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# Massive splenomegaly and pancytopenia revealing sarcoidosis in a child

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**Abstract.** Clinical presentation of sarcoidosis in children is very variable and dependant upon age. Herein, we report the first association of massive splenomegaly and pancytopenia as the revealing mode of sarcoidosis in an 8-year-old girl who, despite bone marrow involvement, had a remarkable good outcome following steroid therapy. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 149-152)*

**Key words:** sarcoidosis, splenomegaly, pancytopenia, child

Sarcoidosis is a multisystemic granulomatous disease of unknown aetiology which is rare in children (1-3). The observed differences in prevalence and in clinical presentation between different ethnic groups support the existence of predisposing genes, with a possible role of the major histocompatibility complex system (4). Sarcoidosis diagnosis requires typical histopathological findings with non-caseating epithelioid-cell granulomas (5). Its prognosis seems to be more severe in younger children with multi-organ involvement (3). Lesions may occur in almost any tissue or organ. Lungs, lymph nodes, eyes, skin, joints and liver are commonly involved, but spleen and bone marrow are rarely diseased. We report here an unusual observation of a young girl with the main clinical features of sarcoidosis at presentation being massive splenomegaly and pancytopenia.

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## Case-Report

An 8-year-old girl was referred to our hospital for pallor and massive splenomegaly. Her parents were healthy and non-consanguineous. She was born in Algeria and moved to France at 6 years old. Medical examination revealed an enlarged spleen whose edge was 18 cm below the lower rib, without hepatomegaly or peripheral adenopathy. Complete blood count (CBC) showed a severe pancytopenia: white blood cell count was 1.160 G/L (neutrophils: 0.628 G/L; lymphocytes: 0.380 G/L; monocytes: 0.180 G/L); hemoglobin concentration was 8 g/dL (MCV: 69 fL, reticulocytes: 12 G/L) and platelet count was 46 G/L. Other blood tests showed a decreased coagulation activity (fibrinogen: 1.4 g/L, prothrombin time: 58%), and mild increases in serum inflammatory markers (C-reactive protein: 35 mg/mL, ESR: 14 mm/h). Although a hemophagocytic syndrome might have been suspected (combination of fever, splenomegaly, pancytopenia and coagulopathy), the absence of hemophagocytic features on blood smear examination ruled out this diagnosis. The research for autoimmunity markers such as

Coombs test or anti-platelet antibodies was negative. An *Escherichia coli* urinary infection was diagnosed and promptly treated. The bone marrow smear showed a normal cellularity without any abnormal cell. A careful screening of the bone marrow smear ruled out the possibility of abnormal storage cells or parasitic infections such as leishmaniasis. The abdominal CT scan confirmed a heterogeneous splenomegaly, without hepatomegaly, but with hypodense perivascular infiltration (figure 1a). Chest and skeletal x-ray were normal. Bone marrow cytogenetic and enzymatic studies were normal and ruled out Gaucher's and Niemann-Pick diseases. Functional lymphocytes tests and humoral immunity tests, including profiles of vaccinal antibodies, were within the normal range. There was no increase in double-negative (CD4-CD8-) T cells.

As the pancytopenia and the splenomegaly remained quite stable, with limited transfusion needs (about 1 red cells pack every 6 weeks), the work-up was completed by a bone marrow trephine biopsy 3 months after the first clinical examination. The hematein-eosin-saffron stained bone marrow tissue sections showed epithelioid granulomas, leading to consider the diagnostic of a granulomatous disease (figure 2a). Because of the high risk of bleeding, biopsy of the spleen is almost never done. Thus, to search for histopathological features, a biopsy of the minor salivary glands was performed, that revealed no epithelioid granuloma but a lymphocytic infiltration (figure 2b). Finally, the increased plasma concentration of angiotensin converting enzyme (ACE: 269 UI/mL) and the presence of bilateral hilar and mediastinal lymph nodes with several lung nodules on the lung CT scan (figure 1b-1c) led to the diagnosis of sarcoidosis (6). Pulmonary function tests showed a decreased dynamic lung compliance (CL-dyn 65% predicted) with normal carbon monoxide transfer factor and normal blood gases. The bronchoalveolar lavage revealed an increased total cell count ($450x10^3$ cells/mL) with 50% lymphocytes and an increased CD4/CD8 ratio of 5.4 (figure 2c). *CARD15* gene screening revealed no mutation and ruled out the hypothesis of Blau syndrome.

