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Case Report

Sarcoidosis-Lymphoma Syndrome: The Impact of Isolated Splenic Sarcoidosis

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Abstract

Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by non-necrotizing granuloma formation in multiples organs. Isolated extrathoracic sarcoidosis has been reported in under 10% of the patients, and so isolated spleen sarcoidosis is extremely rare.

A 68-year-old woman presented to our hospital with 6-month history of anorexia, left hypochondrial discomfort and early satiety, aggravated with high fever, fatigue and generalized myalgia two days before coming to the hospital. The physical examination detected splenomegaly. Laboratory analysis revealed pancytopenia with hemolysis and an elevated angiotensin converting enzyme. Image studies showed splenomegaly with multiple hypoechoic lesions. Infectious and autoimmune etiology was excluded. Bone marrow biopsy excluded lymphoproliferative disease. Patient underwent ultrasonography-guided spleen biopsy finding noncaseating epithelioid cell granulomas. The patient was started on corticosteroids with symptom improvement. Two years after the diagnosis the pancytopenia recurred, and bone marrow biopsy was repeated revealing non-Hodgkin lymphoma infiltration.

Although splenic sarcoidosis was treated and the regular follow-up of the patient it was impossible to predict the development of lymphoma as it is still unknown what is the cause effect link between sarcoidosis and lymphoma.

Keywords: ***Extrapulmonary sarcoidosis, Isolated Splenic Sarcoidosis, Sarcoidosis-Lymphoma Syndrome, Ultrasonography-guided spleen biopsy, Hypersplenism***

Introduction

Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by non-necrotizing granuloma formation [1]. It is hypothesized that failure to eliminate a foreign antigen or lost tolerance to self-antigens in genetically predisposed individual trigger an ongoing immune response leading to granuloma formation and consequent clinical phenotype of sarcoidosis [2].

Age of diagnosis has a bimodal distribution, the most frequent incidence peak is between 25 and 40 years, and a later one is in women over 50 years old [3]. More than 90% of the patients with sarcoidosis have pulmonary involvement [3,4] and the frequency of splenic involvement in sarcoidosis has been reported in 10 to over 50% [5]. However, isolated extrathoracic sarcoidosis has been reported in only approximately 2 to 9% [4,6,7], and so isolated spleen sarcoidosis is assumed to be extremely rare.

The diagnosis of sarcoidosis should include a compatible clinical picture, histological evidence of noncaseating granulomas, and exclusion of alternative diseases [3,8].

Case Description

A 68-year-old woman presented to our hospital with 6-month history of anorexia associated with left hypochondrial discomfort and early satiety. She also described high fever a couple days before coming to the hospital, fatigue and generalized myalgia. The physical examination detected spleen enlargement and tympanic temperature of 40.1ºC, but no other remarkable findings.

The patient had past medical history of arterial hypertension, epilepsy and dyslipidemia for which she was medicated with losartan, carbamazepine and simvastatin. There were no epidemiological risk factors for infectious diseases.

The initial laboratory studies revealed pancytopenia (hemoglobin 6.5g/dL, 3000/µL leucocytes and 55000/µL platelets) with signs of hemolysis (reticulocitosys with a relative response of 6.99%, elevated lactic dehydrogenase of 2922 U/L, indirect hyperbilirubinemia and reduced haptoglobin <7.4mg/dL) and an elevated angiotensin converting enzyme (132 U/L). The peripheral blood smear and immunophenotyping were normal.

Abdominal ultrasonography showed important splenomegaly with multiple hypoechoic lesions and thoraco-abdominal computed tomography scan confirms spleen craniocaudal dimension over 20cm with hypodense nodular regions with geographical distribution and no other relevant findings.

Infectious etiology was excluded, namely viral infections, leishmaniosis or other zoonoses and tuberculosis. Autoimmunity study was also negative (**Table 1**). Bone marrow biopsy excluded lymphoproliferative disease (histopathology description of hyperplasia of erythroid and granulocytic lineages, suggestive of reactive bone marrow, without immunophenotypic findings compatible with lymphoproliferative disease).

