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Case Report

Weight Loss, Lymphadenopathy and Hepatosplenomegaly are Not Always Lymphoma. Sarcoidosis Mimicking Lymphoproliferative Disease: A Case Review

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Received: November 10, 2022; **Published:** November 15, 2022

Abstract

A 12-year-old girl of Afro-Caribbean ethnicity was referred to our Paediatric Haematology Department in the setting of generalised lymphadenopathy, hepatosplenomegaly, constitutional symptoms with appetite and weight loss (10 - 15%) and new-onset shortness of breath on exertion. Initial investigations for lymphoproliferative disorder revealed mild anaemia, thrombocytosis, raised erythrocyte sedimentation rate, and transaminitis. Radiography showed mediastinal lymphadenopathy and splenomegaly. Lack of fever, presence of atypical lymph nodes and atypical lung changes on CT prompted further investigations for differential diagnoses. An elevated ACE enzyme level alongside pathognomonic CT changes and the clinical context brought sarcoidosis into consideration which was subsequently confirmed on cervical lymph node biopsy.

Keywords: *Lymphadenopathy; Hepatosplenomegaly; Lymphoma; Sarcoidosis; Lymphoproliferative Disease*

Background

Sarcoidosis in the paediatric population is extremely rare and is usually a diagnosis of exclusion, suggested by clinical manifestations and supported by observation of a typical granuloma at the histologic examination of a tissue.

By definition, Sarcoidosis is a complex inflammatory disorder with multi-systemic manifestations, characterized by the formation of non-necrotizing epithelioid cell granulomas with multi-organ dissemination [1,2]. The pathophysiologic basis is not clearly understood but the current hypothesis is a combination of genetic predisposition and either organic or mineral environmental exposure, that triggers the inflammatory process and granuloma formation [2]. Sarcoidosis can affect many organs, predominantly the lung [3,4]. There is a wide spectrum of clinical presentations ranging from a sub-clinical form to a life-threatening multi-organ dysfunction, The most common symptoms reported in children were related to lung and mediastinal involvement, however, extra-respiratory manifestations were also frequently observed [5]. Systemic manifestations such as fevers, night sweats, weight loss may also occur [6]. Laboratory tests, such as elevated Angiotensin Converting Enzyme (ACE), erythrocyte sedimentation rate (ESR), anaemia, thrombocytosis, lymphocytosis

or lymphopenia, elevated liver function tests and creatinine, hypercalcemia and hypergammaglobulinemia are not usually reliable for the diagnosis because they are non-specific [2,5]. Chest radiography often shows bilateral symmetrical hilar and mediastinal lymphadenopathy. Classical parenchymal changes include mid and upper zone predominant nodular or reticulonodular opacity and upper zone predominant fibrosis [6].

In this case, we are reporting a case of Sarcoidosis mimicking lymphoma in terms of the clinical presentation.

Case Presentation

A 12-year-old, previously healthy Afro-Caribbean girl was referred by the general practitioner (GP) to the local acute paediatric service for investigation of weight loss, fatigue and deranged liver function. She had an 8-week history of swollen neck lymph nodes following sore throat for which she was treated with 10 days oral antibiotics. She also had a hyperpigmented rash on her trunk, consistent with granuloma annulare (ringworm).

At follow up with the GP, the sore throat had completely resolved, the rash persisted, and in addition she was noted to have lost significant body weight (15% of the normal body weight). She also complained of arthralgia involving her left hip without any arthritis noted, no other joint involvement. She reported shortness of breath since her symptoms started. There was no history of fevers, night sweats, gastrointestinal symptoms, mouth ulcers, ocular symptoms or headaches.

She was referred to our Paediatric Haematology department for suspected lymphoma on the basis of hepatosplenomegaly, raised lactate dehydrogenase (LDH) and weight loss.

