

Sarcoidosis: Various Possibilities of Clinical Presentations

Sarcoidose: Diversas Possibilidades de Apresentações Clínicas
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RESUMO

Objetivo: Relatar dois casos de sarcoidose com diferentes manifestações, visando exemplificar e aprimorar o raciocínio clínico para o diagnóstico da doença. **Métodos:** Estudo descritivo tipo série de casos, realizado com duas pacientes com informações colhidas por meio de entrevista médica com as pacientes e através de seus prontuários eletrônicos registrados. **Resultado:** As pacientes estudadas nos relatos de casos apresentam quadros distintos, o que reforça as diferentes possibilidades de apresentações clínicas. Foi necessário excluir outras doenças reumatológicas para então conseguir fechar o diagnóstico de sarcoidose. **Conclusão:** A variabilidade clínica desta comorbidade é o maior fator envolvido no atraso da suspeita e, conseqüentemente, do diagnóstico. A falta de conhecimento das diversas características da doença resulta no início tardio do tratamento direcionado. **DESCRIPTORIOS:** Sarcoidose, Sarcoidose/manifestações clínicas, granuloma, Sarcoidose/diagnóstico

ABSTRACT

Objective: To report two cases of sarcoidosis with different manifestations, aiming to exemplify and improve clinical reasoning for the diagnosis of the disease. **Methods:** Descriptive case series study conducted with two patients, with information collected through medical interviews with the patients and their electronic medical records. **Results:** The patients studied in the case reports present different clinical pictures, which reinforces the different possibilities of clinical presentations. It was necessary to exclude other rheumatological diseases in order to reach a diagnosis of sarcoidosis. **Conclusion:** The clinical variability of this comorbidity is the major factor involved in the delay in suspicion and, consequently, diagnosis. Lack of knowledge of the various characteristics of the disease results in delayed initiation of targeted treatment.

KEYWORDS: Sarcoidosis, Sarcoidosis/clinical manifestations, granuloma, Sarcoidosis/diagnosis

RESUMEN

Objetivo: Relatar dos casos de sarcoidosis con diferentes manifestaciones, con el fin de ejemplificar y mejorar el razonamiento clínico para el diagnóstico de la enfermedad. **Métodos:** Estudio descriptivo tipo serie de casos, realizado con dos pacientes con información recopilada mediante entrevista médica con las pacientes y a través de sus historias clínicas electrónicas registradas. **Resultado:** Las pacientes estudiadas en los informes de casos presentan cuadros distintos, lo que refuerza las diferentes posibilidades de presentaciones clínicas. Fue necesario excluir otras enfermedades reumatológicas para poder cerrar el diagnóstico de sarcoidosis. **Conclusión:** La variabilidad clínica de esta comorbilidad es el factor más importante que contribuye al retraso en la sospecha y, en consecuencia, en el diagnóstico. El desconocimiento de las diversas características de la enfermedad da lugar a un inicio tardío del tratamiento específico.

DESCRIPTORIOS: Sarcoidosis, Sarcoidosis/manifestaciones clínicas, granuloma, Sarcoidosis/diagnóstico

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INTRODUCTION

Sarcoidosis is an idiopathic multisystem inflammatory disease, whose histopathological characteristic is the presence of noncaseating granulomas. These noncaseating granulomas can infiltrate essentially all organs and tissues, potentially leading to their dysfunction. In addition, it can be self-limiting or persistent¹.

In epidemiological studies of the disease, a predominance has been observed in Nordic populations and in the United States, with a higher frequency in black people. There is also a higher prevalence in females, with the highest incidence between the ages of 20 and 40, with a second peak at age 60. The genetic factors involved in the disease are not yet fully understood, but 5% of patients diag-

nosed with sarcoidosis have a positive first-degree family history.

The clinical expression of sarcoidosis usually occurs in organs and tissues that are most exposed to the environment, such as the eyes, lungs, and skin. Thus, despite being an idiopathic disease, there is a possibility of a relationship with environmental agents³⁻⁴. The literature describes exposure to insecticides and fungi as risk factors,

in addition to occupational activities such as construction, firefighting, and healthcare professions².