Patient underwent ultrasonography-guided spleen biopsy which histopathologic examination showed noncaseating epithelioid cell granulomas, without evidence of lymphoproliferative disease.

Positron emission tomography with 18F-fluorodeoxyglucose was performed for diagnostic guidance and characterization of disease extent, demonstrating heterogeneous

splenomegaly with nodular lesions probably related to active inflammatory granulomatous disease. No other locations of the disease were detected (**Figure 1**).

Given the presence of non-necrotizing granulomas in the spleen, and the absence of alternative possible diseases, it was assumed a diagnosis of splenic sarcoidosis. Corticosteroid therapy was initiated with great symptom improvement, complete resolution of the pancytopenia and mild reduction of the spleen size. The patient remained asymptomatic for over a year with a reduced dose of prednisolone of 5mg/day.

Eighteen months after the diagnosis and 2 years after disease onset, pancytopenia recurred. Bone marrow biopsy was repeated revealing non-Hodgkin B cell lymphoma infiltration. The patient underwent through 6 cycles of chemotherapy and was on remission for the following 6 months until the date of publication of this case report.

Table 1: Complementary diagnostic tests during hospitalization

Blood cultures	Sterile
Hbs Antigen	Negative
HCV Antigen	Negative
HIV 1 / 2 Antibodies	Negative
CMV Antibody (IgM)	Negative
Anti-EBV Antibody (IgM)	Negative
Anti-Parvovirus Antibody (IgM)	Negative
Anti-Mycoplasma pneumoniae Antibody (IgM)	Negative
Anti-Borrelia burgdorferi Antibody (IgM)	Negative
Anti-Leptospira interrogans Antibody	Negative
Toxoplasmose Antibody (IgM)	Negative
Huddleson Reaction	Negative
Ricketsia conori PCR test	Negative
Coxiela burnetti PCR test	Negative
Leishmaniose PCR	Negative
Interferon-Gamma Release Assays	Negative
Rheumatoid factor	Negative (<10 UI/mL)
Anti-cyclic citrullinated peptide antibody	Negative (0,4 UI/mL)
Anti-nuclear antibody	Negative
Anti-double stranded DNA	Negative (<0,5 UI/mL)
Antineutrophil cytoplasmic antibody	Negative (<0,2 UI/mL)
Anti-extractable nuclear antigen	Negative

