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Severe Thrombocytopenia Associated With Excavated Mediastinopulmonary Sarcoidosis: A Case Report

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Abstract
Sarcoidosis is a systemic granulomatous disease of unknown cause. The excavated pulmonary form is an atypical form of sarcoidosis because of its similarity to certain infectious diseases, notably tuberculosis, which is a source of confusion for the clinician and should lead to a search for differential diagnoses. The haematological manifestations of sarcoidosis are rare and may include haemolyticanaemia, leukopenia, eosinophilia and peripheral lymphopenia, but thrombocytopenia remains rare. The causes of thrombocytopenia in sarcoidosis have been identified by a few mechanisms. The purpose of this article is to make the clinician aware of these two particular forms of presentation of sarcoidosis. There are no current guidelines for the treatment of thrombocytopenia in sarcoidosis. However, in emergency situations with major thrombocytopenia, it seems reasonable to apply the current guidelines recommended for idiopathic thrombocytopenic purpura.

Keywords :*Excavatedmediastinopulmonarysarcoidosis, severe thrombocytopenia*

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I. Introduction

Sarcoidosis is a granulomatosis of unknown etiology, with a predominantly pulmonary tropism (1-2-3). Thoracic involvement is classically characterized by bilateral hilar adenopathy (95% of cases), associated or not with diffuse micronodular or reticulomicronodular interstitial infiltrates. However, other atypical and rare pulmonary manifestations of the disease are possible, such as the excavated form (4), and although hematological manifestations such as lymphopenia and anemia are often detected, thrombocytopenia is a rare extrapulmonary complication (1-2%) (5-6).Three mechanisms have been suggested as follows: hypersplenism, medullary invasion by granulomas or an immunological mechanism. Severe thrombocytopenia with haemorrhagic events is exceptional in sarcoidosis (6-7-8), and the aim of this article is to shed light on these two particular and rare forms of sarcoidosis: the excavated pulmonary form, which can lead to confusion with other underlying conditions, including infection: pulmonary tuberculosis, pulmonary aspergillosis, tumor pathology or other granulomatous disease (4); and thrombocytopenia, which can be life-threatening in patients with hemorrhage. We report a case of excavated mediatinopulmonary sarcoidosis presenting with severe thrombocytopenia.

II. Observation

Patient aged 47, with no notion of exposure, former chronic smoker of 16 pack-years weaned 2 years ago, chronic alcoholic in the process of weaning, with no medical or surgical history, symptomatology dates back 4 months and consists of a progressively worsening dry cough with exertional dyspnea, currently classified as mMRC stage II, with fever and night sweats, and weight loss not quantified, physical examination revealed a patient in fairly good general condition (PS 1), skin and mucous membrane examination revealed normally colored conjunctivae with extensive vitiligo lesions, pleuropulmonary examination revealed an eupneic patient, room air Spo2 was 96%, with diffuse bilateral crepitus rales. Abdominal examination was normal, with no hepatosplenomegaly, lymph nodes were free, and the rest of the somatic examination was unremarkable. Chest X-ray showed bilateral diffuse reticulonodular opacities with left apical excavated image and bilateral hilar opacities, **Figure 1**. thoracic CT scan showed bilateral diffuse nodules and micronodules of random distribution with thickened walls of the left upper lobar cavities with no endoluminal images and foci of alveolar condensation involving the posterior segment of the right upper lobe and left fowler, peribronchovascular thickening and interlobular and intralobular septa in the middle lobe, subpleural reticular infiltrate, bilateral apical para-septal emphysema bullae, **Figure 2 (A)** bilateral non-compressive mediastino-hilar adenopathy, the majority of which are calcified, the most voluminous being located in the 4R chain, measuring : 15mm short

axis, **Figure 2 (B),** the phthisiological workup was negative, including BK in sputum (direct examination and culture), and the expertMTBrif, TB Gold quantiferon was also negative, blood count showed normal hemoglobin, with thrombocytopenia at 3000/µL and lymphopenia at 789/µL; blood ionogram, renal, liver and calcium levels were normal; protein electrophoresis showed a moderate increase in alpha-1-globulins and beta-2-globulins, HIV and viral hepatitis serology was negative, tumor markers for extra-pulmonary neoplasia were negative, immunological workup was also negative, including anti-nuclear antibodies, anti-DNA antibodies, Ac anti-soluble antigens, rheumatoid factor, Ac anti-circulating coagulants, Ac anti-NNP cytoplasm, Ac anti-citrullinated cyclic peptides, latex reaction, Ac anti-beta 2 glycoprotein 1 igm, Ac anti-beta 2 glycoprotein 1 Igg, with doubtful Ac anti-cardiolipin Igg and Igm, systemic corticosteroid therapy based on prednisone 40 mg/day was started for 3 weeks with rapid reduction to 10 mg/week, increasing the platelet count to 114,000/µL, and completing the etiological work-up, in particular biopsy of the accessory salivary glands, which showed no specific abnormality; flexible bronchoscopy showed thickening of the interlobar spurs; bronchial biopsy was inconclusive; bronchial aspiration for BK was negative, Sternal biopsy showed peripheral thrombocytopenia, abdominal ultrasound was normal, electrocardiogram was unremarkable, ophthalmological examination was normal, plethysmography showed a mild restrictive ventilatory disorder with hyperinflation, CPT is 4l 370 (77%) and RV is 2l 990 (157%), DLCO is normal, no O2 desaturation on 6-min walk test with a walking perimeter of 420 m, tansthoracic echocardiogram was normal.

