Early-onset childhood sarcoidosis: a case report

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology and it most commonly affects young adults. Childhood sarcoidosis is relatively rare; older children usually present a picture similar to that of adults, with frequent hilar lymphadenopathy and pulmonary infiltration. Early-onset (<4 years of age) childhood sarcoidosis is a unique disease and has a different presentation. It is characterized by arthritis, uveitis, and cutaneous involvement. The prognosis of early-onset childhood sarcoidosis varies in different studies due to the rarity of the disease. The treatment of choice in systemic involvement of childhood sarcoidosis is corticosteroids. Methotrexate can also be considered in the long-term treatment due to its safety, effectiveness, and steroid-sparing effect in children.

CASE PRESENTATION

An 18-year-old woman visited our hospital with multiple tiny pinkish papules and some confluence in papular plaques with scales. Lesions were symmetrically distributed over both forearms, dorsal hands, and fingers (Figure 1).

Tracking the clinical history, at the age of 4 months, the patient had multiple erythematous papules, distributed over the trunk and extremities. A biopsy was performed at the age of 10 months, and granuloma annulare was initially diagnosed. Subsequently, the patient developed joint pain, dyspnea and axillary lymphadenopathy, along with erythematous papular plaques. A second biopsy was arranged in New York Medical Center, and showed multiple sarcoidal granulomatous lesions and panniculitis. Special stains for acid-fast bacilli and the colloidal iron stain tests were negative. Foreign bodies were not indentified under polarized light. Childhood sarcoidosis was diagnosed. Ophthalmologic examination was performed and showed bilateral uveitis.

The patient has been regularly followed up in our pediatric department and has been treated with prednisolone since 4 years old, and methotrexate was initiated when she was 6 years old to reduce the use of steroids. For the past 10 years, she has experienced intermittent episodes of fever, generalized skin rash, arthralgia, and bone pain without limitation of movements. These episodes resolved with an increase in steroid dosage. A series of examinations was performed during that period. Chest X-ray examination showed bilateral lower lung infiltration but no lymphadenopathy. Abdominal computed tomography revealed an infiltrative process involving the liver, spleen, kidney, small right renal stones, and multiple retroperitoneal lymph nodes, as well as superimposed bilateral lower lung infiltration. Hypercalcemia was also noted, but complete blood count, electrolytes, liver function, renal function and bone scan were normal. Tests for antinuclear antibody and rheumatoid factor were negative, and assays for complement components C3 and C4 were within normal ranges. Skin biopsy was repeated because of persistent cutaneous eruption when she was 10 years old, and the biopsy report was consistent with sarcoidosis.

Under treatment with 10–15 mg/day prednisolone and 12.5 mg/week methotrexate, the patient had no subsequent
progression of the disease and chest X-rays did not reveal any infiltration. Steroid dosage was recently tapered because of the stable clinical condition. Then, multiple tiny pinkish papules and some confluent papular plaques with scaling were noted over the upper limbs (Figure 1). To confirm the etiology of the skin eruption, we performed two tissue biopsies; one of a plaque lesion and one of a papular lesion of the right dorsal hand, which revealed nests of noncaseating granulomas infiltrating the dermis (Figures 2 and 3). Special stains for mycobacteria, fungi and bacteria were negative, and sarcoidosis was confirmed.

Discussion

Childhood sarcoidosis is a rare entity with two distinct forms: early-onset and late-onset disease. Early-onset sarcoidosis is a unique disease, defined by onset before 4 years of age and is characterized by the triad of skin rash, uveitis, and arthritis.1 The diagnosis of sarcoidosis is based on compatible clinical presentation and the demonstration of noncaseating epithelioid cell granulomas, from biopsy of an affected organ. Other causes of granuloma such as mycobacterial, bacterial and fungal infection

Figure 1 (A) Multiple pinkish papules and some confluent papuloplaques with scaling distributed over forearms, dorsal hands and fingers. (B) Erythematous plaques over dorsal hand. (C) Multiple erythematous papules over fingers.

Figure 2 (A) Tissue biopsy of the papular lesion showed multiple dense, uniform circumscribed nests of noncaseating granulomas infiltrating the dermis (hematoxylin and eosin, original magnification 40×). (B) Tissue biopsy of the plaque lesion showed noncaseating granulomas infiltrating the superficial dermis. (100×).
need to be ruled out. Childhood sarcoidosis is especially difficult to diagnose because of its variable presentation and ability to mimic other diseases.

Skin lesions are the most common presentation in early-onset childhood sarcoidosis. It occurs in 77% of early-onset sarcoidosis and 24–40% of late-onset cases. The most typical skin eruption in early-onset childhood sarcoidosis is asymptomatic, discrete, macular and papular rash, and follows a waxing and waning course; it first appears on the face and extremities and subsequently spreads to the trunk. Soft, red to yellowish–brown, or violaceous, flat-topped papules appear most frequently on the face. Other skin eruptions including nodules, hyperpigmented or hypopigmented lesions, ulcers, and subcutaneous tumors can also be found. In our patient, the skin lesion first appeared when she was 4 months old and other associated symptoms then followed. The appearance and distribution of the skin lesion changed during the course of treatment and adjustment of medication. Owing to the extremely polymorphic manifestations of the cutaneous lesion, it is challenging for clinicians to make a diagnosis of early-onset sarcoidosis solely based on the skin lesion at the first presentation.

