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Pancytopenia Revealing Medullary Granulomatosis : An Unexpected Diagnosis of Systemic Familial Sarcoidosis

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ABSTRACT

Introduction : Sarcoidosis is a granulomatous disease of unknown origin, characterized by highly variable clinical presentations. Diagnosis is based on compatible clinical features, the presence of non-caseating granulomas on biopsy, and the exclusion of other causes of granulomatous diseases. Extrapulmonary involvement is rare, particularly bone marrow involvement, which is usually observed in the context of systemic sarcoidosis. Bone marrow sarcoidosis is extremely rare. Familial forms are also uncommon, accounting for less than 5% of cases. This article reports a case of medullary sarcoidosis revealed by pancytopenia.

Observation : A 54-year-old hypertensive patient presented with an anemic syndrome associated with prolonged low-grade fever, weight loss, splenomegaly, diffuse papular skin lesions, and minor neurological signs. Laboratory tests revealed pancytopenia, hypercalcemia, polyclonal hypergammaglobulinemia, moderate renal impairment, and elevated angiotensin-converting enzyme levels. Infectious and autoimmune serologies were negative. Bone marrow biopsy revealed non-caseating granulomas, which were also confirmed in skin and salivary gland biopsies. A diagnosis of bone marrow sarcoidosis was established. The patient was treated with corticosteroids, resulting in good clinical and biological improvement, despite persistent thrombocytopenia and the onset of corticosteroid-induced diabetes. A family history of sarcoidosis was later reported.

Discussion : Sarcoidosis is a rare systemic inflammatory condition primarily affecting the lungs. Medullary involvement, though rare, can present as pancytopenia. Bone marrow biopsy is key to diagnosis, and biological abnormalities such as anemia, leukopenia, and elevated sedimentation rate are common. Treatment is based on corticosteroids, but other immunosuppressants may be needed if the response is inadequate. Lymphopenia is often associated with poor prognosis. The rarity of the cases and the diversity of symptoms make medullary sarcoidosis difficult to diagnose.

Conclusion : Bone marrow sarcoidosis is a rare and challenging condition to diagnose. It should be considered in cases of unexplained pancytopenia, particularly when systemic symptoms are present. Bone marrow biopsy is a key diagnostic tool. Corticosteroid therapy remains the first-line treatment and requires close monitoring. This case highlights the importance of a multidisciplinary approach in managing atypical forms of sarcoidosis.

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KEYWORDS:
Sarcoidosis, pancytopenia, granulomatosis, bone marrow, familial sarcoidosis.

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INTRODUCTION

Sarcoidosis is a granulomatous disease of unknown etiology, characterized by its clinical polymorphism and the variety of its modes of presentation. The diagnosis of sarcoidosis is based on the combination of a compatible clinical picture with the presence of non-caseating epithelioid and giant cell granulomas on one or more tissue biopsies, and after exclusion of other causes of granulomatous diseases. Extrapulmonary manifestations of sarcoidosis are rare. Bone

marrow sarcoidosis is rarely encountered clinically. In the few reported cases, bone marrow involvement most often occurs as part of systemic sarcoidosis. Bone marrow sarcoidosis is extremely rare (1). Familial forms of sarcoidosis are rare, representing less than 5% of cases (2). In this work, we report a case of medullary sarcoidosis revealed by pancytopenia.

CASE REPORT

A 54-year-old male patient, with a history of hypertension and facial paralysis, presented with an anemic syndrome consisting of asthenia, dizziness, headaches, and palpitations, without any hemorrhagic syndrome, all in a context of low-grade fever and unquantified weight loss. The patient did not report systemic symptoms, medication use, or exposure to toxic substances, but was originally from a malaria-endemic country.

Clinical examination showed moderately pale conjunctivae and mucous membranes, with splenomegaly extending to the umbilicus, without hepatomegaly or peripheral lymphadenopathy. There was paresthesia in the left lower limb, mild facial paralysis, and diffuse papular skin lesions (Figure 1). The remainder of the physical examination was unremarkable.

Biological investigations revealed pancytopenia on CBC, with normochromic normocytic anemia (Hb at 9 g/dL), thrombocytopenia (41,000/mm³), and lymphopenia (660/mm³). ESR was elevated at 124 mm in the first hour. CRP was high at 19.40 mg/L. Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia. Serologies for HIV, HCV, HBV, and TPHA-VDRL were negative. The Quantiferon test was negative. Liver function tests were normal. Leishmaniasis serology was negative. Renal function was impaired: urea at 0.33 g/L and creatinine at 18.5 mg/L; 24-hour proteinuria at 2.12 g/L. Serum calcium was elevated at 110 mg/L, and total protein was high at 102 g/L. The Bence-Jones protein test showed no monoclonal free light chains, but a monoclonal band was present, corresponding to an immunoglobulin with an undetermined light chain type. Serum free light chain assay showed elevated kappa chains at 335.80 mg/L and lambda chains at 110.20 mg/L, with a kappa/lambda ratio of 3.05.

