CLINICAL VIGNETTE

Development of Scleroderma in a Young Child Following Resolution of Hypereosinophilic Syndrome

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Eosinophilia, defined as > 450 eosinophils/μL in a peripheral blood study, is found in many diseases most often secondary to infectious or allergic etiologies. Hypereosinophilic syndrome (HES) is defined as an absolute eosinophil count (AEC) of more than 1500/μL for 6 months duration, absence of a secondary cause, and evidence of eosinophil-associated pathology.[1] There are 3 subtypes of the hypereosinophilic syndrome: myeloproliferative, lymphocytic, or idiopathic. Common target organs include the skin, lung, and gastrointestinal tract.[2] Less commonly, patients can have potentially life-threatening damage to the cardiovascular system and brain. Corticosteroids are the first-line medical treatment for idiopathic HES.[3]

Involvement of the skin is common in HES including eosinophilic panniculitis and eosinophilic fasciitis. Eosinophilic fasciitis involves superficial tissues; subcutaneous tissue, fascia, and muscle unlike the pathology seen with scleroderma which involves the epidermis and dermis.[4] Yet, eosinophilic fasciitis has been associated with progression to scleroderma which is associated with increased synthesis of collagen that leads to sclerosis and fibrosis secondary to activation of T lymphocytes.[5] Most often eosinophilic fasciitis leads to linear scleroderma, but there are reports of systemic sclerosis occurring in consequence of eosinophilia and eosinophilic fasciitis in the setting of tryptophan exposure.[6]

A 10-month-old previously healthy girl presented for fever, periorbital edema, and petechial rash. She was diagnosed with a viral illness and discharged home. The fevers persisted and the edema became more generalized. She subsequently developed poor oral intake and increasing irritability and was hospitalized. Review of systems was notable for a recent upper respiratory illness, ear infection, and a persistent cough. There was no tryptophan exposure. Physical examination revealed a well-developed, well nourished, but irritable girl. There was bilateral anterior cervical lymphadenopathy, hepatosplenomegaly, significant facial edema and 3+ pitting edema in the extremities. The remainder of the exam, including heart, lungs, and skin, was normal.

Complete blood count was notable for a WBC count of 6.8 $x10^3$/μL with an AEC of 1428/μL which increased to 2924/μL on serial studies. T cell immunophenotyping demonstrated CD3 - 2255 cells/ul, CD4- 1285 cells/ul, CD8- 766 cells/ul, CD 16/56- 354 cells/ul, CD19-1324 cells/ul. Liver function tests revealed ALT of 239 U/L and AST of 239 U/L. Albumin and total protein levels were low. C3 and C4 were low normal. ANA was positive at 1:180 with a non-specific pattern. Urinalysis was negative for protein. Extensive evaluation for an infectious etiology including blood and urine cultures, tests for various parasites, hepatitis panel, CMV, EBV, histoplasmosis, coccidioidomycosis, and toxoplasmosis proved negative. Chest X-ray showed bilateral pleural effusions and echocardiogram revealed a pericardial effusion without compromise of heart function.

A liver biopsy showed marked eosinophilia without signs of fibrosis. A bone marrow biopsy showed increased numbers of eosinophils but no evidence of malignancy. A lymph node biopsy was also negative for malignancy. A presumptive diagnosis of HES was made. She was started on diuretics and tapering doses of prednisone which resulted in a decrease in eosinophil count. However, at age 27 months, she subsequently developed recurrent episodes of vomiting and diarrhea, prominent abdominal distension, thickening and nodularity of the intestinal wall as well as areas of stricture suggestive of small bowel obstruction. Laparotomy and gastrointestinal biopsy revealed microscopic fibrosis and eosinophilic infiltration into the esophagus, small bowel and colon, with prominent atrophy of the muscularis propria consistent with eosinophilic gastroenteritis. The gastrointestinal symptoms progressively worsened, and the patient was started on total parental nutrition and treated with azathioprine and subsequently methotrexate.

At the age of 3, she developed scalp scarring, thigh dimpling, and chest lesions that were concerning for scleroderma versus eosinophilic fasciitis. Biopsy of the lesions was consistent with morphea scleroderma with no eosinophils present. She was started on hydroxychloroquine and D-penicillamine which resulted in improvement of her skin lesions. At the age of 6, she had an apneic episode for which she underwent cardiac evaluation. EKG was notable for right bundle branch block and intermittent tachyarrhythmia. An echocardiogram revealed a pericardial effusion. She was diagnosed with acute pericarditis and started on steroids. She then developed periods of non-sustained ventricular tachycardia with occasional premature ventricular contractions. Endomyocardial biopsy showed myocarditis with lymphocytic infiltrate and endocardial fibrosis. At the age of 9, she again presented with symptoms of sclero-

dermatous cardiac disease with runs of ventricular tachycardia which required placement of an automated implantable cardioverter-defibrillator (AICD). In the 10 years following, she has done reasonably well off of medications, with mostly gastrointestinal manifestations of scleroderma. Her AICD was removed because of her clinical improvement and her skin lesions largely resolved.

This infant was diagnosed with HES and developed diffuse cutaneous systemic scleroderma with significant myocardial fibrosis leading to cardiac arrhythmias requiring AICD placement. A decade later, despite lack of immunosuppression, she remains relatively asymptomatic from her scleroderma except for gastrointestinal manifestations. Her favorable outcome contrasts with the slowly progressive course associated with this disease. Furthermore, the development of scleroderma following HES is reminiscent of but distinct from the pathologic fibrosis that has previously been described with eosinophilic fasciitis and eosinophilia-myalgia syndrome.[6] These syndromes are associated with eosinophilia, but also have a large fibrosis component and improve with immunosuppression. Other diseases in the differential diagnosis include Systemic Mastocytosis, Hyper-IgE Syndrome, leaky genetic disorders and hypomorphic RAG mutations.

Eosinophilic disorders and scleroderma share common immune dysfunction that may provide a better understanding of these diseases and how they overlap. Autoimmunity and vasculopathy are key features contributing to inflammation and fibrosis of effected organs in systemic sclerosis. One possible pathway involves type 1 interferon activation leading to TH2 cell production of IL4 and IL13, both contributing to eosinophil recruitment. Deposits of eosinophil and eosinophil byproducts have been detected in effected organs in patients with systemic sclerosis. The release of toxic cationic proteins could lead to end organ fibrosis; a possible explanation for organ damage.

This case may represent a subtype of scleroderma with a distinct pathophysiology and prognosis that has not yet been described.

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