The young age of the patient and the bone marrow involvement are major factors of disease severity. As such, monthly methylprednisolone pulse therapy (300 mg/m²/day for 3 consecutive days) was initiated in association with daily oral prednisone which was

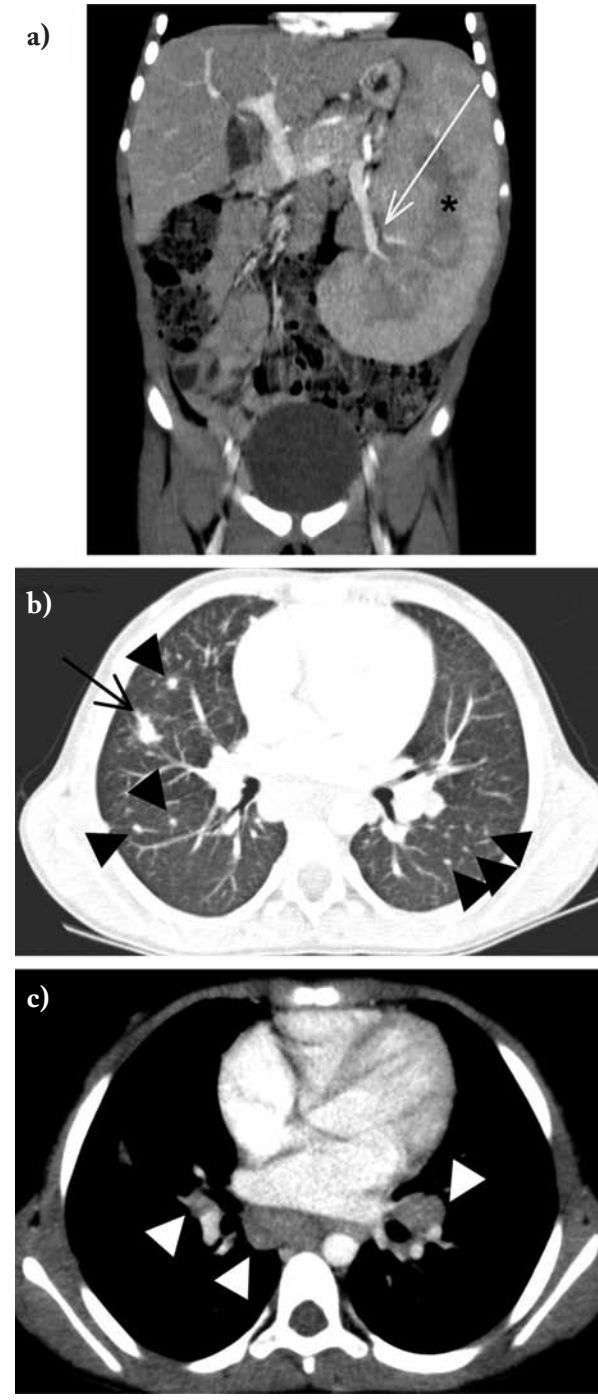


**Fig. 1. Initial CT scans. (a)** Abdominal CT scan showed a massive heterogeneous splenomegaly (*) and a hypodense perivascular infiltration (white arrow). **(b)** Thoracic CT scan revealed bilateral lung micronodules, predominantly in the left lung (short arrows) and one irregular nodule in the right upper lobe (long arrow), that resulted from the confluence of numerous micronodules. **(c)** Thoracic CT scan showed bilateral hilar and mediastinal lymph nodes (white arrows).

