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Primary immune thrombocytopenia in a patient with sarcoidosis

Pierwotna małopłytkowość immunizacyjna u chorej na sarkoidozę

Abstract

Sarcoidosis is a disease characterised by a highly variable clinical course. While it may be accompanied by various immune disorders, it is rarely accompanied by disorders of the haematopoietic system. We report a case of sudden-onset primary immune thrombocytopenia co-existing with sarcoidosis. The prevalence of primary immune thrombocytopenia in patients with sarcoidosis is estimated at about 2% and about 1% of patients with thrombocytopenia are diagnosed with sarcoidosis. Three potential pathomechanisms leading to the development of thrombocytopenia in sarcoidosis have been described, namely: (1) the presence of antiplatelet antibodies, (2) presence of epithelioid cell granulomas in the bone marrow and (3) hypersplenism.

Key words: sarcoidosis, primary immune thrombocytopenia, mediastinal lymph node enlargement, mediastinal lymphadenopathy

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Introduction

Sarcoidosis is a granulomatous disease of unknown aetiology which most commonly involves the lungs and lymph nodes. Other organs, such as the skin, eyes and heart are less commonly involved. The clinical picture of sarcoidosis is highly variable, which results from the fact that, in addition to the organs mentioned above, sarcoidosis may develop in any other anatomical location [1]. For this reason, in addition to the commonly observed clinical syndromes, the disease may manifest with unusual signs and symptoms in unusual locations [2, 3]. The impact of racial differences on the affected organs is well known. One of the reasons for the high variability of the clinical picture of sarcoidosis may be the difference in the evolution and severity of its clinical manifestations.

In some patients, sarcoidosis may co-exist with other conditions and the clinical picture may be dominated by the manifestations of the co-morbidities. Autoimmune diseases, particularly autoimmune diseases of the thyroid gland, are the most frequent co-morbidities seen in patients with sarcoidosis [4, 5]. In very rare cases, sarcoidosis may co-exist with blood and/or haematopoietic system disorders with one such condition being idiopathic immune thrombocytopenia, previously known as idiopathic thrombocytopenic purpura (ITP). The aetiology of idiopathic immune thrombocytopenia has not been fully elucidated and the condition involves the formation of antiplatelet antibodies which cause platelet destruction or suppress platelet formation in the bone marrow. It is believed that idiopathic immune thrombocytopenia may develop in association with *Helicobacter pylori*

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infection [6]. Another postulated pathomechanism leading to the development of idiopathic immune thrombocytopenia may be the relative deficiency of endogenous thrombopoietin (eTPO), an important regulator of platelet formation [7]. The reduced platelet count leads to abnormalities of haemostasis and the resulting clinical manifestations. We report a case of primary immune thrombocytopenia co-existing with sarcoidosis.

Case report

A 33-year-old woman with no previous medical history, a non-smoker working as a nurse, presented to the hospital with numerous ecchymoses, skin petechiae and mild haemoptysis. The skin changes had appeared two days before and the haemoptysis developed on the day of presentation. The patient denied symptoms of infection and had not taken any medication before. For the past six months she had felt weak and her exercise tolerance had been lower than usual.

The patient was admitted to the Department of Haematology, Oncology and Internal Medicine, Medical University of Warsaw, Poland. The patient's general condition on admission was good and the physical examination revealed a slim figure (BMI 19.5 kg/m²) and numerous ecchymoses located mainly in the skin of the lower extremities. No other abnormal findings were observed. The complete blood cell count revealed thrombocytopenia (platelet count 6.0 G/l), a red blood cell count of 4.48 T/l, a haematocrit of 37.5%, a haemoglobin concentration of 13.1 g/dl and a white blood cell count of 4.08 G/l. The differential blood cell count was normal. The values of the coagulation parameters were normal (INR 0.99, APTT 32.9 s, fibrinogen 262 mg/dl, D-dimers 186 ng/ml). The tests for hepatitis B, hepatitis C and for human immunodeficiency virus (HIV) were all negative. The chest X-ray revealed a widened superior mediastinum on the right, widened pulmonary hili and a normal picture of the pulmonary parenchyma. The abdominal ultrasound scan did not reveal any pathologies of the liver and spleen or any enlarged lymph nodes.