Sarcoidosis patients may be asymptomatic, and the most common radiological finding is bilateral and symmetrical hilar adenopathy. Löfgren and Heerfordt are two classic syndromes, with acute presentation and progression within a few weeks⁴. The most common clinical form is Löfgren syndrome, which is characterized by: hilar adenopathy, erythema nodosum, anterior uveitis, and arthritis (less frequent). In Heerfordt syndrome, the patient usually presents with more exuberant fever, parotid gland enlargement, anterior uveitis, and peripheral facial paralysis (unilateral or bilateral)⁵.

Most patients present with chronic progression, involving different clinical manifestations. The most commonly affected organ is the lung, with dyspnea and dry cough being common. Among the dermatological manifestations, the most common are: infiltrated and painless maculopapules, erythema nodosum, and lupus pernio. Meanwhile, ophthalmic involvement is mainly characterized by anterior uveitis and may present with associated posterior uveitis. In addition to these manifestations, dry syndrome due to destruction of the lacrimal glands is also described, presenting with keratoconjunctivitis, making routine ophthalmological examination essential in all patients, including asymptomatic ones. Other organs such as the liver (altered liver function tests), spleen (splenomegaly), and bone marrow (lymphopenia) may be affected, in addition to cardiac sarcoidosis and neurosarcoidosis. Hypercalcemia and nephropathy are other possible manifestations⁶.

The diagnosis of sarcoidosis requires compatible clinical findings and the presence of noncaseating granulomas in the biopsy of the af-

ected organ, with the exclusion of possible differential diagnoses. Early and accurate diagnosis of sarcoidosis remains challenging, as initial presentations can vary and many patients are asymptomatic⁵.

The differential diagnosis of sarcoidosis is broad due to nonspecific symptoms and diverse clinical presentations, as other pathologies present with similar clinical and radiological findings. The formation of noncaseating granulomas is not exclusive to sarcoidosis, as there are other entities characterized by diffuse granulomatous infiltration of multiple organs and tissues. Other diseases should be investigated and ruled out in patients with a suspected diagnosis of sarcoidosis, such as mycobacteriosis, mycosis, neoplasms, and berylliosis⁶.

The prognosis is variable and depends on epidemiological factors, mode of onset, initial clinical course, and involvement of specific organs. Treatment for sarcoidosis is based on glucocorticoid therapy. Disease progression often leads to pulmonary involvement or, in some cases, death due to complications of progressive pulmonary fibrosis or cardiac involvement, including sudden cardiac death (arrhythmias) or congestive heart failure (myocarditis)².

Sarcoidosis is an underdiagnosed disease, and therefore, greater awareness is needed. The aim is to improve the clinical reasoning of healthcare professionals due to the richness and quantity of clinical manifestations present⁷. In addition, the secondary objective is to include sarcoidosis as a differential diagnosis of several other diseases that are already well known globally⁴.

MATERIAL AND METHOD

Design

This work consists of a descriptive case series study conducted with two

patients from a private practice located at Barra Business Center, number 3301, in 2020. Two case reports will be presented, based on information collected through medical interviews with the patients and their electronic medical records registered in the aforementioned practice's system.

Scientific research methodology

The literature review for this study was based on articles found in search engines and databases in Portuguese, English, and Spanish over the last 10 years. Articles referring to sarcoidosis were used as inclusion criteria, with no exclusion criteria required.

Data analysis methodology

Data analysis will be performed based on the correlation of data from the literature with the two case reports used as the basis for this study.

CASE REPORTS

Case 1: MVMA, female, 54 years old, brown skin, born in Rio de Janeiro, waitress. She sought care at a rheumatology clinic after being referred by an ophthalmologist with a complaint of eyelid ptosis, without other complementary evaluations. She had a history of emergency room visits due to edema and bilateral arthralgia in her ankles two months prior, where an X-ray was requested, which showed no abnormalities. She received nonsteroidal anti-inflammatory medication and analgesics, without resolution of the condition. Given this, an MRI was requested. After two weeks, the condition progressed to her wrists, associated with frequent fainting and vertigo along with eyelid ptosis, xerophthalmia, diplopia, and occasional visual blurring, without paresthesia.

Comorbidities include hypertension and chronic left patellar chondropathy, for which she has already undergone arthroscopy. No reports of

autoimmune diseases in the family. Sedentary patient, no history of smoking or alcoholism. Menarche at age 12, G3P2A1 (induced), menopause at age 51 without hormone replacement therapy, no history of previous fractures.