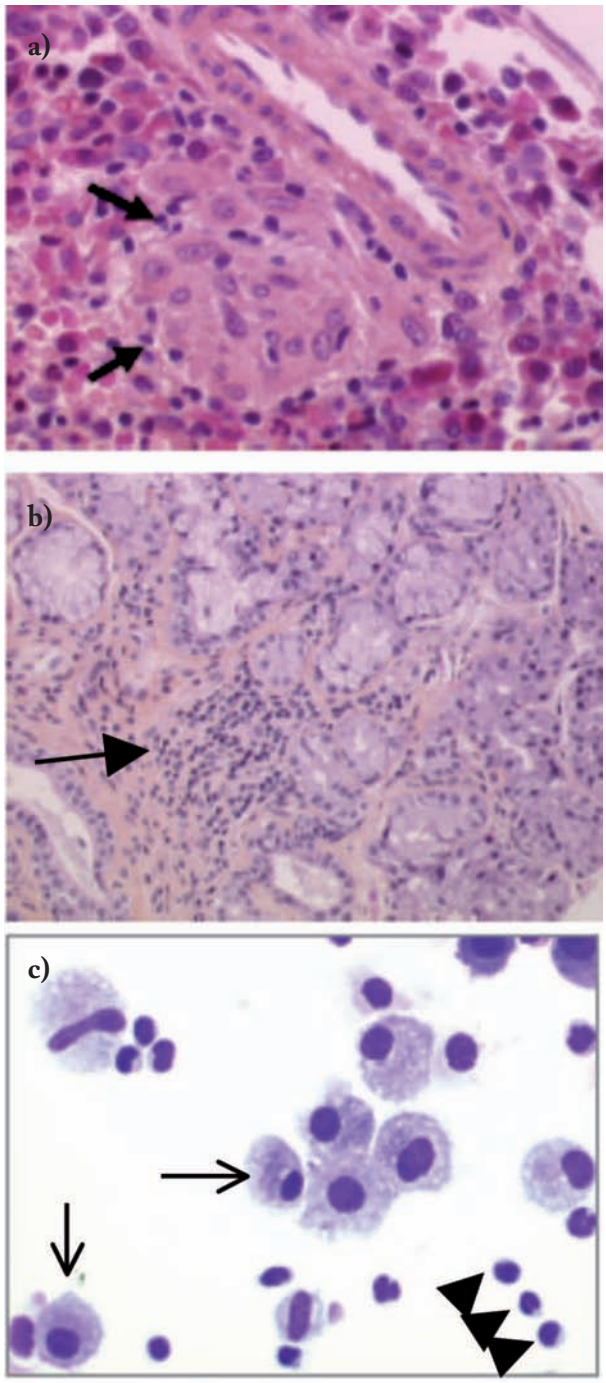


**Fig. 2. Pathology. (a**) The hematein-eosin-saffron stained tissue section of the bone marrow showed an epithelioid granuloma (black arrows) (x400). **(b)** The hematein-eosin-saffron stained tissue section of minor salivary glands showed a lymphocytic infiltrate. **(c)**. The bronchoalveolar lavage May-Grünwald Giemsa stained cytospin showed alveolar macrophages (long arrows) and numerous lymphocytes (short arrows)

gradually decreased over a 5 months period. Her general conditions improved and, six months later, CBC was normal, splenomegaly had significantly decreased and the chest X-ray and CT scan showed a decrease of the hilar lymphadenopathies and the pulmonary nodules. During the 4 following years, till February 2012, 3 recurrences of the disease occurred that were controlled by new courses of pulse steroids (300 mg/kg/day for 3 consecutive days). However, as previously described, the CLdyn remained decreased and the ACE increased (7).

## Discussion

Childhood sarcoidosis is a rare multisystemic disorder with variable clinical presentation depending upon age. Whereas children less than 4 years old tend to present florid clinical features, the clinical manifestations of older children are more similar to those observed in adults (8, 9).

The diagnosis of sarcoidosis is uneasy and based upon a combination of clinical symptoms and paraclinical findings, only confirmed by typical histopathological findings with non-caseating epithelioid-cell granulomas. Biopsy of any accessible organ is thus advised. In children with lung involvement, pulmonary function tests usually show a restrictive lung syndrome with a decrease of the vital capacity and/or CLdyn (as found in the presented case) (1).

In young children, symptoms of sarcoidosis may overlap with those of an autosomal dominant granulomatous disease of childhood formerly named Blau syndrome and related to a mutation of the *CARD15* gene. Our patient had no skin, joint or eye involvements which are characteristic features of the Blau syndrome. Moreover, no *CARD 15* gene mutation was found. The autoimmune lymphoproliferative syndrome may also mimic severe and early sarcoidosis (10). This diagnosis was ruled out by the absence of double-negative (CD4-CD8-) T cells and the presence of normal blood levels of Fas ligand.

The association of massive splenomegaly and pancytopenia as manifestations of sarcoidosis in a young child is unusual. In adults with sarcoidosis, haematological cytopenia is exceptional, found in less than 1% of cases (11). Two different mechanisms have been described so far to explain haematological

dysfunction in sarcoidosis. The most frequent is an auto-immune mechanism, leading mainly to thrombocytopenia, sometimes associated with anaemia (12-14). It is noteworthy that this subtype of sarcoidosis is usually associated with hypogammaglobulinemia or common variable immunodeficiency (15). The other described mechanism for haematological dysfunction is the infiltration of the bone marrow by sarcoidosis granuloma (16) However, pancytopenia has been exceptionally observed in adults and, to our knowledge, it had never been reported so far in children with sarcoidosis (17-21). Spleen involvement, based on clinical examination, is more common. It has been reported in 5% to 18% of unselected sarcoidosis patients (22). Moreover, a splenomegaly, with or without associated nodules, has been described in up to 33% of the patients (22;23). Massive splenomegaly, similar to that observed in this case, remains however a very exceptional feature, and is likely to be associated with bone marrow involvement (21, 24-28).

In addition to its unusual presentation, the outcome of the present case is also peculiar. Although spontaneous sarcoidosis resolution occurs sometimes in children, this evolution is much less frequent than in adults. Despite treatment, numerous children have indeed residual organ system damage and/or progressive disease (1). Nowadays, corticosteroids remain the mainstay of sarcoidosis therapy and are indicated in cases of severe lung or eye lesions, and of cardiac, neurological, or multiorgan involvement (5). The reported patient has been treated by steroid pulses with remarkable good results: normalization of the spleen size and of the haematological variables. After 4 years of follow-up, 3 recurrences occurred that were controlled by new courses of pulse steroids. Although corticosteroids still remain the gold-standard therapy up to now, investigations of novel drugs and biological agents targeting CD4 type 1 helper T cells are underway, that may provide more effective and better tolerated therapies (3, 5).

To conclude, it should be kept in mind that, although exceptional, the association of pancytopenia and massive splenomegaly could be the mode of presentation of sarcoidosis in children. Moreover, despite bone marrow involvement, a favourable outcome could be obtained under pulse steroid therapy. To the best of our knowledge, no similar case had ever been reported previously.

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