Thoracoabdominopelvic CT scan revealed splenomegaly (22.5 cm splenic span), without deep lymphadenopathy or peritoneal reaction. Echocardiography was normal.

Bone marrow evaluation via myelogram showed multilineage dysplasia without excess blasts, and karyotype was normal. Bone marrow biopsy revealed morphological and immunohistochemical aspects of granulomatous marrow without caseating necrosis or signs of tumor infiltration (Figure 2). Investigation of other sarcoidosis localizations was carried out: transthoracic echocardiography was normal, serum angiotensin-converting enzyme was elevated at 244 µ/L, and biopsies of the skin and salivary glands showed the same sarcoid granulomas. Renal biopsy was not performed due to thrombocytopenia. Ophthalmologic examination was normal. Pulmonary function tests and DLCO were also normal.

Given this presentation, the differential diagnoses considered were:

- Multifocal tuberculosis
- Visceral leishmaniasis
- Light chain multiple myeloma
- Amyloidosis
- Systemic sarcoidosis

The diagnosis of systemic sarcoidosis with bone marrow involvement was retained, based on splenomegaly with paresthesias, pancytopenia, elevated ACE levels, biological inflammatory syndrome, and histological evidence of sarcoid granulomas on bone marrow, salivary gland, and skin biopsies, along with the exclusion of the aforementioned differential diagnoses.

Therapeutically, the patient was started on corticosteroids at a dose of 1 mg/kg/day with a gradual tapering regimen, resulting in good clinical and biological improvement. A family history of sarcoidosis was later reported (a brother with pulmonary and digestive involvement treated with corticosteroids, and a father with undocumented disease).

