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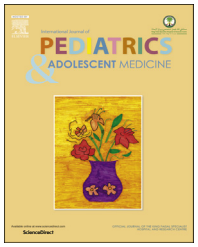

INSTRUCTIVE CASE

Childhood systemic sarcoid-like necrotizing granulomatous disease: Another piece of the puzzle

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Abstract Necrotizing sarcoid-like granulomatous disease is a disorder of unknown etiology that is rarely described in childhood; it affects various organs and has a diverse clinical course. Here, we report the case of a girl with multisystem recalcitrant necrotizing sarcoid-like granulomatous disease. The diagnosis is based on histopathology and the exclusion of other disease entities known to cause granulomatous disease.

1. Introduction

Granuloma formation is a special type of inflammation that can occur in a wide variety of diseases, both infectious and non-infectious. However, the offending agent is often unknown to be sarcoidosis or granulomatous angiitis. Diagnosis relies on clinical history, laboratory findings demonstrating an inflammatory process and histological examination of the suspected lesions. It is necessary to differentiate inflammatory granulomatous entities from tuberculosis and other infections or malignancies [1]. The rarity of non-infectious granulomatous disorders including necrotizing sarcoid-like granulomatosis and the scarcity of awareness may delay the appropriate diagnosis and treatment [2,3].

We describe a girl with recalcitrant necrotizing sarcoid-like granulomatous disease; the diagnosis is based on histopathology and the exclusion of other disease entities known to cause granulomatous disease.

2. Case report

A 13-year-old Pakistani girl was referred to our hospital with a three-year history of recurrent fever associated with generalized body weakness and diffuse musculoskeletal pain. She had a history of weight loss and recurrent

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abdominal pain without a change in bowel habits. She was observed and evaluated in different hospitals; she had persistently high white blood cell (WBC) and platelet counts as well as a high erythrocyte sedimentation rate (ESR). Other workup including bone marrow aspiration (BMA) and cultures were negative. However, Bartonella IgG levels were elevated. The initial clinical diagnosis was systemic onset juvenile idiopathic arthritis. Accordingly, she was treated with naproxen (250 mg twice daily), a high dose of prednisone (2 mg/kg/day), methotrexate (1 mg/kg/week) and tocilizumab (IL6 inhibitor). Because partial improvement was observed, tocilizumab was switched to anakinra (IL1 inhibitor) (100 mg daily). However, her symptoms recurred with bloody diarrhea. Further evaluation showed negative stool analysis and culture for any infectious disease. After undergoing upper and lower endoscopy, it was determined that there was no ulceration, and histopathology showed mild non-specific inflammation, which is not consistent with inflammatory bowel disease. An abdominal ultrasound and magnetic resonance imaging showed paraaortic lymphadenopathy, hepatic and splenic lesions. A lymph node biopsy revealed necrotizing granulomatous lymphadenitis with negative culture for mycobacterial and fungal infection. The family decided to use a mixed herbal medicine that was a mixture of NSAIDs. There was a family history of tuberculosis (TB).

Upon arrival to our hospital, she was febrile (38.9 °C) and appeared unwell with the same complaints mentioned above. She had scattered lymphadenopathy, decreased air entry bilaterally with crepitation, and hepatosplenomegaly. She was determined to have proximal muscle weakness and localized thoracic vertebral tenderness. Another physical examination was unremarkable.

The clinical impression at that time was infection (specifically TB), Crohn's disease, chronic granulomatous disease and autoimmune disease (namely sarcoidosis); other diagnoses such as malignancy i.e., lymphoma were considered as well.

The laboratory findings revealed a white blood cell count of 19.4×10^9/l, hemoglobin level of 90 g/l, platelet level of 679×10^9/l, elevated ESR level (108 mm/h) and elevated C-reactive protein level (213 mg/l). Her liver enzymes were elevated (ALT 136 U/l and AST 214 U/l), Gamma-glutamyltransferase level was GGT 104 IU/l and albumin level was 23 g/l. However, her renal function and muscle enzymes were within normal range. Her complement level (C3, C4) was normal, and her autoantibodies (antinuclear antibodies and antineutrophil cytoplasmic antibodies) were negative.

