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# Pediatric-onset adult type sarcoidosis: A case report

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**ABSTRACT**

Sarcoidosis, a multisystem disorder of unknown etiology that involves multiple organs, is rare in children. The true incidence and prevalence of childhood sarcoidosis is unknown. As in adults, many children with sarcoidosis may be asymptomatic; the disease may remain undiagnosed. A complete and systematic evaluation of the patient is essential for the sarcoidosis diagnosis in children. Here, we describe a case of 12-year-old female who presented with 2 years history of uveitis and hepatosplenomegaly. A chest computerized tomography revealed scattered peripheral pulmonary nodules and bilateral hiliar lymphadenopathy. Bone marrow aspiration and liver biopsy were not diagnostic. A lung biopsy showed non-necrotizing epithelioid cell granulomas. She was diagnosed with sarcoidosis according to demonstration of granulomatous inflammation and the exclusion of confusable entities.

***Key words:*** *sarcoidosis, pulmonary; children; uveitis; hepatomegaly; splenomegaly*

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## INTRODUCTION

Childhood sarcoidosis is a rare multisystem granulomatous disorder of unknown cause, usually characterized by nonspecific constitutional symptoms, pulmonary manifestations, lymphadenopathy, as well as skin and eye involvement.[1,2] The clinical presentation of the disease has been described in minor series of children of different ethnicities. The course and prognosis of sarcoidosis in children is different compared to adults, and may correlate with the mode of onset and the extent of the disease. The true incidence and prevalence of childhood sarcoidosis is unknown because of the rarity of the disease and small number of reported cases in childhood.[2] Infants and children younger than 5 years usually present with the triad of skin, joints, and eye involvement without typical lung disease. However, older children have involvement of the lungs, lymph nodes, and eyes more frequently, as seen in adults.[1]

In 2001 a mutation was found in the nucleotide-binding oligomerization domain 2/caspase activation recruitment domain 15 (NOD2/CARD15) gene among patients with a history of familial granulomatous arthritis. This finding led to a new perspective and allowed us to understand the complexity and heterogeneity of the pediatric sarcoidosis.[3] Blau syndrome and early onset sarcoidosis constitute the familial and sporadic forms of the pediatric sarcoidosis characterized by the association with mutations in NOD2 gene.[4] However, a lot of pediatric cases diagnosed with sarcoidosis have no mutation in NOD2 gene and generally present with systemic and visceral manifestations. Within this group, there are two identified entities including infantile-onset panniculitis with systemic granulomatosis and pediatric-onset adult sarcoidosis.[5]

Early diagnosis of sarcoidosis in children is often difficult because of the lack of awareness and unfamiliarity with its clinical features.[6] Here we report a 12-year-old girl diagnosed with pediatric-onset adult sarcoidosis.

## CASE REPORT

In November 2012, a 12-year-old girl was admitted to Hacettepe University Faculty of Medicine, Pediatric Infectious Diseases Unit with a 1.5 years history of low-grade and recurrent fever, multiple peripheral lymph node enlargement, and abdominal distention. She also reported malaise and loss of appetite. There had been no improvement with empirical treatment with a variety of antibiotics including

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β-lactams. In her past medical history, she had anterior uveitis 2 years ago and family history was unremarkable.