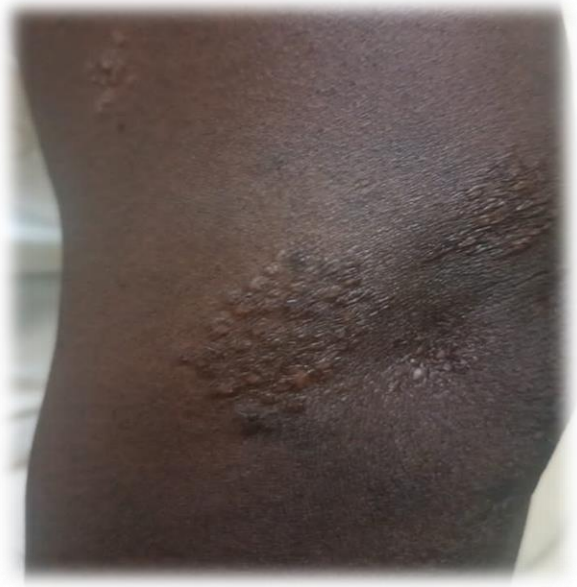

Figure 1 : Diffuse papular skin lesions

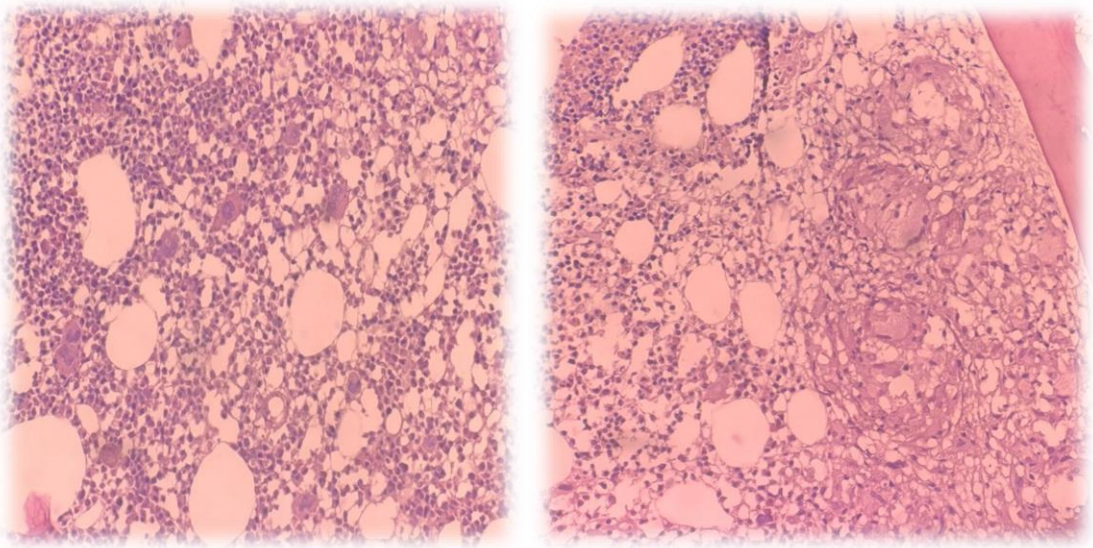

Figure 2 : Representative microphotographs of a bone marrow biopsy showing non-caseating granulomatous inflammation consistent with a diagnosis of sarcoidosis.

DISCUSSION

Sarcoidosis is a systemic disease of unknown etiology, primarily affecting the respiratory system and lymphatic pathways, and is characterized by the formation of immune granulomas in affected organs. The most frequent visceral involvements outside the lungs are superficial lymph nodes, skin, and eyes (3).

Bone marrow involvement in sarcoidosis is rare but has been previously reported (4). Familial forms of sarcoidosis are also rare, representing less than 5% of cases (2). Sarcoidosis is recognized worldwide. It affects individuals of all racial and ethnic groups and can occur at any age, although it typically develops before the age of 50, with an incidence peak between 20 and 39 years (1). The typical characteristics of sarcoidosis are well described (5), and when they are present, they make it easier to include the disease in the differential diagnosis. The presentation can be acute, developing over a few weeks, and such patients often present with constitutional symptoms such as fever, fatigue, malaise, anorexia, or weight loss. The chronic form generally presents with respiratory symptoms. About 10% of these patients have symptoms related to organs other than the lungs and may develop permanent damage in those organs (5).

Sarcoidosis is known to be capable of infiltrating the bone marrow. However, it is rare for it to manifest solely with isolated bone marrow involvement, without radiological abnormalities or signs of dissemination to other organs. Therefore, establishing a diagnosis of sarcoidosis based solely on a bone marrow biopsy is unusual (6). Nevertheless, Lower et al., in a study of 21 cases of sarcoidosis associated

with anemia, observed bone marrow infiltration in 17 cases, underlining the importance of biopsy in sarcoidosis cases presenting with cytopenia (6).

When sarcoidosis affects the bone marrow, it presents with certain specific clinical features. Yanardag et al., in a study of 50 sarcoidosis patients, reported that 5 showed signs of bone marrow infiltration. In these patients, peripheral blood abnormalities such as anemia and leukopenia were observed, and extrathoracic involvement was more frequent (7). In addition, other signs suggestive of bone marrow infiltration by sarcoidosis include elevated erythrocyte sedimentation rate, hypergammaglobulinemia, increased angiotensin-converting enzyme levels, and false-positive rheumatoid factor and antinuclear antibodies (8). In the present case, abnormalities such as anemia, lymphopenia, and thrombocytopenia were observed.

There is no established treatment protocol for pancytopenia related to bone marrow involvement in sarcoidosis, and more cases need to be collected to analyze treatment responses. There are only a few case reports regarding treatment outcomes in sarcoidosis. Lower et al. reported that most patients with sarcoidosis-related anemia improved with oral prednisone treatment (6). Kalajian et al. treated a 41-year-old patient with anemia and leukopenia due to cutaneous and bone marrow involvement using methotrexate and mycophenolate mofetil, with favorable outcomes. Studies suggest that lymphopenia may be a poor prognostic factor, and in cases of steroid treatment failure, other immunosuppressants should be considered early (9).

In the case presented here, the clinical and biological response to corticosteroid treatment was favorable, with normalization of renal function, a decrease in ESR from 124 mm to 78 mm after three months of treatment, and improvement in the complete blood count, although thrombocytopenia persisted without hemorrhagic syndrome. A corticosteroid-induced diabetes also appeared and was managed with well-balanced insulin therapy.

CONCLUSION

Medullary sarcoidosis is a rare and often challenging form to diagnose, presenting with a wide range of clinical manifestations, such as pancytopenia. Although bone marrow involvement is uncommon, it should be considered in patients with systemic symptoms and unexplained blood abnormalities. Diagnosis relies on a combination of clinical, biological, and histological evaluations, with bone marrow biopsy remaining essential. Corticosteroid therapy is the first-line treatment, requiring close monitoring to adjust the treatment according to clinical and biological response. This case highlights the need for increased vigilance and a multidisciplinary approach in managing this complex disease.

Informed Consent

Written informed consent was obtained from the patient for the writing and publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

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