Un caso de Sarcoidosis Multisistémica peculiar

Sarcoidosis – an unusual multisystemic disease.

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ABSTRACT

Sarcoidosis is a chronic multisystemic disease of unknown etiology, characterized by the formation of non-caseous granulomas, most commonly with lung, intrathoracic lymph node, skin and ocular involvement. We present the case of a 69-year-old male with hyperthyroidism due to a toxic nodule who underwent a thyroidectomy but kept losing weight. Afterwards he developed photopsias, hepatosplenomegaly and pancytopenia. Exams revealed non-caseous granulomatous involvement of thyroid, eye, liver and bone marrow. Corticosteroid therapy was initiated with overall improvement but the patient developed hypercortisolism and hyperglycemia and did not tolerate steroid taping. Azathioprine was started, allowing improvement with low dose steroids.
This case illustrates an infrequent case of sarcoidosis with exclusive extra-thoracic disease, highlighting the rare bone marrow and thyroid involvement causing an unspecific presentation.

INTRODUCTION

Sarcoidosis is a chronic, inflammatory, multisystemic disease of unknown etiology. It is characterized by the formation of non-caseous granulomas, most commonly in the lungs, intra-thoracic lymph nodes, skin and eye but it can affect virtually any organ. Isolated extra-thoracic involvement is rare and can make the diagnosis more difficult[1-3].
In most patients, prognosis is excellent with most remaining asymptomatic or going into remission without consequences. Less than 5% of patients die from sarcoidosis[1]. Evidence based guidelines for treatment are lacking for most of the presentations. There is no cure and treatment is based mainly on corticosteroids[4,5].
We describe one patient with an atypical sarcoidosis presentation with extra-thoracic involvement only.

CASE REPORT

A 69-year-old Caucasian man, with no relevant personal or familiar history besides a previously diagnosed hyperthyroidism, lost 20% of his weight within a year, in spite of treatment with thiamazole. Thyroid scintigraphy showed a toxic nodule so a partial thyroidectomy was performed. Thyroid histology reported nodular hyperplasia, with an inflammatory lymphohistiocytic reaction with multinucleated giant cells, secondary to colloid extravasation. After the surgery, he continued to lose weight. The patient developed photopsias and in clinical re-evaluation he presented hepatosplenomegaly on examination. He denied night sweets, fever, myalgia, anorexia and respiratory symptoms.
Laboratorial tests revealed pancytopenia, renal dysfunction, high velocity sedimentation rate (VSR), beta2-microglobulin, and high angiotensin-converting-enzyme (ACE) value (Table1).
The chest radiography and computed tomography were unremarkable. An ocular angiography was performed revealing a granulomatous choroiditis.
Thyroid histology was reviewed, identifying thyroid involvement with non-caseous granulomatous inflammation, consistent with thyroid sarcoidosis (Image 1).

Table 1. Laboratory tests before and after the onset of systemic corticoid therapy.

	1 month before therapy	Onset therapy with prednisolone	After 1 week of prednisolone	After 4 weeks	Reference Values
Hemoglobin	11.2	9.0	10.5	13.7	13.5 – 17.5 g/dL
Leucocytes	2170	1380	4590	6790	4000-10 000 ^10 ^{9}/L
Eosinophils	70	3	20	50	<0.50^10^9/L
Platelets	122 000	82 000	156 000	140 000	150 000 - 400 000^10^9/L
VSR	31	50	-	13	<20 mm/h
Beta$_2$-microglobulin	19.75	-	-	-	0.9-2 mg/L
C reactive protein	0.87	1.78	-	-	<0.60 mg/dL
Creatinine	-	3.28	-	1.46	0.70-1.30 mg/dL
Calcium	-	10.3	-	9.2	8.5-10.1 mg/dL
Aspartate aminotransferase	40	40	-	17	15-37 UI/L
Alanine aminotransferase	42	42	-	33	16-63 UI/L
Alkaline Phosphatase	130	130	-	-	46-116 UI/L
Rheumatoid Factor	-	6.5	-	-	<18 UI/mL
ACE	114	114	-	28.2	20-70 U/L
Interferon gamma release assays (IGRA)	-	Negative	-	-	

