídeo (LCR).

El análisis del LCR reveló datos sugestivos de meningitis tuberculosa. La confirmación se obtuvo mediante reacción en cadena de la polimerasa (PCR) específica para *Mycobacterium* tuberculosis, que resultó positiva en el LCR, corroborando el diagnóstico de neurotuberculosis.

Se inició tratamiento antituberculoso estándar con isoniazida, rifampicina, pirazinamida y etambutol, junto con corticosteroides (dexametasona) para reducir la inflamación y el riesgo de complicaciones neurológicas. A las pocas semanas, el paciente mostró mejoría clínica con reducción progresiva de la fiebre y cefalea, así como mejoría en la orientación y el estado general.

Este caso subraya la importancia de considerar la tuberculosis extrapulmonar en pacientes de regiones endémicas que presentan síntomas neurológicos y sistémicos inespecíficos[1]. La neurotuberculosis es una manifestación grave que requiere diagnóstico y tratamiento temprano para prevenir complicaciones neurológicas permanentes. La imagen de TC cerebral con lesiones hipodensas y realce periférico plantea un diagnóstico diferencial amplio, incluyendo abscesos, metástasis y granulomas tuberculosos, siendo fundamental la confirmación microbiológica para establecer el diagnóstico definitivo y el manejo adecuado.[2]

**CONFLICTO DE INTERESES**
Los autores declaramos que no existe ningún conflicto de intereses.

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**CONSIDERACIONES ÉTICAS**
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