Physical examination revealed a well-appearing female with normal vital signs. She had enlarged cervical and axillary lymph nodes and hepatosplenomegaly. Abdominal ultrasound showed increased liver (13 centimeter) and spleen (12 centimeter) lengths. Lymph nodes were typically firmed, non-tender, and freely movable. Ophthalmologic examination revealed visual acuity of 1.0 in both eyes. Slit-lamp examination of the right eye was normal; however, there were +1 cells in the anterior chamber and keratic precipitates, with posterior synechia in the left eye *(Figure 1)* Fundus examination revealed perivascular sheathing especially marked in the left eye. Fundus fluorescein angiography confirmed focal segmental vasculitis in the periphery of both eyes *(Figure 2)*. The other aspects of physical examination were normal. Initial laboratory tests revealed a hemoglobin of 9.7 g/dl (range: 11.7-15.5), platelet count of 377,000/ml (range: 150,000-388,000), leukocyte count of 5,800/μl (range: 4,100-11,200), C-reactive protein (CRP) of 0.26 mg/dl (range: 0-0.8), and erythrocyte sedimentation rate of 51 mm/h (normal < 20). She had no eosinophilia and her peripheral smear examination was normal. Blood biochemistry for renal and liver function tests and urinalysis were normal. Tuberculin skin test was negative. Serum levels of IgA, Ig G and IgM were 700 mg/dl (range: 82-453), 1870 mg/dl (range: 751-1560) and 647 mg/dl (range: 46-304), respectively. Primary immunologic work-up including lymphocyte subset and nitroblue tetrazolium (NBT) test was found to be normal as well as immunoglobulines. Angiotensin-converting enzyme (ACE) level was 75 U/L (range: 7-50). Autoantibodies including anti-nuclear antibody, cytoplasmic antineutrophil antibody, and perinuclear antineutrophil_cytoplasmic antibody were all negative. Serum calcium level was 9.3 mg/dl. Cervical and abdominal ultrasonography revealed enlargement of the submandibular and cervical glands with a maximum 15 mm diameter and hepato-splenomegaly. Pulmonary function tests and pulmonary pletismography were normal.

Bone marrow biopsy was performed two times to exclude malign processes and some infectious diseases associated with the involvement of reticuloendothelial system such as visceral leishmaniasis. Examination of bone morrow biopsies was normal. Bilateral hiliar adenopathy with parenchymal involvement in the lower lobes was revealed in chest X-ray *(Figure 3A)*. A chest computerized tomography

FIGURE 1. *Slit-lamp examination of the right eye was normal however there were +1 cells in the anterior chamber and keratic precipitates, with posterior synechia in the left eye*

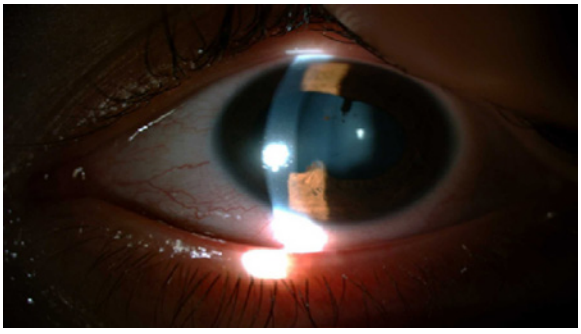


Figure 2. *Fundus examination revealed perivascular sheathing especially marked in the left eye. Fundus fluorescein angiography confirmed focal segmental vasculitis in the periphery of both eyes (a: right eye, b: left eye)*

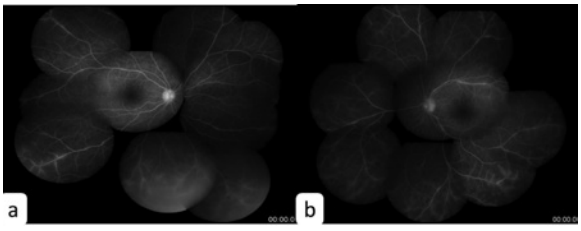
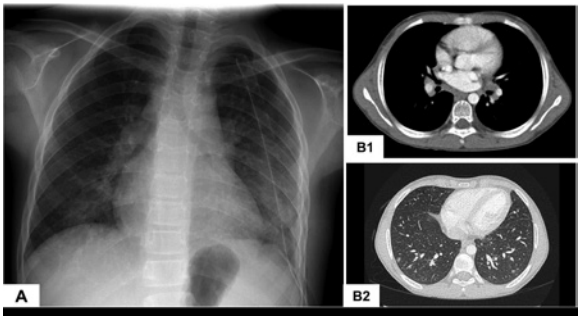