Physical examination revealed only arthritis of the left wrist and ankle without limitation of range of motion and with pain on joint palpation. Bilateral crepitus in the knees. Absence of Lasegue's sign with grade

V strength in all limbs and preserved facial mimicry. The following tests were performed and were negative: Patrick Fabere, Tinel, Phalen, Patte, Jobe, Neer.

Magnetic resonance imaging (MRI) of the ankle showed tibiotalar and posterior subtalar joint effusion on the right and fibular tendinopathy on the left without joint effusion.

Given the unclear synovitis, investigations were initiated for Sjögren's syndrome, vasculitis, systemic lupus

erythematosus (SLE), and sarcoidosis. Laboratory tests, brain MRI, X-rays of the hands and feet, and ultrasound (USG) of the wrists were requested, and the patient was referred to an ophthalmologist for a dry eye test (Schirmer test). In addition, the patient was prescribed prednisone 40 mg/day for 30 days (dosage: 0.5 mg/kg).

At the follow-up appointment, the patient showed complete resolution of eyelid ptosis and arthralgia.

Table 1: Laboratory tests (11/28/17)

| | |
|--------------------|----------|
| Hemoglobina | 13.8 |
| Leucócitos | 5400 |
| Neutrófilos | 3780 |
| Linfócitos | 918 |
| Plaquetas | 291,000 |
| VHS | 35 mm |
| Glicemia em jejum | 116 |
| Creatinina | 0.76 |
| Ureia | 20 |
| LDL | 147 |
| Cálcio | 9.8 |
| Potássio | 3.3 |
| Fosfatase Alcalina | 92 |
| GGT | 31 |
| Albumina | 4.4 |
| TGO/TGP | 15/12 |
| CPK | 39 |
| FR | Negative |
| ANTI DNA | Negative |
| ANCA | Negative |
| ANTI-RO | Negative |
| ANTI-LA | Negative |
| ANTI-SM | Negative |
| HEPATITE B E C | Negative |
| HIV | Negative |
| VDRL | Negative |
| PCR | 0.84 |

Source: prepared by the author

Ophthalmologist (11/29/17): negative Schirmer test. Ultrasound of hands and wrists (12/11/17) - Already using prednisone - joint effusion in left wrist without synovial thickening.

Given synovitis to be clarified and lymphopenia, in addition to negative antibodies for vasculitis, systemic lupus erythematosus (SLE), and Sjögren's syndrome, the main diagnostic hypothesis raised was sarcoidosis. The following tests were requested: gallium scintigraphy, angiotensin-convert-

ing enzyme (ACE) dosage, 1,25 OH vitamin D, and prednisone weaning was initiated.

At the follow-up appointment, the patient reported that she had weaned off prednisone as prescribed, but when she reached a dose of 10 mg/day, she developed periorbital edema and worsening eyelid ptosis. She then increased the medication dose to 20 mg/day on her own. She also brought the requested tests.

Given the test results and the compatible clinical picture, bilateral adenopathy associated with arthritis, lambda sign on scintigraphy and lymphopenia, and complaint of xerostomia, sarcoidosis was considered the main possible diagnosis. The proposed course of action was to resume prednisone weaning and start methotrexate (final dose of 20 mg/week). The patient went into remission and corticosteroids were discontinued.

Case 2: FLS, female, 38 years old, white, born in Rio de Janeiro, sought a rheumatologist's office for investigation of granulomatous disease suggested by lymph node biopsy. She reported arthralgia localized in the right shoulder, knee, wrist, and elbow for 3 months. In addition, she also presents with mechanical neck pain and sporadic bilateral xerophthalmia. She denies fever, recent or previous infections, oral/nasal/genital ulcers, UTI or recurrent diarrhea, skin lesions, psoriasis, Raynaud's, IBD, muscle weakness, dysphagia, chest pain, dysuria, hematuria, foamy urine, tinnitus, rhinitis/asthma, recurrent sinusitis, nasal bleeding or crusting, or facial paralysis.

Past history reports hepatitis A at age 28. Denies comorbidities, previous tuberculosis, transfusions, and allergies. No reports of autoimmune diseases in the family. Physical examination reveals prominent bilateral submandibular lymph nodes that are palpable, soft, painless, approximately 2-3 finger widths in size, and not adherent. No arthritis or limited movement. Patrick Fabere and Lasegue tests were negative.