Due to the presence of a symptomatic haemorrhagic diathesis and the markedly reduced platelet count the patient received a transfusion of 3 units of platelet concentrate, although no increase in platelet count could be achieved (the post-transfusion platelet count was 1.0 G/l). Based on the clinical picture and the results of the investigations the diagnosis of suspected primary immune thrombocytopenia was established and the patient was

started on prednisone 1 mg/kg PO, followed by immunoglobulins 0.5 g/kg for 3 days up to a total dose of 102 g. As a result of the treatment platelet count increased to 70 G/l, which allowed us to undertake more invasive investigations necessary for the differential diagnosis of thrombocytopenia. As the radiographic picture suggested mediastinal lymphadenopathy, we assumed that the most likely cause could be a lymphoproliferative process.

A bone marrow trephine biopsy was performed and the myelogram revealed a picture consistent with primary immune thrombocytopenia; the histopathological examination of the trephine biopsy revealed normal composition and differentiation of haemopoietic cells; megakaryocyte counts and morphological forms were normal. The chest CT scan revealed the enlargement (up to 35 mm in diameter) of the paratracheal and hilar (bilaterally) lymph nodes, subcarinal lymph nodes and the aortopulmonary window lymph nodes. The other findings included sparse small extralobular nodules of perivascular location in the middle lobe and in the posterior segment of the right upper lobe (Figures 1 and 2). The abdominal CT scan revealed isolated slightly enlarged (up to 12 mm in the short axis) lymph nodes in the abdominal cavity: bilaterally in the vicinity of the diaphragmatic crura and in the vicinity of the aorta on the left below the ostium of the left renal artery. In the scan, the spleen was not enlarged, although it hosted a small 8-mm hypodense mass of unknown nature.

The patient was qualified for mediastinoscopy in order to obtain tissue samples from the mediastinal lymph nodes and the procedure was performed at the Department of Thoracic Surgery, The Institute of Tuberculosis and Lung Diseases in Warsaw. The histopathologic examination of the tissue samples collected from the right inferior paratracheal lymph nodes revealed coalescing epithelioid cell granulomas without signs of necrosis but with extensive fibrosis. In light of this histologic picture sarcoidosis was considered as the most likely differential diagnosis.

In order to complete the diagnostic evaluation the patient was admitted to the Department of Internal Medicine, Pneumology and Allergy, Medical University of Warsaw. Due to primary immune thrombocytopenia she was still taking prednisone 40 mg/day.

The patient's general condition on admission was good, no signs of purpura were present and the only significant finding on physical examination was the mediastinoscopy scar. Laboratory tests revealed a normal platelet count (236 G/l), nor-



Figure 1. Transverse reconstruction of thorax computed tomography with *maximal intensity projection (MaxIP)* post-processing (mediastinal window at the level of the right main stem bronchus division into upper lobe bronchus and bronchus intermedius. Enlarged subcarinal and the right hilum lymph nodes are clearly seen. Smaller lymph nodes are also recognizable in the left hilum



Figure 2. Transverse reconstruction of high resolution computed tomography of the lung with the use of *maximal intensity projection (MaxIP)* post-processing method showing multiple, well defined nodules with perivascular distribution (predominantly in the lateral segment of the middle lobe)

mal serum levels of calcium (2.39 mmol/l), normal levels of angiotensin-converting enzyme (34.5 U/l; normal range < 50 U/l) and slightly elevated serum levels of gammaglobulin (1.45 g/dl). The spirometry and whole body plethysmography revealed normal values of lung volumes and no signs of airway obstruction (carbon monoxide diffusing capacity and lung compliance were not determined due to technical reasons). The results of sputum testing for acid-fast bacilli (both smears and cultures) performed three times were all negative. The tuberculin skin test was negative (0 mm). The echocardiogram revealed normal dimensions of the cardiac chambers, normal global contractility and the absence of segmental contractility abnormali-