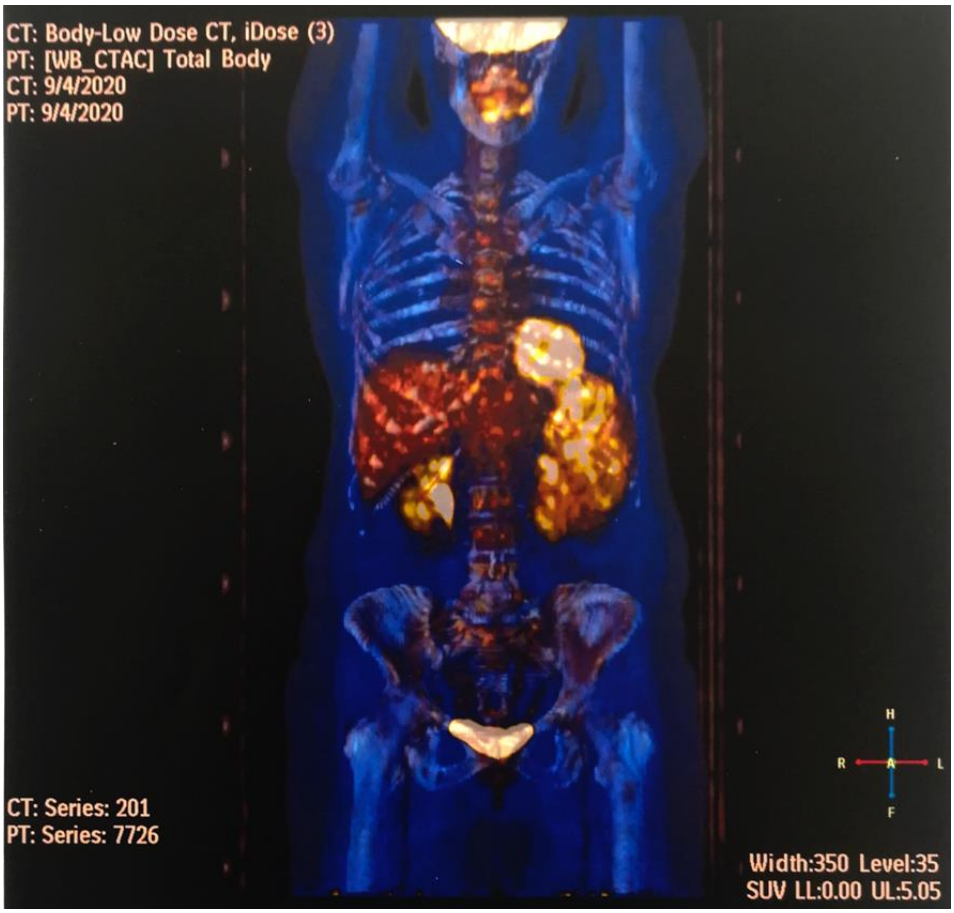

Figure 1: Positron emission tomography with 18F-fluorodeoxyglucose demonstrating heterogenous splenomegaly with multiple nodular lesions.

Discussion

The authors present a case of chronic isolated splenic sarcoidosis which later developed to B cell non-Hodgkin Lymphoma, a clinical presentation described in the literature as a Sarcoidosis-Lymphoma Syndrome.

It is known that longstanding inflammation and immune dysregulation present in sarcoidosis patients increase their risk of developing malignancies, and hematopoietic cancers are the most likely manifestation [9,10].

Brincker et al. were the first to report an increased risk of cancer in sarcoidosis, with a series in which lymphoma occurred 11 times more frequently in the sarcoidosis group, compared to the expected risk of lymphoma in the general population, and naming this the Sarcoidosis-Lymphoma Syndrome [11]. More recent studies describe more modest increases in risk, ranging from 1.87 to 5.5-fold [4,12].

In sarcoidosis patients, chronic inflammation has been established as a contributing factor in carcinogenesis [13]. Besides, the increased mitotic activity of lymphocytes in affected tissues could promote cell mutation and subsequent malignant transformation. This hypothesis is supported by studies that report hematologic malignancies as the most frequent cancer in sarcoidosis patients [12-14].

Diffuse splenic involvement appears to be a risk factor for persistent chronic sarcoidosis and higher granuloma burden in the spleen is associated with worst prognosis [3,15].

In the Sarcoidosis-Lymphoma Syndrome, lymphoma typically occurs 2-8 years after the diagnosis of sarcoidosis [16], mainly in patients with a chronic active form of sarcoidosis [17] and non-Hodgkin lymphoma is the most commonly reported subtype [18].

In the described clinical case, the diffuse splenic involvement led to chronic sarcoidosis probably conditioning a higher predisposition to lymphoma development.

Conclusion

Overall, the presence of extra-thoracic sarcoidosis warrants close monitoring of patients, particularly those with chronic active disease or splenic involvement, considering the potential association between sarcoidosis and lymphoma.

Declaration of Interest Statement

"The authors declare that there is no conflict of interest regarding the publication of this paper."

List of Abbreviations

Not applicable.

Data Availability

Not applicable.

Conflicts of Interest

"The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper."

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Authors' Contributions

ARP, research design, data collection drafting of the paper and spelling revision.

FC, RS, MF, EP, research design, data collection and intellectual content revision.

All authors read and approved the final manuscript.

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