FIGURE 3. *Bilateral hiliar adenopathy with parenchymal involvement in the lower lobes was revealed in chest X-ray (A). An enhanced computed chest tomography showed bilateral hiliar adenopathy (B1) and scattered peripheral pulmonary nodules (B2)*



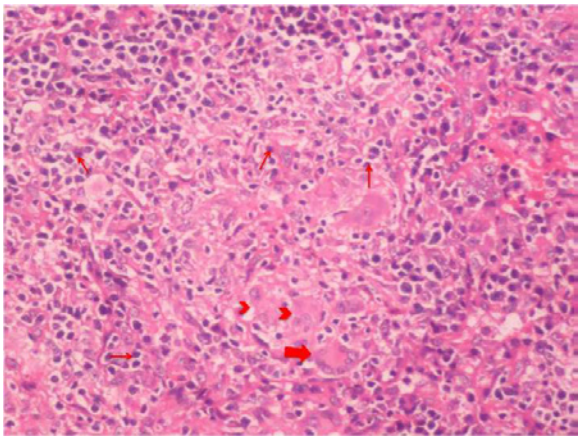
(CT) revealed bilateral hiliar adenopathy *(Figure 3B1)* and scattered bilateral peripheral pulmonary nodules *(Figure 3B2)*.

Peripheral lymphadenopathy disappeared within days on physical examination; therefore a liver biopsy was performed in order to confirm the diagnosis. However, it only revealed chronic inflammation without any granuloma formation. Thereafter, an open lung biopsy was performed and showed multiple granulomas without necrosis with multinucleated giant cells surrounded by lymphocytes consistent with sarcoidosis *(Figure 4)*. Special stains for acid-fast bacilli and fungal organisms were negative and also the aerobe biopsied tissue culture was negative. NOD2 gene mutation analysis was not performed. The patient was diagnosed as sarcoidosis and prednisolone (1 mg/kg/day, per oral) was initiated. Systemic findings as well as ocular findings of patient improved with steroid at the end of 3 months. The dose of steroid was tapered and 6 months follow-up was uneventful.

## DISCUSSION

Sarcoidosis is less common in children than in adults. In a 15-year study in Denmark, the incidence of sarcoidosis was 0.06 cases per 100,000 children younger than 4 years of age, increasing gradually with age to 1.02 cases per 100,000 children who were 14 to 15 years old[7]. Since sarcoidosis is a multisystem disease and affects most organs, the clinical presentation can vary greatly.[2]

FIGURE 4. *Lung biopsy showing granulomatous inflammation without necrosis with multinucleated giant cells (thick arrow), epithelioid histiocytes (arrow head) and lymphocytes (thin arrow), (Hematoxylene-eosin)*



Although lesions can occur in any tissue or organ, the lung is the most commonly organ involved in sarcoidosis.[2] Our patient had first presented the sign of ocular involvement, followed by recurrent episodes of fever and organomegaly. Ocular involvement may be the initial manifestation in sarcoidosis and may progress to severe visual impairment.[7] Younger children aged up to 5 years express a clinical triad of arthritis, skin lesions and uveitis. In the 8-15 age group, the clinical course is more similar to that of adults.[8] The most common ocular manifestations are uveitis which an early feature of sarcoidosis and conjunctival nodules. More than 80% of uveitis cases manifested before or within 1 year after the onset of systemic diseases.[8] The most common type of sarcoid-associated uveitis is the form of anterior uveitis. Anterior uveitis with posterior segment involvement and systemic disease are poor visual prognostic factors.[9] Our patient presented with anterior uveitis with posterior segment involvement in both eyes. Fluorescein angiography confirmed the posterior segment activity; peripheral segmental vasculitis and perivascular sheathing.

Blau syndrome or early onset sarcoidosis (NOD2 mutation-associated sarcoidosis) generally present with polyarthritis, dermatitis and uveitis. Sarcoidosis without NOD2 mutation such as pediatric-onset adult sarcoidosis is primarily characterized by systemic features including pulmonary and lymph node involvement. Additionally incidence tends to increase in early adolescence.[3-5] Although we could not perform NOD2 gene analysis, our patient seems likely pediatric-onset, NOD2 mutation negative, adult-type sarcoidosis according to the type of clinical presentation.