Investigations

Laboratory investigations revealed mild anaemia [Haemoglobin: 102 g/L (normal range 115 - 155 g/L)] and thrombocytosis [(Platelets: 573 X 109/L (normal range 150 - 450 X 109/L)], with total white cell count and leucocyte subsets within normal limits and raised erythrocyte sedimentation rate (ESR) 120 mm/hr (normal range 0 - 10 mm/hr) with low C-reactive protein 9 (normal range 0 - 20). In addition, the patient had deranged liver function [Alanine aminotransferase (ALT): 466 U/L (normal range 10 - 55 U/L), alkaline phosphatase: 612 U/L normal range 105 - 420 U/L), albumin: 35 g/L (normal range: 37 - 56 g/L), lactate dehydrogenase (LDH): 814 U/L (normal range 380 - 640 U/L), gamma glutamyl transferase (GGT): 177 U/L (normal range 14 - 25 U/L)].

On admission at the local hospital, extensive blood work-up for infections was negative: Epstein-Barr Virus polymerase chain reaction (PCR), Cytomegalovirus PCR, Adenovirus PCR, hepatitis A, B, C PCRs and serology, nasopharyngeal viral screening, mycobacterial testing (Quantiferon tuberculosis (QTB).

In view of the loss of weight and breathlessness, a CT chest was requested along with an abdominal ultrasound. The abdominal ultrasound demonstrated hepatosplenomaly, retroperitoneal lymphadenopathy measuring up to 1.7mm, with both kidneys enlarged, revealing bilateral low attenuation renal infiltrates. Computed tomography (CT) of the chest revealed mediastinal and hilar lymphadenopathy with widespread subpleural reticulation, airway prominence and parenchymal nodules (Figure 1).

Angiotensin Converting Enzyme was elevated - 227 U/L (N: 0 - 90), C1Q antibody was elevated- 27 U/ml (N:0.0 - 15.0 U/mL) with a low C1Q level of 16 (N: 50 - 250 mg/L).

The patient's weight stabilised during the hospital admission, however lethargy and breathlessness on exertion persisted. In view of the subpleural reticulation and parenchymal nodular lung changes on the chest CT and elevated serum ACE, the patient was referred to the rheumatology team.

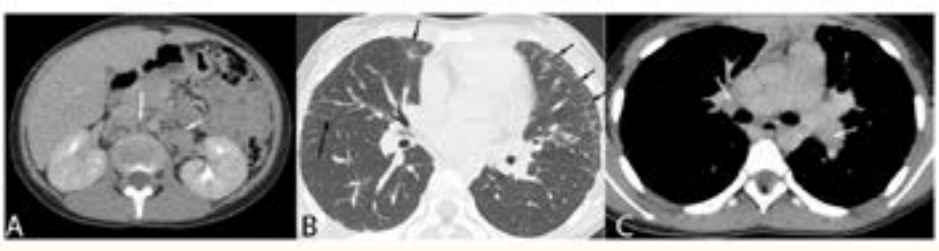

Figure 1: *(A) Upper abdominal CT image demonstrating retroperitoneal lymphadenopathy (white arrows), (B) representative lung windows demonstrating subpleural reticulation and fissural nodularity (black arrows) and (C) representative mediastinal windows demonstrating bilateral hilar adenopathy (white arrows).*

Skin punch biopsy was done from the hyperpigmented rash over the abdomen- (Granuloma annulare)- showing hyperparakeratosis and mild spongiosis. Dermal non-caseating granulomas comprising epithelioid histiocytic and focal multinucleate giant cells were seen with a mild chronic inflammatory cell infiltrate and a cervical lymph node biopsy also revealed non-necrotising granulomatous lymphadenopathy. These findings were consistent with sarcoidosis.

Pulmonary function tests revealed restrictive lung disease (FEV1- 39%) with low TLCO adjusted for haemoglobin suggestive of restrictive lung disease.

Later, she developed an acutely painful eye and was reviewed on an emergency basis at a specialized ophthalmology hospital where she was noted bilateral retinal periphlebitis, characterized by segmental perivascular sheathing of the affected vessels (Figure 2). The retinal vasculitis responded well to the oral course of Prednisolone with complete resolution of the perivascular sheathing (Figure 3). The patient was started on MTX 20 mg/week, that was subsequently switched to MMF 1g bd because of deranged liver function, and both eyes remained quiescent with no recurrence of intraocular inflammation for two years. In December 2021 there was a bilateral recurrence of retinal periphlebitis (Figure 4) for which the patient was treated with systemic steroids. After an initial bilateral improvement, right eye showed a progressive worsening of the periphlebitis, with progression of the perivascular sheathing and new areas of vascular involvement, necessitating intravenous methylprednisolone and escalation to anti TNFalpha therapy (Figure 5).