ties. The 24-hour ambulatory electrocardiogram revealed no significant rhythm or conduction abnormalities. The consulting ophthalmologist did not identify any changes typical of sarcoidosis in the eyes. In order to collect samples from the bronchial mucosa and from the groups of lymph nodes from which no samples had been collected during the mediastinoscopy the patient underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The tissue samples of the bronchial mucosa revealed a mild inflammatory infiltrate and foci of fibrosis without the presence of granulomas or abnormal cells. The cytologic examination of the material obtained during the EBUS-TBNA did not reveal any abnormal cells. Based on the clinical picture and the results of the investigations the final diagnosis of sarcoidosis and primary immune thrombocytopenia was established. The patient has been in the care of the pulmonology clinic and the haematology clinic for three months now and continues to be treated with prednisone, which is now being tapered off.

Discussion

Due to the high variability of signs and symptoms, the diagnosis of sarcoidosis can often be difficult and requires numerous investigations and an extensive differential diagnosis. Even in patients with the involvement of typical organs, such as the lungs and the mediastinal lymph nodes, the diversity of radiological manifestations may be high enough to make the diagnosis quite challenging [8]. Coexistence of sarcoidosis with other conditions may be an additional difficulty. In such cases, the clinical manifestations may result from sarcoidosis, the co-morbid condition or both. Diseases co-existing with sarcoidosis may include: autoimmune thyroiditis, coeliac disease, Crohn's disease, Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis [4, 5].

The diagnosis of sarcoidosis is definite, if non-caseating epithelioid cell granulomas can be demonstrated in a histopathological examination in the context of typical clinical manifestations and a characteristic radiographic picture. On the other hand, it is necessary to rule out other conditions in which granulomas may be present (e.g. mycobacterioses, fungal infections, brucellosis, cat scratch disease, Whipple's disease, berylliosis). In some patients in whom granulomas are detected but whose clinical picture is not characteristic of any of the known granulomatous diseases, the diagnosis of granulomatous lesions of unknown significance (GLUS) is made. Another issue is the occurrence of the so-called sarcoid reaction, which

should be included in the differential diagnosis, particularly in cases of sarcoidosis of atypical course. Sarcoid reaction may accompany various malignancies with the most common ones being lymphomas, seminomas and carcinomas (e.g. carcinomas of the kidney, prostate and lung) [8–10].

The clinical manifestations preceding the development of the haemorrhagic diathesis in our patient were very limited (asthenia and reduced exercise tolerance), which may be interpreted as an argument supporting the diagnosis of sarcoidosis rather than a malignancy. However, due to the fact that the thrombocytopenia was accompanied by a marked mediastinal lymphadenopathy, we initially included haematopoietic malignancies in the differential diagnosis as the most likely causes. We considered the possibility of sarcoidosis when we obtained the results of the histopathological examination of the mediastinal lymph nodes. Additional investigations allowed us to rule out other infectious causes, mainly tuberculosis. In order to rule out sarcoid reaction accompanying a potential malignancy we decided to perform bronchoscopy with sampling of tissues from other sites than those from which biopsies had been collected during the mediastinoscopy.

The reason for the diagnostic concerns in the case of our patient was the sudden onset of thrombocytopenic purpura of a fulminant course, which rarely accompanies sarcoidosis. The most common haematological abnormalities reported in sarcoidosis include leukopenia, lymphopenia and normocytic anaemia [11]. The disorders of the haematopoietic system that rarely co-exist with sarcoidosis include autoimmune haemolytic anaemia and primary immune thrombocytopenia [4]. In studies published in the 1960s, the prevalence of primary immune thrombocytopenia in patients with sarcoidosis was estimated at 2% [12] and 1% of the patients with thrombocytopenic purpura were reported to be subsequently diagnosed with sarcoidosis [13]. Co-existence of sarcoidosis and haematopoietic malignancies were also described in literature. A patient was reported in whom sarcoidosis preceded the onset of polycythaemia vera [14].

