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Case-based Review

Bone marrow involvement: Atypical presentation of early-onset childhood sarcoidosis

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Abstract

Childhood sarcoidosis is a chronic multisystemic, non-caseating granulomatous disease of unknown etiology. Early-onset disease classically presents with a triad of skin rash, uveitis, and arthritis, but bone marrow involvement is rare. We report a 9-1/2- year old Indian female child who presented with bleeding manifestation, skin rash, uveitis, and arthritis. Bone marrow biopsy showed multiple non-necrotizing granulomas comprising epithelioid cells, mature lymphocytes, and multinucleated giant cells with few eosinophils in the background, with negative staining for acid-fast bacilli or fungi. She was treated successfully with oral prednisolone. This is the first report of an early-onset childhood sarcoidosis with bone marrow involvement from India.

Keywords: Bone marrow granulomas, bone marrow sarcoidosis, early-onset childhood sarcoidosis, pediatric sarcoidosis, pancytopenia, uveitis

Introduction

Childhood sarcoidosis is a chronic multisystemic, non-caseating granulomatous disease. The exact incidence and prevalence of pediatric sarcoidosis is unknown due to rarity of the disease; however, the overall incidence is 0.22-0.29 cases per million per year in Danish children with an incidence of early-onset sarcoidosis (age≤4 years) about 0.06/100,000 person/year (1, 2). It has a biphasic presentation in adults (between 20 and 50 years and second peak between 50 and 65 years) with most of the pediatric cases recorded around the age of 13-15 years with no clear sex predilection (3, 4). Though the precise etiology of the disease is not known, literature suggests that it is the result of an exaggerated immune response to an unknown antigen (microbes and certain environmental factors such as dust) in a genetically susceptible person (3, 5). Clinical presentations are greatly varied and depend on organ involvement. In childhood disease, lungs, lymph nodes, eyes, skin, liver, and spleen are frequently involved. However, early-onset disease (in children less than 5 years) manifests with a classic triad of skin rash, uveitis, and arthritis (3-6). Bone marrow is infrequently involved in adult disease (7, 8) but is rarely reported in pediatric sarcoidosis. Here, we describe a case of early-onset disease with bone marrow involvement.

Case Presentation

A 9-1/2- year old Indian female child, second by birth order, a product of non-consanguineous marriage presented with bleeding from nose and brown-red colored vomitus containing digested food particles one day prior to admission. She had a history of intermittent fever, loss of appetite, generalized weakness, paleness of body, and inadequate weight and height compared with same-aged children. On further inquiry, she had a past history of nasal bleed and multiple nodular skin lesions over the dorsum of both hands and feet at the age of 3 years, which was suggestive of granuloma annularae on biopsy. She also suffered from generalized abdominal distension at 4 years and 6 years of age with nasal bleed during each episode without hematemesis. She received antituberculous treatment for the same. She had no history of jaundice, cough, visual complaints, or other bleeding manifestations. Birth and family histories were not significant. She was developmentally normal and fully immunized as per national immunization program.

Informed consent was taken from the parents prior to clinical examination. On anthropometry, she was stunted and wasted with normal upper segment to lower segment ratio for her age. Vitals were stable. On physical examination, she had significant pallor and active bleeding from nose. Peripheral lymph node was not palpable, except for non-significant cervical lymphadenopathy. Both hands showed flexion deformity of the interphalangeal joints without any signs of inflammation. Dorsal aspect of both palms had

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hypopigmented, macular, non-itchy scar marks (Figure 1). Malar rash, jaundice, signs of vitamin deficiency, and subcutaneous bleeding was not evident.

Ophthalmic examination revealed a vision of 6/9 in both eyes. Both corneas were bright with few nebulomacular corneal opacities near limbus from 2-4 o'clock position suggestive of sub-epithelial infiltrates on the left cornea. Iris color patterns were abnormal with few nodules noted in both irises. Both pupils were fixed, irregular, festooned with a posterior synechiae in 360 degrees, which was suggestive of chronic iridocyclitis (Figure 2). Iris pigments were dispersed over the lens in both eyes. Both lids, conjunctiva, anterior chamber, lens, posterior chamber, and fundus were within normal limits. Systemic examinations were within normal limits, except the palpable left lobe of liver with mild splenomegaly.