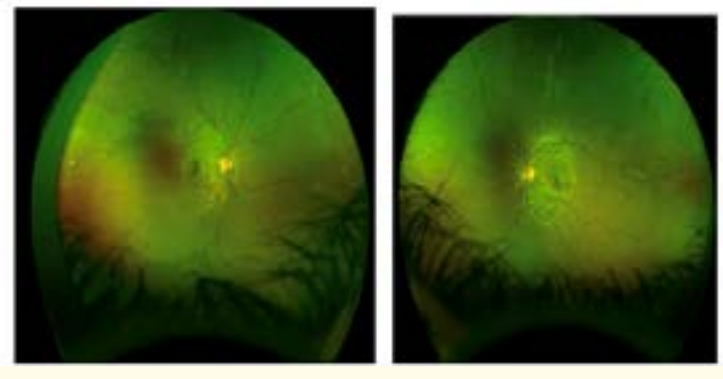

Figure 2: *Ultra-wide field pseudocolour fundus photograph of bilateral retinal periphlebitis, with segmental perivascular sheathing of the affected vessels.*

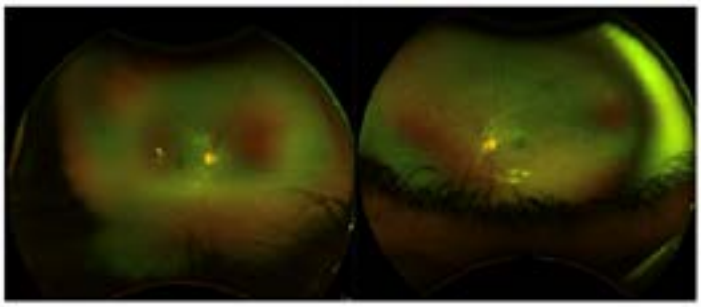

Figure 3: *Ultra-wide field pseudocolour fundus photograph showing resolved retinal periphlebitis, with no involvement of retinal vessels.*

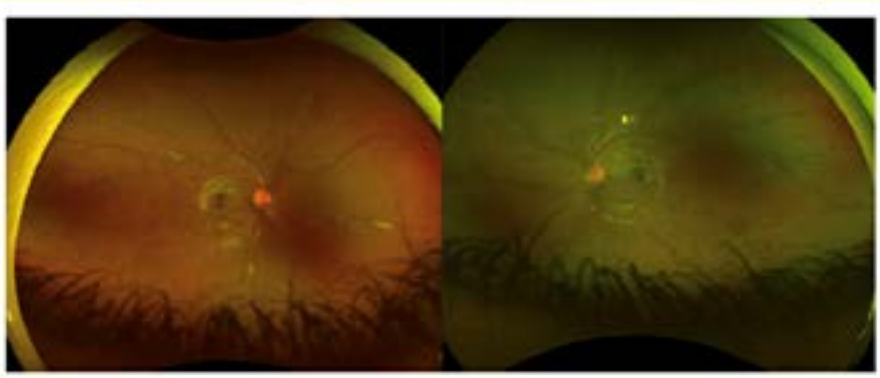

Figure 4: *Ultra-wide field pseudocolour fundus photograph showing bilateral recurrence of retinal periphlebitis, with segmental perivascular sheathing of the affected vessels.*