While there is no single laboratory test that is diagnostic for sarcoidosis, there are several supportive results including elevated acute phase reactants, hypercalcemia, anemia, leukopenia, and eosinophilia.[2,10] Angiotensin-converting enzyme (ACE) can be significantly elevated and useful as a marker of disease activity, but the test is not specific for sarcoidosis. Physiological values of ACE vary according to age with a higher normal range of serum values in children. Therefore ACE levels remains unclear in diagnosing and managing sarcoidosis.[11] ACE level of our patient was close to upper limit of the normal range and was not a supportive marker for the diagnosis.

The lung is the organ most commonly involved in sarcoidosis. Physical examination

is often unremarkable and bilateral hiliar lymphadenopathy with or without parenchymal involvement is the most common radiographic finding.[12] In addition to chest radiograph findings, a chest CT may reveal parenchymal disease. Parenchymal involvement is usually an interstitial pattern, although nodular, alveolar, and fibrotic patterns are also described.[13] There were no pulmonary symptoms in our patient and physical examination was unremarkable. Radiological findings were consistent with sarcoidosis and the diagnosis of sarcoidosis was confirmed with a lung biopsy. A biopsy specimen confirms the diagnosis of sarcoidosis by revealing non caseating epithelioid cell granulomas and by excluding other known causes of granulomatous inflammation like fungal, mycobacterial, and parasitic infections, and vacuities such as Wegener's granulomatosis.[14]

Additionally hepatosplenic sarcoidosis most commonly manifests as organomegaly, as in our patient. Of patients with systemic sarcoidosis, 24% to 94% have biopsy-documented hepatic sarcoidosis. The spleen is more frequently involved than the liver in systemic sarcoidosis. Splenic involvement is confirmed in up to 60% of patients by biopsy.[15] Although liver was considered as an easily accessible organ for an initial biopsy, we were not able to confirm the diagnosis of sarcoidosis with the findings of liver biopsy.

Peripheral lymphadenopathy was common (40% of 48 children) in the Danish study[10]; and this localization contributed to the diagnosis in 15 of them. In our case, however, peripheral lymphadenopathy disappeared during evaluation of the patient; and we had to perform liver and lung biopsies for the definitive diagnosis.

It is necessary that chronic infections including mycobacteria and fungi by using reasonable staining and cultures should be excluded for the diagnosis of sarcoidosis in a child with granulomatous inflammation. Patient having different primary immunodeficiency disorders can present with granulomatous inflammation without an identifiable infectious cause and should be excluded by evaluation of neutrophil function and analysis of circulating lymphocyte subsets and serum levels of immunoglobulin's.[5,14] We did not find any infectious origin by evaluating the tissue staining and cultures in the present case. Additionally, all the primary immunologic work-up of our patient including lymphocyte subsets and immunoglobulins were in normal limits. Therefore, we excluded the confusing entities for the diagnosis of sarcoidosis.

Up to two-thirds of untreated patients undergo spontaneous remission within the first two years after symptom onset. Corticosteroids are indicated for treatment of multisystem disease or severe involvement of a specific organ including the lungs and eye, and for neurologic or cardiac sarcoidosis. Methotrexate and other immunosuppressant as well as cytotoxic agents and newer biologic therapies have been used as steroid-sparing agents to decrease or avoid side effects related to prolonged corticosteroid therapy.[2,10] Steroid treatment was used to treat our patient with clinical improvement.

Various clinical presentation of sarcoidosis especially according to age often poses a diagnostic challenge to clinician. Consequently the diagnosis took 2 years because of remitting and relapsing disease course of our patient. Prompt clinical and laboratory evaluation with imaging studies, followed by tissue findings are imperative for early diagnosis and treatment of sarcoidosis. ■

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