The patient's abdominal CT scan showed enlarged retroperitoneal lymph nodes near the iliac vessels in the left inguinal chain and prominent mesenteric lymph nodes. In addition, a chest CT scan showed multiple lymphadenopathies in the mediastinal and hilar chains bilaterally, forming supraclavicular and bilateral axillary conglomerates.

As a course of action, routine labo-

Table 2: Laboratory tests on January 3, 2018

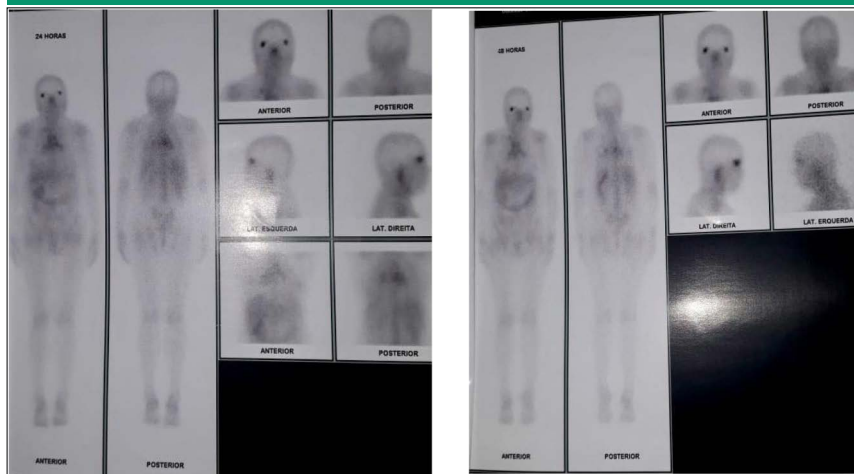
| | |
|-------------------|---------|
| Hemoglobin | 14,2 |
| White blood cells | 7700 |
| Neutrophils | 5313 |
| Lymphocytes | 1540 |
| Platelets | 265.000 |
| VHS | 25 mm |

Source: prepared by the author

Gallium scintigraphy (01/22/18): active inflammatory process in the ocular region associated with probable bilateral hilar adenopathy; this find-

ing is highly suggestive of sarcoidosis. Radiotracer (gallium-67 citrate) hyperuptake in the following segments: bilateral ocular region (marked), parotid glands (discrete), and bilateral mediastinum (moderate) ("Lambda" sign).

Figures 1 and 2: Gallium scintigraphy



Source: image provided by the patient

ratory tests were requested for antibodies, ANCA, ACE dosage, 1.25 vitamin D, serology for HIV, hepatitis B and C, CMV, toxoplasmosis, and VDRL, and referral to an ophthalmologist for dry

eye testing. In addition, a PPD test, new chest, abdomen, and neck CT scans, and ultrasound of the shoulder, hands, wrists, and knees were requested. The patient was referred to a hematologist

for follow-up.

Patient returns to the clinic with test results (Table 4).

Table 3: Laboratory tests 08/21/2020

| | |
|-------------------------|-----------------------------------|
| Hemoglobin | 11.3 |
| White blood cells | 3270 |
| Lymphocytes | 857 |
| Platelets | 228,000 |
| VHS | mm |
| Lactate | Negative |
| Uric acid | 4.9 |
| Creatinine | 0.72 |
| Urea | 29 |
| LDL | 115 |
| Calcium | 9.3 |
| Potassium | 3.8 |
| Alkaline phosphatase | 64 |
| GGT | 46 |
| CPK | 314 |
| ECA | 110.4 |
| TGO/TGP | 44/79 |
| PTH | 24 |
| FR | Negative |
| FAN | Negative |
| ANTI DNA | Negative |
| ANCA | Negative |
| ANTI-RO | Negative |
| ANTI-LA | Negative |
| ANTI-SM | Negative |
| C3 | 151 |
| C4 | 26 |
| PROTEIN ELECTROPHORESIS | Polyclonal hypergammaglobulinemia |
| HEPATITIS B AND C | Negative |
| PPD | 0 mm |
| HIV | Negative |
| VDRL | Negative |

Source: prepared by the author

Given the test results and clinical picture, sarcoidosis was considered as a possible diagnosis, and a gallium bone scan was requested. In addition, the lymph node biopsy was reevaluated by a hematologist to rule out lymphoma.