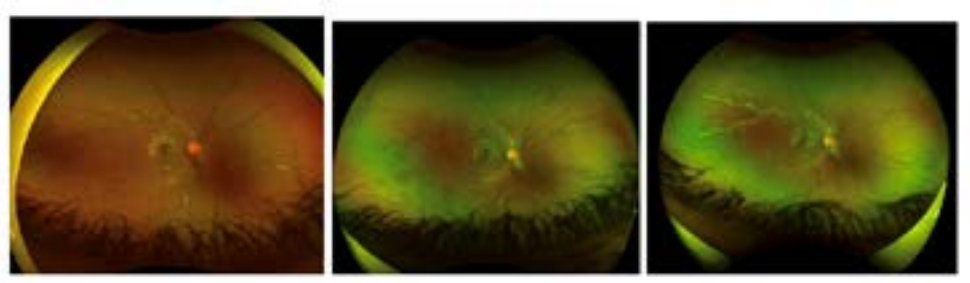

Figure 5: *Ultra-wide field pseudocolour fundus photograph showing worsening of retinal periphlebitis in the right eye, with progressing segments of perivascular sheathing.*

Differential diagnosis

The differential diagnosis of sarcoidosis is extremely broad because its various clinical manifestations resemble other disorders [7]. The diagnosis is based on clinical manifestations, radiographic findings, histopathologic detection of non-caseating granulomas in the affected organ, having excluded other diseases [8]:

- In this case presentation, lymphoproliferative disorders/lymphoma are the first differentials that come to mind given the weight loss, lymphadenopathy and hepatosplenomegaly. The CT chest findings, in addition to the raised ACE, widened the possible differentials to include sarcoidosis. Histopathology then confirmed the latter.
- Other causes of granuloma should be excluded such as: Blau syndrome, tuberculosis, leprosy, syphilis, fungal infections, berylliosis, malignancies, immune deficiency such as combined immunodeficiency, eosinophilic granuloma, Crohn's disease, Behcet disease, Sjögren syndrome, histiocytosis and rarely drug induced granulomatosis [2,7].
- Other inflammatory causes of uveitis should be excluded as vasculitis.
- Other causes of elevated ACE levels in patients with pathologies other than sarcoidosis, such as Hyperthyroidism, Diabetes mellitus, Cirrhosis of the liver, Gaucher's disease, malignancies and Silicosis. Furthermore, other factors affect the production of ACE, such as genetic factors and the use of ACE inhibitors. Therefore, serum ACE levels are considered supportive rather than definitive diagnostic indicator of sarcoidosis [8,9].

Treatment and outcome

After confirmation of the diagnosis, the patient was started on a weaning course of systemic corticosteroids and subcutaneous methotrexate (MTX) (dose: 15 mg/m^2/week, maximum of 20 mg/week) and steroid eye drops. There was complete resolution of generalized lethargy, breathlessness on exertion, rashes and weight gain was noted. She had complete resolution of the painful eye. Her liver function tests improved.

Liver function tests became deranged whilst on MTX which required cessation of the medication after 6 months of treatment. Mycophenolate mofetil (MMF) was the second choice of maintenance therapy given the fact that there was lung, liver and lymph node involvement. To date, this has been well-tolerated without any significant side effects. Treatment with disease-modifying anti rheumatic drugs (DMARDs) is essential to control disease activity and to allow tapering corticosteroids for the long-term management of Sarcoidosis. After 6 months of treatment, corticosteroid eye drops were also stopped in our patient as chorioretinitis showed significant improvement.

After one year of treatment, follow up abdominal ultrasound showed persisting mild hepatomegaly while the chest CT showed marked improvement in lung lesions and resolution of splenic hilar, periportal and retroperitoneal lymph nodes.

MMF was continued as single agent, till she suddenly developed an acutely red eye with a diagnosis of periphlebitis. Steroid eye drops were restarted together with Adalimumab injection every 2 weeks. The child is currently being followed up under the joint care of Pediatric Respiratory, Rheumatology and Ophthalmology department.

Discussion and Conclusion

Sarcoidosis is a multi- system disease which usually manifests in adults in the lungs, skin and/or lymph nodes, with very few cases in children [10,11]. The incidence and prevalence of sarcoidosis are both influenced by age, race and geographical localization, although part of this variation can be explained by regional differences [12,13]. Its prevalence in the UK is 1 in 10,000 people [11]. The reported incidence is 0.29 - 0.8 per 100,000 children [2,3,14-16]. However, the actual incidence is unknown due to the rarity of the disease among the pediatric age group [1]. Although it is seen in patients of all ethnicities, people of African heritage are more commonly affected [11].