A chest computed tomography (CT) scan showed pleural effusion with normal lung parenchymal tissue. However, there were enlarged bilateral supraclavicular and paratracheal lymph nodes. A tuberculin skin test (TST) was negative along with a normal QuantiFERON TB gold test. The angiotensin-converting enzymes were borderline at 54 U/l (normal range <52). She had normal serum immunoglobulin levels, T and B-lymphocytes markers as well as a normal oxidative burst assay.

She completed a capsule endoscopy, which revealed a normal intestine.

A thoracolumbar X-ray showed multiple wedge compression vertebral fractures and osteopenia, which were confirmed by bone densitometry (Z-score <-2).

A BMA and biopsy were negative for malignancy, granulomas or infections. An abdominal CT scan confirmed multiple enlarged mesenteric and retroperitoneal lymph nodes with multiple focal hypodense splenic lesions (Fig. 1). The histopathology of lymph node and splenic biopsy revealed necrotizing granulomatous inflammation (Fig. 2). An acid-fast bacilli (AFB) stain was negative in tissue culture. A nucleic acid amplification test using strand displacement amplification was negative for AFB. The final report of tissue culture including mycobacterial and fungal was negative. A serology (IgG and IgM) and polymerase chain reaction (PCR) test for Bartonella was negative.

We proposed a diagnosis of systemic sarcoid-like necrotizing granulomatous disease especially with the presence of necrotizing granulomatous inflammation and inconclusive extensive workup, which failed to suggest an alternative diagnoses. Accordingly, we started intravenous methyl prednisolone (30 mg/kg) weekly for four doses, oral prednisone (0.5 mg/kg/day), azathioprine (2 mg/kg/day), calcium and vitamin D supplements and cyclic pamidronate (every three months) treatment. Recently, infliximab and cyclosporine (4 mg/kg) were initiated, and she received four doses of infliximab (5 mg/kg). Fortunately, she experienced significant clinical improvement, and her inflammatory markers improved as well.

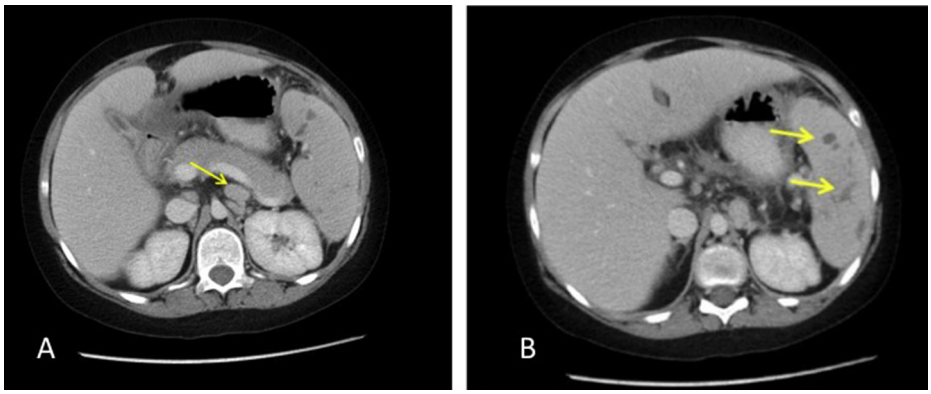

Figure 1 Abdominal CT scan that showed multiple enlarged mesenteric and retroperitoneal lymph nodes (1A) and a bulky spleen (measured to be 12.7 cm) with multiple focal hypodense lesions; the largest was 2.2 cm in its transverse dimension (1B).