DISCUSSION

Sarcoidosis is a multisystemic disease of unknown etiology, characterized by tissue infiltration by non-caseating granulomas in the affected organs. The prevalence and incidence of sarcoidosis are not well known worldwide due to the challenges associated with verifying the number of asymptomatic patients. The disease affects individuals of all ages, regardless of race or ethnicity, with a higher incidence among people aged 20 to 40 years, and is much more prevalent in females. Many researchers have hypothesized the role of genetic susceptibility, environmental factors, and autoimmunity in the development of this disease, but no single cause has been identified to date¹².

The disease is often diagnosed when changes are identified on a chest X-ray (up to 50% of patients) during a routine examination. It can be acute, subacute, or chronic; however, in most cases, it is completely asymptomatic. Early diagnosis is essential for patient management. To establish a confirmed diagnosis, patients must undergo an evaluation with clinical tests, taking into account the involvement of specific organs^{1,12}.

The patients studied in the case reports present different clinical pictures, which reinforces the different possibilities of clinical presentations. In the first report, the patient complained of eyelid ptosis associated with bilateral xerophthalmia, diplopia, blurred vision, as well as arthralgia in the wrists and ankles, lipothymia, and vertigo. Physical ex-

amination revealed only arthritis of the left wrist and ankle, without limitations of range of motion or pain on joint palpation. Comparatively, in the second report, the patient reported arthralgia localized in the shoulder, knee, wrist, and elbow, along with bilateral xerophthalmia. Physical examination revealed bilateral submandibular lymph nodes that were soft, painless, and approximately 2 to 3 finger widths in size, without adhesion. The approach was similar in both visits, with laboratory and imaging tests requested and referral to an ophthalmologist for dry eye testing.

In the first report, the following hypotheses were considered: Sjögren's syndrome; Takayasu's arteritis; ANCA-associated vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis); systemic lupus erythematosus; and sarcoidosis. In the second case, the following diagnoses were suggested for investigation: lymphoma; tuberculosis; HIV; syphilis; hepatitis B and C; toxoplasmosis; cytomegalovirus; and sarcoidosis.

Sjögren's syndrome is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, especially the salivary and lacrimal glands. The most characteristic finding of the disease is "dry syndrome," which results from progressive glandular destruction and decreased production of saliva and tears. A number of other conditions can mimic this syndrome, such as HIV or HCV infection and sarcoidosis. The diagnosis of Sjögren's syndrome is confirmed when we find the clinical and laboratory findings listed in Table 5. The patient studied in the first case has a negative Schirmer test, in addition to negative autoantibodies, ruling out the diagnostic hypothesis of Sjögren's syndrome¹⁸.

Takayasu arteritis is a vasculitis characterized by preferential involve-

ment of the aorta and its primary branches. It is characterized by reduced blood pressure and pulses in the upper limbs compared to the lower limbs. As a result, claudication and paresthesia in the upper limbs, headache, postural dizziness, and syncope occur. Hypertension is common due to stenosis of the renal arteries. Another common cause of morbidity is ocular involvement, which includes visual deficits and amaurosis fugax, which may be postural, in addition to retinopathy. ESR is almost always elevated, but it is not a reliable marker of disease activity. The diagnostic criteria for Takayasu arteritis are listed in Table 6; at least three of the six criteria must be present. Even though she presented with a clinical picture of retinopathy, dizziness, syncope, elevated ESR, and hypertension, which could be suggestive of Takayasu arteritis, the patient in the first case did not meet the clinical diagnostic criteria¹⁹.

Regarding ANCA-associated vasculitis, which were considered as differential diagnoses, Wegener's granulomatosis affects medium and small vessels, with the formation of granulomas, resembling sarcoidosis. Churg-Strauss syndrome is a vasculitis with clinical manifestations such as constitutional symptoms, such as arthralgia at the onset of the disease, which was reported in the case of the first patient. Finally, microscopic polyangiitis is a systemic necrotizing vasculitis that affects medium and small caliber arteries, with patients typically presenting general symptoms, such as the polyarthralgia described in the first case. Thus, ANCA was requested with a negative result, which, together with the lack of criteria and other compatible symptoms, in addition to the reported arthralgia, led to the exclusion of vasculitis as a definitive diagnosis of the patient's condition²⁰.