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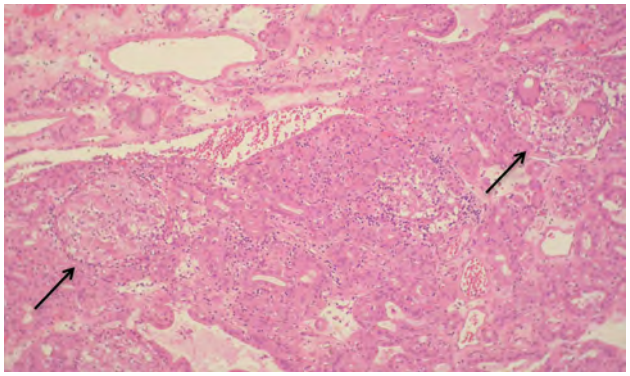
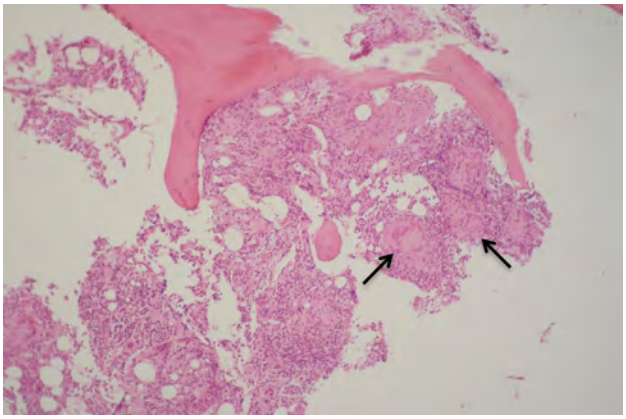
Cómo citar este artículo: Gorgulho A, Antunes AP, Sequeira C, Salgueiro Marques A
Un caso de Sarcoidosis Multisistémica peculiar. Galicia Clin 2022; 83-1: 42-45
Recibido: 04/01/2021 ; Aceptado: 10/05/2021 // https://doi.org/10.22546/64/2436

Figure 1. Histopathological examination of thyroid tissue (H&E stain, magnification 100x), showing epithelioid granulomas (black arrows).



Due to pancytopenia progression, a myelogram and bone biopsy were performed, also showing a bone marrow granulomatous inflammatory process. (Figure 2)

Figure 2. Histopathological examination of bone marrow tissue (H&E stain, magnification 100x), showing epithelioid granulomas (black arrows).



Liver biopsy also exhibited a granulomatous hepatitis, with epithelioid granulomas.

Infectious causes for granulomatous diseases, such as Q-fever, Epstein Barr-virus, Cytomegalovirus, Human Immunodeficiency Virus, tuberculosis and brucellosis were excluded, as well as autoimmune causes (with negative anti-nuclear [ANA], anti-SSA, anti-SSB and anti-neutrophil cytoplasmic [ANCA] antibodies and negative rheumatoid factor).

Assuming the diagnosis of sarcoidosis, the patient started corticosteroid therapy, with prednisolone. After only one week of treatment we could see a clinical improvement in photopsias (with choroidal infiltrates reduction) and analytically in pancytopenia and renal function (see Table 1).

A slow and progressive reduction on corticosteroids dose was initiated: the patient was on prednisolone 40mg for a month and 30 mg for another month but the patient started showing steroids side effects with hyperglycemia and signs of hypercortisolism. The dose was reduced for 5 mg/day over the third month and at this point the abdominal ultrasound no longer displayed hepatosplenomegaly; on ophthalmologic examination there was only atrophy of the choroid lesions and myelogram and bone biopsy were normal, with no granulomas found.

The patient did not tolerate the corticosteroid dose reduction, with worsening pancytopenia and fatigue. Considering the inability to taper corticosteroids and the steroids side effects, azathioprine 2mg/kg/day was started which allowed us to maintain 5mg of prednisolone with resolution of pancytopenia and symptoms, and normal myelogram and bone marrow biopsy.