A study was performed on forty-one patients with pulmonary sarcoidosis in the French Reference Centre for Rare Lung Diseases (Respi-Rare), the majority of patients were of Afro-Caribbean origin [3].

Sarcoidosis is thought to result from the combination of genetic predisposition plus exposure to an external stimulus. There are numerous susceptibility genes that have been associated with the development of Sarcoidosis such as HLA-DQA1, HLA-DRA, and HLA- DRB5, ACE, ANXA11, BTNL2, LTA, MAPK, OS9, TAB1 and TAB2 (a downstream gene associated with NOD2 protein signaling), and TNFA [14-17].

Clinical presentations can be significantly variable and non-specific since it is a multisystem disease, and any organ system may be involved [18]. Childhood sarcoidosis has two forms: early-onset sarcoidosis (occurs in children <4 years old) characterized by arthritis, uveitis, and cutaneous involvement and late-onset sarcoidosis (more common form occurring mostly in patients aged 13 - 15 years), presenting with a picture similar to that of adults; with frequent hilar lymphadenopathy and pulmonary infiltration [19]. Cough, dyspnea, crepitations and rhonchi at auscultation are the classic features related to lung involvement. Chest X-rays are normal in 44% of cases, However, in 95% of children, high-resolution CT scans reveals abnormalities, mainly nodules with ground-glass opacities and hilo-mediastinal lymphadenopathies [3,18]. Ocular manifestations in childhood sarcoidosis may be iritis with granulomatous keratic precipitates, iris nodules, choroidal or retinal granuloma, peripheral multifocal choroiditis or conjunctival granuloma [20,21]. Cutaneous presentations may be erythematous rash, nodules, violaceous plaques, hyper or hypopigmentation and ulcers. Musculoskeletal features of sarcoidosis include joint effusions, pain, and rarely, osseous involvement [20].

Unlike some other conditions associated with granulomas, there is no gold-standard diagnostic test for sarcoidosis. The diagnosis can be considered reliable in the presence of suggestive clinical and radiologic manifestations, and histological evidence of non-necrotizing granulomas, when all alternative diseases are reasonably excluded [18,22]. Elevated serum ACE is supportive but non-specific and there are cases diagnosed as sarcoidosis with normal serum level [23] however, serum ACE is helpful in monitoring disease activity [1].

Prognosis of pulmonary sarcoidosis in pediatrics is good if diagnosed early. Late diagnosis may have poor prognosis with regard to ocular and lung disease [1]. However, sarcoidosis remains an enigmatic disease with high variability in severity, extent and long-term outcome studies in children are lacking. A study of 52 patients who had pediatric-onset sarcoidosis concluded that almost half of the patients needed a long-term treatment and around one fifth of patients had severe sarcoidosis long term consequences in adulthood [24]. At present there is no curative treatment and, since a large number of cases have a self-limiting course (with spontaneous remission in few years), treatment should be administered with this in mind [18,25,26]. Systemic steroids and methotrexate are the cornerstones of therapy in sarcoidosis [1,21]. Second-line drugs include different alternatives such as TNFα-antagonists, cyclophosphamide, mycophenolate mofetil (MMF) and tacrolimus [18].

Learning Points:

- Childhood sarcoidosis is an extremely rare multisystem granulomatous disorder.
- The symptoms are non-specific and the diagnosis is by exclusion, so it should be considered part of the differential diagnosis when assessing a child with hepatosplenomegaly and B symptoms.
- In this case, the subpleural reticular change, and parenchymal modules as well as elevated serum ACE were highly suggestive of sarcoidosis. Mediastinal lymph nodes with lung infiltrates, lymphadenopathy, uveitis and rashes may raise suspicion of Pediatric Sarcoidosis in older children.
- Most children have a self-limiting course, some may experience a more chronic presentation.
- Treatment includes steroids, methotrexate and occasionally MMF. DMARDs are essential for long term control of sarcoidosis.

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Volume 11 Issue 12 December 2022