The diagnosis of mediastinopulmonary sarcoidosis with hematological involvement was accepted.

The patient was put on oral corticosteroid therapy with prednisone 40 mg/d for 3 months, tapering off by 10 mg every 4 weeks to a maintenance dose of 10 mg maintained for 6 months. In view of the severe thrombocytopenia with a high risk of bleeding, the patient was also put on intravenous immunoglobulin 1 g/kg on D1, which increased the platelet count to 120,000/µL without the need for a second dose on D3.

The patient's progress was marked by clinical, biological and functional improvement, with radiological stability.

III. Discussion

While the classic pulmonary features of sarcoidosis (hilar adenopathy, interstitial infiltrate) easily lead to diagnosis, it is important not to overlook the possibility of atypical (pulmonary nodules, cavitations, etc.) and potentially serious pulmonary manifestations of the disease (4).

Although rare, the association of thrombocytopenia and sarcoidosis has been fully documented. A review of 381 cases of thrombocytopenic purpura showed that five patients had sarcoidosis (1%), and in a series of 324 patients with sarcoidosis, 2% had thrombocytopenia defined as a platelet count below 100,000/µL. Moulis et al. reported that sarcoidosis accounts for 0.62% of all patients with immune thrombocytopenia and 3.47% of patients with secondary immune thrombocytopnenia (9).

The causes of thrombocytopenia in sarcoidosis have been identified as three main mechanisms. Several mechanisms may be involved in the same patient. The first pathophysiological mechanism of thrombocytopenia in sarcoidosis is related to hypersplenism and splenomegaly. Thrombocytopenia related to hypersplenism in sarcoidosis should always be suspected in a patient presenting with splenomegaly and varying degrees of cytopenia (leukopenia, anemia, thrombocytopenia); the second is granulomatous infiltration of the bone marrow in sarcoidosis, which appears to be rare and not clearly associated with thrombocytopenia; and the third mechanism is autoimmunity, with autoantibodies against platelets leading to increased peripheral destruction (immune thrombocytopenia)(6-10-11). Several studies have shown that severe thrombocytopenia in sarcoidosis is most likely secondary to an immune process (9-12), In the case of our patient, there was no splenomegaly, his sternal biopsy showed peripheral thrombocytopenia and there was no secondary cause identified, so immune thrombocytopenia is evoked. Moreover, there was a good response to immunosuppressive therapy, supporting an immune process causing platelet destruction.

The exact molecular mechanism by which sarcoidosis leads to immune thrombocytopenia remains unclear. CD8+ T cells have been shown to participate in platelet apoptosis in immune thrombocytopenia, and the number of CD8+ T cells expressing cytolytic molecules such as perforin, granzyme B and granulysin has been shown to be increased in patients with sarcoidosis compared with those without sarcoidosis (5-13).

There are no current guidelines for the treatment of thrombocytopenia in sarcoidosis. In the literature, steroids can be recommended as first-line treatment, and may act on all the pathophysiological mechanisms involved (granulomas in the bone marrow, splenomegaly and autoimmune processes). However, in emergency situations with major thrombocytopenia, it seems reasonable to apply the current guidelines recommended for idiopathic thrombocytopenic purpura. These situations require intensive treatment: methylprednisolone (1 g/day for two days) or/and intravenous immunoglobulin (IG-Iv) (1 g/kg per day for 3 days) and, if necessary, platelet transfusions. Splenectomy should be reserved for patients whose thrombocytopenia is not controlled by steroids or IG-Iv. Aziathioprine, cyclophosphamide, vincristine and adalimumab, rituximab may also be used (6-10).

IV. Conclusion

Excavated lung involvement and thrombocytopenia in sarcoidosis are rare events. Different pathophysiological mechanisms are responsible for thrombocytopenia in sarcoidosis. Granulomas in the bone marrow or hypersplenism may be involved. In all other cases, immune thrombocytopenia should be suspected. Steroids remain the most effective treatment and should be offered as first-line therapy.