In contrast to late-onset sarcoidosis, early-onset sarcoidosis usually lacks multisystemic involvement and may not affect the lungs and lymph nodes. Hilar lymphadenopathy, the leading feature of the late-onset form, is rare in early-onset sarcoidosis. Hepatomegaly, splenomegaly, and retroperitoneal lymph node infiltration occur in up to 40% of children with sarcoidosis at some point during the clinical course. Mild elevation in liver biomarkers may be noted, but severe liver involvement with sarcoid hepatitis is rarely seen in children. In our patient, although infiltration was noted when she was young, no specific abnormalities were seen during regular follow-up.

Anterior segment disease comprising uveitis or iritis is the most common ocular manifestation in 90% of cases of early-onset childhood sarcoidosis. However, early ocular involvement is asymptomatic, as in our case, and regular examinations should be conducted. Arthritis in early-onset childhood sarcoidosis is persistent, relatively painless, nondestructive, and affects predominantly the large joints. A good range of joint movement characterized by boggy synovial proliferation and tendon sheath effusions is noted. As in our patient, no destruction of joints and no limitation of movement are noted after long term follow-up.

The diagnosis of early-onset childhood sarcoidosis should be distinguishable from juvenile rheumatoid arthritis, which is also characterized by a combination of skin, joint and eye manifestations. Juvenile rheumatoid arthritis is characterized by painful joints with limitation of movements and destructive changes on radiographs. There is no method of distinguishing the uveitis that occurs in these two conditions; however, the antinuclear antibody test is positive in 88% of patients with juvenile rheumatoid arthritis, but negative in sarcoidosis. Skin changes may appear distinct between the two diseases at onset. The rash in juvenile rheumatoid arthritis is pink, evanescent and macular, whereas the eruption in early-onset childhood sarcoidosis is papules or plaques with scaling. In our patient, the tiny erythematous papules needed to be differentiated from lichen scrofulosorum, which is a unique reaction pattern (tuberculids) of the skin caused by hematogenous dissemination of mycobacterium, and is also characterized by asymptomatic, skin to pale-red-colored, flat-topped, pinhead-sized, follicular papules that are dispersed over the trunk.

Derangement of calcium metabolism manifested as hypercalcemia and/or hypercalciuria occurs in up to 30% of children. Hypercalcemia may occur even in the presence of normocalcemia and may contribute to nephrocalciosis and nephrolithiasis as seen in our patient. Renal dysfunction is most often due to hypercalcemia, but may occasionally be elicited by granulomatous interstitial nephritis. In a previous study, at follow-up, the laboratory test results were within the normal reference intervals.

The current treatment of choice for childhood sarcoidosis with multisystemic involvement is corticosteroid. The patients may follow a course of chronic relapse and steroid dependence, similar to our patient, during the initial few years. Immunosuppressants such as methotrexate and azathioprine are steroid-sparing agents. Methotrexate has been used in various manifestations of sarcoidosis, such as skin disease, uveitis, and musculoskeletal complications; oral administration is safe and effective and has few side effects in childhood. Combination therapy with steroids and methotrexate shows significant clinical improvements, in addition to the successful tapering of the prednisone dose, as in our case. Cutaneous lesions generally respond to therapy administered for systemic involvement but may recur after the treatment is discontinued. Other treatment options including antimalarial drugs, thalidomides, oral retinoids, and psoralsen and ultraviolet A light appear to be effective in controlling cutaneous manifestations.

Hydroxychloroquine is considered as the standard therapy, either in combination with steroids, or as monotherapy for long-term treatment. The primary benefits are the ability to suppress cutaneous lesions and safety in women of child-bearing age. Hydroxychloroquine with steroids was considered in our case when the cutaneous lesions were the persistent problem. The prognosis and natural history of sarcoidosis in children are unclear because of the rarity of the disease and the small number of reported cases. The prognosis is reported to be as good as that in adults, with most children experiencing considerable improvement in clinical manifestations, chest X-ray findings, and pulmonary function test results. In a Danish follow-up study, 80% of the subjects recovered completely without functional impairment. However, a case series of six patients and a long follow-up period (mean: 14 years) revealed blindness (4 patients), growth retardation (3 patients), heart involvement (2 patients), renal failure (1 patient), and even death (1 patient). Further studies are required to understand better the long-term prognosis of this disease.

Here, we presented a rare case of a typical presentation of early-onset childhood sarcoidosis and the follow-up condition. Notably, skin manifestations are very common in this type and present differently from late-onset and adult type. This case reminds us to include childhood sarcoidosis in the differential diagnosis in
pediatric patients who present with multiple papular eruptions along with systemic manifestations. Early diagnosis and regular ocular examination are important to avoid serious complications.

References