DISCUSSION

The main feature of sarcoidosis is granulomatous inflammation, with non-caseous granuloma formation. More than 90% of the patients have pulmonary involvement (hilar lymphadenopathy and/or pulmonary infiltrates)[1]. Extra-thoracic organs most frequently involved are the skin (macules, papules and plaques), eye and liver/spleen, but isolated extra-pulmonary manifestations are rare[1,2].

Our patient has its peculiarities; he is an elder man, with atypical presentation, with multiple organ involvement and no intra-thoracic manifestations, in addition to the rare involvement of the thyroid, the bone marrow and posterior eye segment.

We consider that the hyperthyroidism was the first sarcoidosis manifestation, although not recognized at that point, allowing the progression of the disease to its multi-organ involvement.

Sarcoidosis of the thyroid gland is very infrequent and not many reports are available, but multiple presentations have been described, such as hyperthyroidism, hypothyroidism (and subclinical forms of both), goiter or even granulomas mimicking nodules/tumours[6].

This situation is so unusual that the granulomatous inflammation was only noticed in the histology review, with given importance to the rest of the patient's context.

Continued weight loss with pancytopenia led to the finding of bone marrow granulomas that is not a common finding either. A Spanish review of 40 cases of bone marrow granulomas concluded that 50% were of infectious etiology with tuberculosis being the most frequent infection (20%), followed by brucellosis, typhoid fever and kala-azar[7]. In that same study only 5% of the granulomas were sarcoidosis. In patients with bone marrow granulomas is imperative to exclude infectious diseases but sarcoidosis should not be overlooked.

Ocular sarcoidosis involvement is frequent (25-80% of patients) and any segment can be affected, but the most common is to find anterior segment uveitis[1]. Our patient had a more infrequent posterior-segment involvement (choroiditis).

Hepatic sarcoidosis is frequently asymptomatic, therefore believed to be underestimated. Hepatomegaly is found in 5-15% of patients and elevated serum aminotransferases in just over 10%, but histologic evidence of disease is present in 75% of hepatic biopsies performed on sarcoidosis patients. Nearly 60% of patients with hepatic involvement have constitutional symptoms such as fever, anorexia and weight loss, as well as night sweats[1].

Diagnosis is based on clinical and radiologic findings supported by histologic evidence of non-caseous granulomas in one or more organs, after exclusion of other granulomatous diseases. Our patient had a compatible clinical picture, but did not present the usual thoracic radiological findings suggestive of sarcoidosis, so the demonstration of non-caseous granulomas in the multiple organs involved, with negative tests for infectious and autoimmune causes, was determinant for the diagnosis. Laboratory evaluation is often not helpful, nevertheless peripheral lymphopenia, elevated beta2-microglobulin and hypercalcemia point to sarcoidosis. Elevated ACE (synthetized in granulomas) is classically associated with sarcoidosis (also seen in our patient) but it has low specificity and sensitivity and is considered to be a poor therapeutic guide[1,3].

Early diagnosis and management can prevent future complications.

Treatment is widely accepted if organ function is threatened[1]. Corticosteroids remain the cornerstone of treatment, with the most common dosage for induction being 0.5 mg/kg ideal body weight (usually 20 to 40 mg/day), for 1-3 month and further step-by-step decrease[4]. Patients should be reassessed every 4 to 12 week intervals

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for evidence of symptomatic worsening or development of glucocorticoid-related adverse effects.

Steroid-sparing therapies such as metothrexate, azathioprine, leflunomide or mycophenolate mofetil may be considered in patients with persistent symptoms, inability to taper steroids or intolerable side effects [4].

In conclusion, this case highlights the everyday challenges of the internist to understand and diagnose complex multisystemic diseases, such as the enigmatic sarcoidosis that may present itself in "mysterious" ways. Increased suspicion is needed to faster diagnose this entity provide adequate treatment in a timely manner.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this work.

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

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

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