Another diagnosis considered for the first patient was SLE, which is a chronic multisystemic autoimmune disease whose most striking feature is the development of inflammatory foci in various tissues and organs. It progresses with periods of exacerbations and remissions, mainly affecting the skin (dermatitis), joints (arthritis), serous membranes (serositis), glomeruli (glomerulitis), and the central nervous system (encephalitis). The 2012 SLICC classification lists the diagnostic criteria used to characterize SLE, shown in Table 7. The lack of minimum clinical criteria, given that the patient only scores for polyarthralgia and neurological manifestations, in addition to the absence of immunological criteria, excludes the diagnosis of SLE²¹.

After careful analysis of the picture presented in the first report, the previously proposed differential diagnoses were excluded. The clinical manifestations present are: visual blurring, dry eye syndrome (xerophthalmia), and polyarthritis of the large joints. These symptoms, combined with the presence of lymphopenia in laboratory tests and scintigraphy (gallium-67) with characteristic signs, confirmed the diagnosis of sarcoidosis.

The second patient in the study presents with polyarthralgia and significant lymphadenopathy. Lymph node changes may be a sign of systemic disease such as neoplasia or infectious diseases. The patient's age, along with a medical history to specify the duration of symptoms, associated symptoms, exposure, and/or relevant antecedents, are fundamental in this process. The physical examination should cover the patient's general characteristics, such as the presence or absence of hepatosplenomegaly, for example, and the lymph node in terms of location, size, consistency, fixation/adherence, and presence of pain/logistical signs²².

Lymphomas are among the leading causes of malignant neoplasms and are characterized by lymphadenopathy, which is typically painless and sometimes without any other systemic symptoms. Localized disease, mainly cervical and supraclavicular, is more typical of the Hodgkin variant, while generalized findings are more common in the non-Hodgkin form, with varying degrees of hepatosplenomegaly. It is important to remember that lymphomas can affect contiguous organs, causing variable signs and symptoms. Age is the factor most closely related to suspected cancer, as individuals over 40 years of age have a 10 times higher risk. On physical examination, the supraclavicular chain is the only independent predictor for biopsy, but toxoplasmosis, sarcoidosis, and tuberculosis can alter this chain as the main non-neoplastic causes²².

Findings in the medical history such as cat scratches, eating undercooked meat, frequent direct contact with sand, tick and insect bites, risky sexual behavior (including multiple partners), and travel to areas with endemic infections may suggest lymphadenopathy of infectious cause. In this case, consider diseases such as HIV, syphilis, hepatitis B and C, toxoplasmosis, and cytomegalovirus. Analyzing the second report, the diseases investigated as diagnostic hypotheses were ruled out after negative results of specific tests requested, such as serology for HIV, hepatitis B and C, CMV (IgM), toxoplasmosis (IgM), and VDRL²². The patient was advised to consult a hematologist to rule out lymphoma, in addition to awaiting the PPD result. The diagnosis of tuberculosis should be considered, as it is a granulomatous disease but with caseous granuloma, which differs from that found in sarcoidosis, making this the main diagnostic hypothesis for the case.

-FINAL CONSIDERATIONS

Sarcoidosis is an idiopathic multisystem inflammatory disease, whose histopathological characteristic is the presence of noncaseating granulomas. These noncaseating granulomas can infiltrate essentially all organs and tissues, and may evolve with their dysfunction.

The clinical variability of this comorbidity is the major factor involved in the delay in suspicion and, consequently, diagnosis. Examples of this situation are reported in this study, in which the patients described presented with distinct clinical pictures compatible with sarcoidosis. Lack of knowledge of the various characteristics of the disease results in a delayed start of targeted treatment.

Healthcare professionals should improve their clinical reasoning, considering the different possibilities of clinical presentations of sarcoidosis. This will lead to its inclusion as a differential diagnosis of several other diseases that are already well known globally. Finally, it is necessary to disseminate knowledge of the signs and symptoms, with the aim of encouraging a multidisciplinary approach for a better understanding of the disease.

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