Her hematological investigations of past and present admissions are mentioned in Table 1. Bone marrow biopsy showed multiple non-necrotizing granulomas comprised of epitheliod cells, mature lymphocytes and multinucleated gaint cells with few eosinophils in background with negative staining for acid fast bacilli and fungii (Figure 3). Serum angiotensin-converting enzyme level [59 U/L (8.00-65.00 U/L)] and serum ferritin [6.10 ng/mL (7.00-140.00 ng/mL)] were within normal limits. Antinuclear antibody, rheumatoid factor, ASO titer, and C-reactive protein were negative. Serologies for hepatitis B, C, and HIV virus were negative. Bronchoalveolar lavage and tracheal aspirate showed alveolar macrophages, lymphocytes, and few acute inflammatory cells; however, staining for AFB, fungi or other bacteria was negative. Blood culture, tracheal fluid culture, and bronchoalveolar lavage fluid culture was negative for fungi or bacilli. Her tubercular workup, including tuberculin test, cartridge based nucleic acid amplification test (CBNAAT) for *Mycobacterium tuberculosis* on sputum, gastric aspirate, and bronchoalveolar lavage was negative. Her renal function tests, liver function tests, lipid profile, serum electrolytes, and blood sugar were within normal limits. Her serum vitamin D was 6.64 ng/mL, parathyroid hormone level 67.39 pg/mL (15-68.3 pg/mL), and she had a normal serum calcium level.

Esophagogastroduodenoscopy did not reveal variceal bleed. Chest radiograph was within normal limits, but pulmonary function tests were suggestive of a mild restrictive lung disease. Radiographs of both hands showed mild perivascular sclerosis with joint space reduction in bilateral 3rd and 4th proximal interphalangeal joints. Periarticular osteopenia was noted in left 2nd and 3rd and the right 1st, 2nd, 3rd, and 4th metacarpophalangeal joints with minimal sublux-

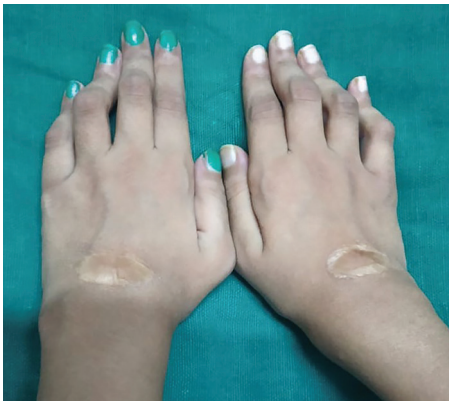

Figure 1. Deformity of both hands.

Main Points

- Late onset childhood sarcoidosis manifests with a multisystem disease similar to the adult type, while early onset childhood sarcoidosis though usually presents with the classical triad of – skin involvement, uveitis and arthritis - rarely presents with bone marrow involvement.
- Unexplained pancytopenia due to bone marrow involvement is nonspecific, rare; and may be a solitary finding of the disease. Early onset childhood sarcoidosis with bone marrow involvement has not been described previously in Indian pediatric population.
- Bone marrow biopsy showing multiple non necrotizing granulomas is diagnostic and response to steroids is dramatic in such individuals.

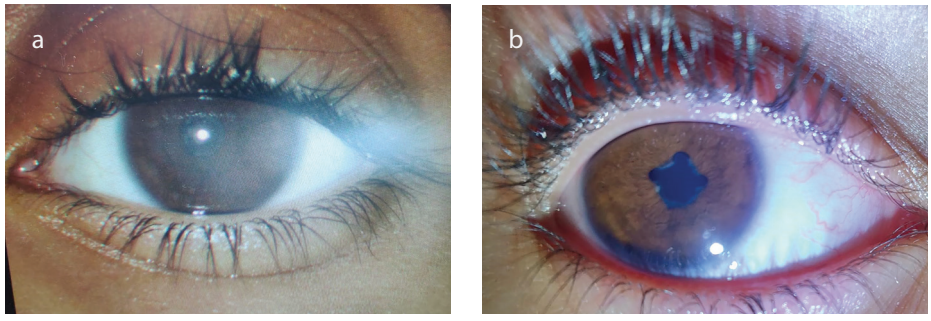

Figure 2. a, b. Posterior synechiae (a); festooned pupil (b).