Legend :

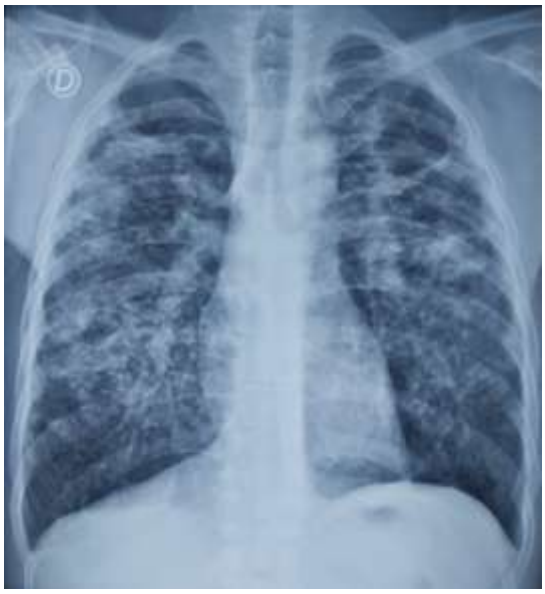

Figure 1: Chest X-ray: bilateral diffuse reticulonodular opacities with left apical excavated image and bilateral hilar opacities

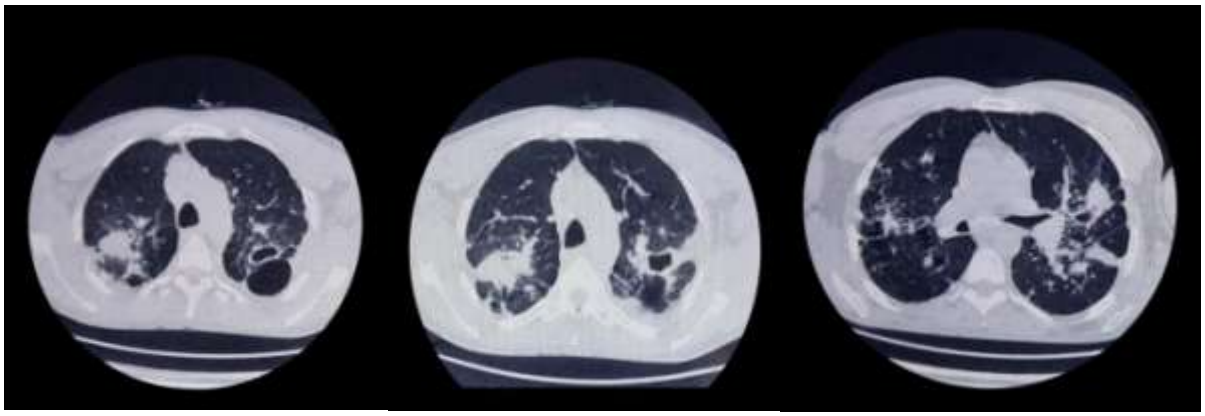

Figure 2 (A) Thoracic computed tomography (parenchymal window): bilateral diffuse nodules and micronodules of random distribution with thickened-walled left upper lobar cavitary images without endoluminal images and foci of alveolar condensation involving the posterior segment of the right upper lobe and left fowler ,peribronchovascular thickening and

interlobular and intralobular septa in the middle lobe ,subpleural reticular infiltrate ,bilateral apical para-septal emphysema bullae

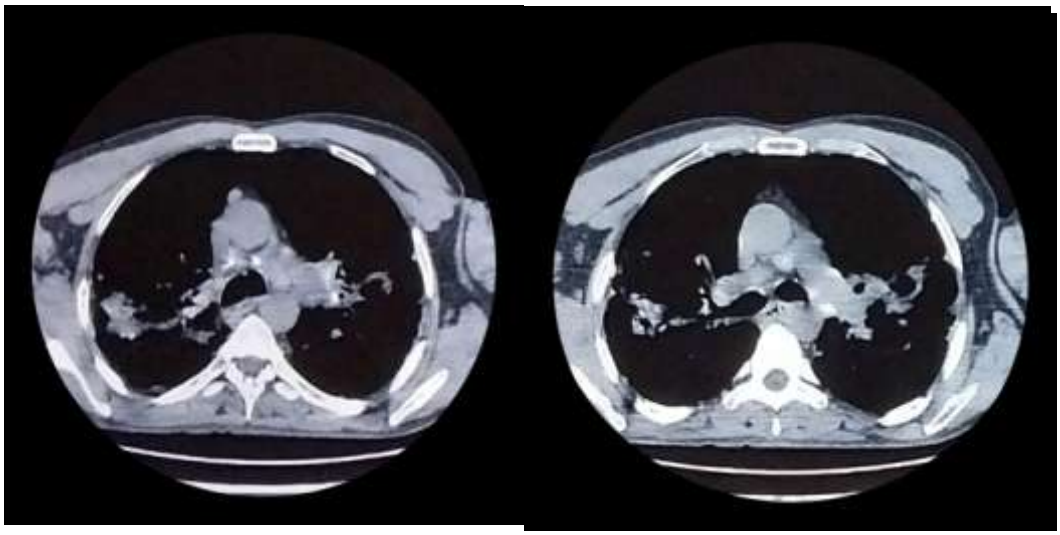

Figure 2 (B): Thoracic computed tomography (mediastinal window) non-compressive bilateral mediastino-hilar adenopathy, the majority of which are calcified, the largest of which is located in the 4R chain, measuring 15mm in minor axis

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