The co-existence of sarcoidosis and thrombocytopenia may involve three different mechanisms [15]. The first and most common is related to the presence of antiplatelet antibodies which result from stimulation of B cells to form polyclonal antibodies, including antiplatelet antibodies. In the second mechanism, bone marrow involvement with the formation of non-caseating granulomas is observed [16]. The histopathological examination

of the bone marrow in our patient did not reveal the presence of granulomas. The third mechanism involves hypersplenism leading to excessive destruction of platelets [15]. Our patient's spleen was not enlarged and her red blood cell and white blood cell counts were both normal. The good response to treatment (prednisone, immunoglobulins) and the persistently normal platelet count over the 3 months of follow-up are the arguments against hypersplenism. The clinical course and the response to treatment suggest a role of antiplatelet antibodies, although their presence has never been documented. It should be noted, however, that in about 40% of the cases of primary immune thrombocytopenia the presence of antiplatelet antibodies cannot be confirmed and their determination is not routinely recommended [17, 18].

Whether the thrombocytopenia co-existing with sarcoidosis may be considered primary or secondary immune thrombocytopenia is disputable. We assumed it to be primary immune thrombocytopenia according to the nomenclature included in most of the previous reports.

We found several reports of sarcoidosis co-existing with immune thrombocytopenia, but only one described a thrombocytopenia of such a sudden onset and such a fulminant course as the thrombocytopenia in our patient [19].

Due to the rare co-existence of thrombocytopenia and sarcoidosis little is known about the courses of these two conditions. Mahevas et al. reviewed the literature (covering the years 1972–2005) and identified 31 cases of sarcoidosis co-existing with thrombocytopenia [15]. In 16 patients, the symptoms of thrombocytopenic purpura preceded the diagnosis of sarcoidosis, while in the remaining patients, the diagnosis of sarcoidosis preceded the onset of thrombocytopenia. The mean platelet count was 12 G/l (range: 2–83 G/l). Two patients died from haemorrhage. About half of the patients (15/31) were diagnosed with stage I sarcoidosis.

In 2009, the same authors presented an analysis of 20 patients in whom both conditions had been diagnosed [20]. The mean platelet count was 11 G/l and as many as 35% had symptomatic bleeding. Most patients had been managed with glucocorticosteroids and half of them had received immunoglobulins, which led to complete or partial remission of thrombocytopenia in most of them. Due to the chronic course of immune thrombocytopenia 60% of these patients received long-term treatment with maintenance doses of glucocorticosteroids (an average of 10 mg of prednisone daily). Only 2 patients (10%) required splenecto-

my and a further 2 (10%) were successfully treated with rituximab. Of note is the fact that during the 6 years of follow-up, in the group of patients with sarcoidosis co-existing with primary immune thrombocytopenia, as many as 70% had pulmonary sarcoidosis and as many as 55% had relapses of sarcoidosis. This analysis suggests that immune thrombocytopenia accompanying sarcoidosis may have an acute onset and a fulminant course. Although the prognosis in terms of platelet count increase in such patients — is good, the course and prognosis of sarcoidosis in such individuals may be worse than in others.

Limitations of our study include the fact that the diagnostic evaluation of the respiratory system was performed after the initiation of prednisone and the lack of a complete assessment of pulmonary function. Another deviation from the widely accepted diagnostic algorithm was the decision not to perform bronchoalveolar lavage (BAL). The decision resulted from positive result of a mediastinoscopy, and the fulminant clinical course of disease. The histopathological examination of the resected lymph node revealed the presence of non-caseating epithelioid cell granulomas. According to Grutters et al. [5], in patients with the histopathological diagnosis of granulomas, BAL is of secondary importance. Therefore, in this particular clinical situation, the decision not to perform BAL seems justified.

Conclusions

Sarcoidosis may co-exist with haematopoietic disorders, including primary immune thrombocytopenia. The course of primary immune thrombocytopenia in patients with sarcoidosis may have a relatively fulminant course and lead to a considerable reduction in platelet counts. A haemorrhagic diathesis may be the first sign in these patients.

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