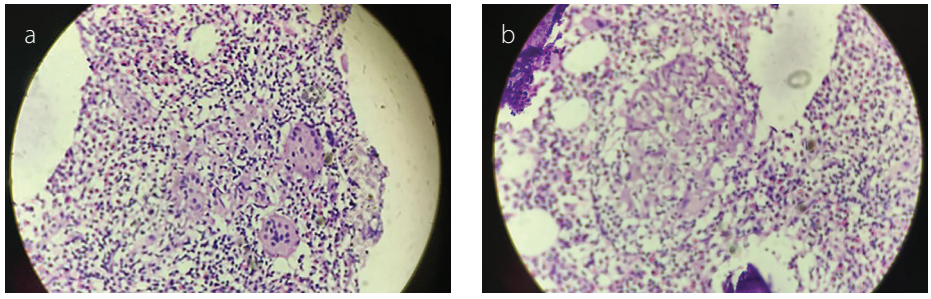

Figure 3. a, b. Low power microscopy (a); high power microscopy (b). Bone marrow shows non-necrotizing epithelioid granuloma.

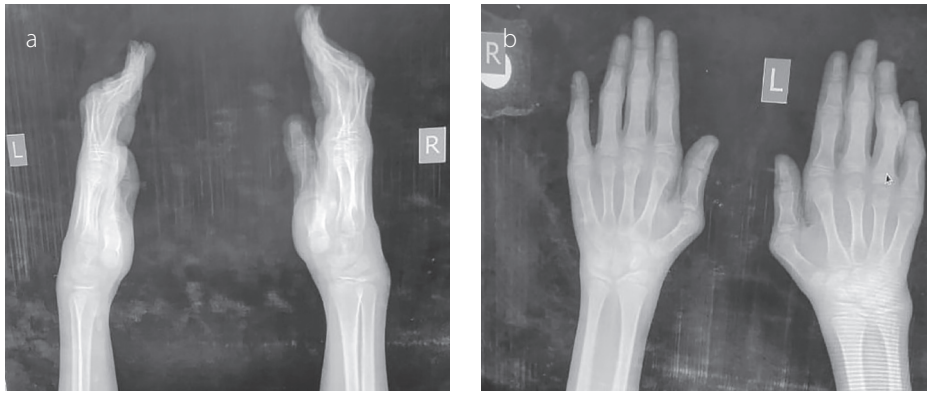

Figure 4. a, b. Lateral view (a); anteroposterior view (b). Radiograph of both hands showing perivascular sclerosis, periarticular osteopenia subluxation of bilateral first metacarpophalangeal joints with joint space reduction.

Table 1. Hematological investigation.

Admission	Parameters	Finding
Past	Hb	8.3 g%
	Total leucocyte count	3000/cumm
	Platelet count	95,000/cumm
	International normalized ratio	1.14
	Peripheral smear	Normocytic hypochromic RBCs with platelet depletion
	Bone marrow	Hypercellular marrow with M:E ratio 2:1. Erythropoiesis shows erythroid hyperplasia with normoblastic maturation. Myelopoiesis shows hyperplasia of granulocytic precursors.
		Thrombopoiesis shows slightly increase in megakaryocytes. Lymphocytes 15%
	Biopsy of skin nodule	Presence of granulomas in the dermis
	Lymph node biopsy	Suggestive of reactive lymphadenitis
Present	Hb	9.1 g%
	Total leucocyte count	3700/cumm
	Platelet count	82,000/cumm
	Peripheral smear	RBCs: Microcytic, hypochromic with mild anisopoikilocytosis with reduced platelet count.
	Reticulocyte count	3%
	International normalized ratio	1
	Bone marrow aspiration	Cellular bone marrow aspirate shows mild erythroid prominence with M:E ratio of 1.3:1 with normoblastic maturation. Granulocytic series cells show cells at all stages of maturation. Blast constitutes 3% of all nucleated cells. Megakaryocytes are adequate. Lymphocytes constitute 15% of all nucleated cells. No atypical cells, parasites, or fungi.
	Bone marrow biopsy (Figure 3)	Cellular bone marrow with overall cellularity of 80-90%. Multiple non-necrotizing granulomas. These granulomas comprise of epithelioid cells, mature lymphocytes, and multinucleated giant cells with few eosinophils in the background. Normal hematopoietic elements in the form of maturing granulocytic cells, erythroid precursors, and adequate megakaryocytes. No hemoparasites, and staining for acid-fast bacilli and fungi were negative.
	Flow cytometry	B lymphocytes - expressing CD19, CD20
		T lymphocytes - expressing CD15
		Myeloid cells - expressing CD13, CD33
		Myeloblast (1.2%) - positive for CD34, CD13, CD11, and HLADR
		Hematogones (7.25%) - positive for CD19, CD10, and CD34
		No evidence of leukemia/lymphoma