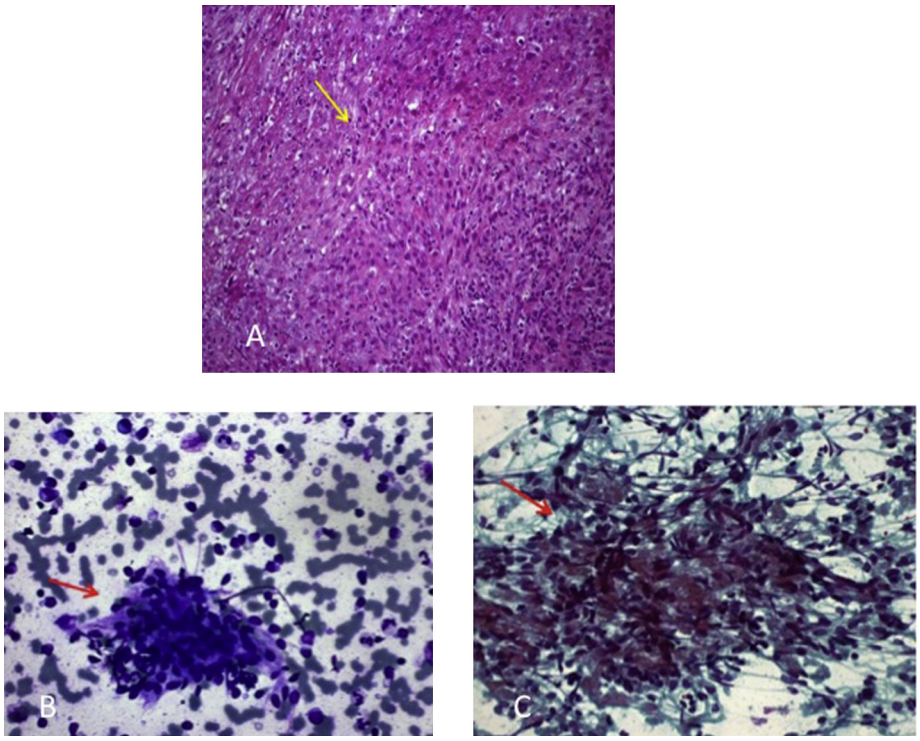

Figure 2 Histopathology of lymph node and splenic biopsy revealed ill-defined necrotizing granulomas. A shows a H&E stain of the lymph node (20×). B and C show a diff quick stain and pap stain of splenic granuloma.

3. Discussion

Non-infectious granulomatous diseases make up a heterogeneous group that includes sarcoidosis, granulomatous angiitis and Crohn's disease. Typically, affected children experience recurrent fever and systemic manifestations.

Sarcoidosis is recognized as a systemic granulomatous disease of unknown origin that affects various organs and has a diverse clinical course; it is characterized by non-necrotizing (non-caseating) granulomas [4,5]. Recently, sarcoidosis became classified as one of the auto-inflammatory syndromes [6]. Children younger than four years of age typically presented with a triad of rash, arthritis and uveitis. Sarcoidosis in older children involves several organs, and its clinical appearance resembles the adult type of the disease. However, patients including children might present with necrotizing sarcoid-like granulomatous disease and an intractable clinical course without an easily identifiable cause. Knowing that typical clinical and laboratory findings do not exist, a definitive diagnosis could be difficult in the presence of atypical non-caseating granulomas [3,7,8]. Those patients encompass a challenging group, both in terms of diagnosis and treatment, as they are relatively difficult to distinguish from typical sarcoidosis patients because of the clinical and histologic overlap of these conditions. On the other hand, sarcoidosis simply presents both clinically and histologically with a variety of phenotypes [9,10].

We describe a child with periodic systemic manifestations in whom extensive investigations were inconclusive. However, multiple histologic examinations revealed areas of necrotizing sarcoid-like granulomas. Obviously, our patient does not fit into any of the distinct forms of childhood sarcoidosis. Nonetheless, other disease entities known to cause granulomatous disease such as TB and Crohn's disease were ruled out.

Clearly, there is no permanent cure for these diseases. However, corticosteroid remains the main stay of treatment. Although the history of anti-tumor necrosis factor-α agent use in children with sarcoidosis is limited, these drugs may be helpful for those patients experiencing a severe and refractory disease. We believe that our patient experienced severe disease with a recalcitrant clinical course and persistently elevated inflammatory markers. The introduction of prednisone, infliximab and methotrexate achieved partial control of the disease.

It is not our intent to comprehensively review childhood sarcoidosis. Rather, we suggest that the entity of idiopathic (necrotizing sarcoid-like) granulomatous disease is on the spectrum of sarcoidosis.

Conflicts of interest

The authors declare that they have no financial or other relationship that constitutes a conflict of interest.

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