ation of the bilateral first metacarpophalangeal joints (Figure 4). Ultrasound and computed tomography of the abdomen and thorax showed moderate hepatosplenomegaly with multiple pre-paraaortic, pretracheal, precarinal, and prevascular lymph node enlargement with the largest node measuring 1.3×1.1 cm. Electrocardiogram did not reveal conduction abnormality, and 2D echocardiography was within normal limits. Diagnosis of early-onset childhood sarcoidosis was made on the basis of skin lesions, ophthalmic findings, arthritis, and non-necrotizing epithelioid granuloma in bone marrow.

The nasal bleed was controlled with anterior nasal packing. She was treated with steroids (prednisolone 1 mg/kg/day) in two divided doses and discharged after four weeks. Her hematologic parameters improved without any further episodes of nasal bleed. She was in regular follow-up every two months.

Discussion

Childhood sarcoidosis is a chronic, multisystem, granulomatous disease of obscure etiology. Its exact incidence and prevalence is unknown because of the rarity of the disease; however, lifetime risks are more common in Swedes, Danes, and African-Caribbean children. Various reviews reported that the incidence of clinically recognized sarcoidosis ranges from 0.22-0.29/100,000 children per year, and most of the cases are reported in teenagers [13-15 years of age] (2-4). Documented prevalence of sarcoidosis among Indian children is not known, but in the recent years sporadic cases are frequently reported (9-11).

Despite the worldwide occurrence of sarcoidosis, the etiology of the disease is unknown.

Most researches propose a model of granuloma formation in children, which involves the interplay of environmental triggers by a variety of antigens (occupational or infectious agents) as well as immunologic/genetic/epigenetic factors that trigger an enhancement of cellular immune response. The Th1 (CD4+Tcell) polarized immune response results in an increased cytokine activity of TNF, IFN gamma, interleukin. Th17 effector cells (secreted by IFN gamma) recruit and proliferate immune cells, while genetic factors (CARD15/NOD2 mutation) may play a role by interacting with mycobacterial/bacterial/viral components and promoting the activation of NF-kB and tumor necrosis factors receptor-associated factor 3 (TRAF3) signaling pathways, thereby triggering granulomatous inflammation. Other immunologic abnormalities reported in patients with sarcoidosis include B-cell hyperactivity, increased levels of immunoglobulin, circulating immune-complexes, and depressed cutaneous delayed hypersensitivity reactions (3-6). There is a continuous debate regarding association of Mycobacterium tuberculous infection and sarcoidosis. In spite of all the clinical similarities between the two diseases and the dilemmas of diagnosis and management, the causal relationship remains doubtful (12). Similar to our case, most of the clinicians in high tuberculosis prevalence settings prescribe anti-tubercular drugs to such patients.

The clinical presentation of sarcoidosis varies greatly and depends on organ involvement. Childhood sarcoidosis has two forms; older children usually manifest with a multisystem disease similar to the adult features with frequent lymphadenopathy and pulmonary involvement as well as generalized signs and symptoms. In contrast, early-onset disease has a classic form and is characterized by the triad of skin rash, uveitis, and arthritis (3). Skin lesions are the most common presentation, occurring in 77% of early-onset disease. They can vary from asymptomatic to discrete, maculopapular rashes, which initially appear on the face and extremities. Other skin eruptions including nodules, hyperpigmented, or hypopigmented lesions, ulcers, and subcutaneous tumors are also reported (9, 10, 13). Arthritis of childhood sarcoidosis usually presents as boggy tenosynovitis with relatively painless effusions and a good range of movement of multiple joints of both upper and lower limbs in 15-58% cases, but osteolytic lesions are also reported. Sarcoid arthritis, most of the time, is confused with juvenile idiopathic arthritis (14-16). Anterior segment disease comprising uveitis or iritis is the most common ocular manifestation in 84% cases of early-onset disease and 24%-58% of childhood sarcoidosis. Uveitis is characterized by keratic precipitates, iris nodules, and focal synechiae formations. Conjunctival granuloma formation is the second most common ocular manifestation, while choroidal granuloma and peripheral multifocal calchoroiditis are very specific for ocular sarcoidosis (3). Blau syndrome, a rare autosomal dominant inflammatory disease, caused by sporadic mutation of NOD2 gene characterized by a clinical triad of granulomatous dermatitis, recurrent granulomatous uveitis, and systemic polyarthritis is similar to early-onset childhood sarcoidosis. Though our case was a 9-1/2-year old, she was symptomatic since the age of 3 and presented with generalized signs and symptoms like fever, loss of appetite, inadequate weight gain, history of nodular lesions over the dorsum of hands (biopsy was suggestive of granuloma annularae), arthritis, and uveitis. Similar presentations in childhood sarcoidosis are reported in Indian literature by other authors (3, 17, 18). We could not perform genetic study in our patient due to financial constraints.

Childhood sarcoidosis is a multisystem inflammatory disorder that can involve any organ but most frequently affects lymph nodes, lungs, liver, spleen, skin, eyes, musculoskeletal system, kidney (6%), brain, heart (conduction abnormality), and deranges the calcium metabolism (3, 6, 19, 20). However, bone marrow involvement in pediatric sarcoidosis is not known. Anemia and leukopenia are the clinical presentations in 4%-40% of the sarcoidosis cases; however, a study done by Yanardağ et al. (21) on 92 adult patients with bone marrow biopsy of 50 cases revealed anemia in 11 (22%), both anemia and leucopenia in 3 (6%), and non-caseating granulomas in 10% cases. Bhargav et al. (22) identified granulomas in 72 specimens out of 6,988 bone marrow biopsies. They revealed 11% granulomas were associated with sarcoidosis (22). A retrospective review done by Wang et al. (23) observed that 0.97% of the bone marrow biopsies showed granulomatous lesions, and infection was the most common etiology followed by malignancies and autoimmune diseases. A study done by Brackers et al. (24), reported that 0.59% of the bone marrow biopsies revealed granulomatous lesions, and 21% had sarcoidosis. Patel et al. (8) reported systemic sarcoidosis with bone marrow involvement, which responded to therapy with adalimumab. Pena-Garcia et al. (7) reported a case of cutaneous sarcoidosis with bone marrow involvement, while Hameed and Skibinska (25) reported scar sarcoidosis with bone marrow involvement in adults; however, none of the studies from India reported childhood sarcoidosis with marrow involvement in children and adults (11, 26). Our study probably reports the first case of sarcoidosis with bone marrow involvement from India.

The currently accepted diagnostic standard is the demonstration of non-caseating granuloma in one or more organs in the setting of consistent clinical and radiological findings. The classic sarcoid granuloma consists of sharply circumscribed epithelioid histiocytes with foreign body giant cells surrounded by a rim of lymphocytes. Raised acute phase reactant, anemia, leukopenia, and eosinophilia are commonly seen in blood counts. Elevated levels of angiotensin-converting enzyme are found in over 50% of the children with late onset disease, but this is not specific. In our case, a diagnosis of sarcoidosis was made with the help of clinical and radiological findings with the classic epithelioid, non-caseating granuloma on bone marrow biopsy.

Prednisolone is the mainstay of treatment in sarcoidosis. It acts by inhibiting the release of inflammatory cytokines and blocking granuloma formation. Other drugs including low dose methotrexate, azathioprine, cyclophosphamide, chlorambucil, and cyclosporine have been used for treatment along with newer drugs, such as cytokines and their antagonists. Infliximab, a human-mouse chimeric anti-tumor necrosis factor alpha antibody has been already used in adults and Blau syndrome (19). We treated our case with prednisolone successfully. To the best of our knowledge, our study reports the first case of early-onset sarcoidosis with bone marrow involvement from India.

Early-onset childhood sarcoidosis is not always a benign disease with possible dissemination and vital organ involvement. Unexplained pancytopenia, though nonspecific and rare, may be a solitary finding of the disease. Although bone marrow involvement is an infrequent manifestation, a pediatrician should have a high index of suspicion. Bone marrow biopsy is important to establish the diagnosis since aspiration is inconclusive. Corticosteroid is a promising drug to treat such a rare disease.

Informed Consent: Informed consent was obtained from the parents of the patient.

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