Immunol Genet J, Vol. 4, No. 2, June 2021, pp.119-123 **DOI: https://doi.org/10.18502/igj.v4i2.9988**

Case Report

Eosinophilic Fasciitis/Generalized Morphea Overlap: A Rare Manifestation in a Patient with X-Linked Agammaglobulinemia

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Received: 15 April 2021; Accepted: 19 May 2021

Abstract

X-Linked Agammaglobulinemia (XLA) is a prototype of humoral immunodeficiency disorders manifested by recurrent sinopulmonary infections and characterized with low to absence of immunoglobulin production due to absence of B lymphocytes.

There are many reports of unusual complications of this genetic disease such as Pneumocystis carinii pneumonia, enteroviral infections with diverse manifestations, neutropenia during severe infections and also uncommon reports of some autoimmunities. Moreover, Rheumatological diseases are reported as a manifestation of XLA among which dermatomyositis is a known and expected condition. Other connective tissue diseases are rarely reported.

In this report, the researchers described a known case of XLA disease with progressive body pain, muscle ache, tender and tense skinand finally confirmed as a rare occurrence of Eosinophilic Fasciitis / Morphea Overlap.

Keywords: X-Linked Agammaglobulinemia; Morphea; Eosinophilic Fasciitis; Rheumatologic Manifestation; Sensorineural Hearing Loss

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How to cite this article

Nabavi M, Arshi S, Bemanian MH, Fallahpour M, Bakrani V, Shokri S. Eosinophilic Fasciitis/Generalized Morphea Overlap: A Rare Manifestation in a Patient with X-Linked Agammaglobulinemia. Immunology and Genetics Journal, 2021; 4(2): 119-123. DOI: https://doi.org/10.18502/igj.v4i2.9988

Introduction

XLA is a primary humoral immunodeficiency characterized by severe hypogammaglobinaemia and increased susceptibility to infections. (1).

Symptoms include significant hypogammaglobinaemia or agammaglobulinemia and absence of Blymphocytes. The diagnosis is confirmed by identifying a mutation in the BTK gene. (2) Although no autoantibodies are produced in Bruton's disease, up to 28 percent of patients in one report had inflammatory complaints and several patients had been diagnosed with autoimmune diatheses such as hypothyroidism and inflammatory bowel disease (3).

Scleroderma is a fibrosing disorders ranging from localized scleroderma (morphea) to systemic sclerosis. Classification includes localized scleroderma, deep morphea encompasses morphea profundus, eosinophilic fasciitis (EF) and pansclerotic morphea of children (4). Scleroderma is an uncommon phenomenon in XLA which has been reported as a case report (5).

Eosinophilic fasciitis (EF) is characterized by painful swelling and progressive induration of fascia and subcutaneous tissue. The condition has been associated with heavy exercise, muscle trauma, burns, arthropod bites, some drugs, radiotherapy, chemical exposure and para-neoplastic syndromes (6). Differential diagnosis includes scleroderma, poly myositis and peripheral T cell lymphomas (7). MRI can be used to support the diagnosis and suggest the optimal site for biopsy (8).

Case presentation

A 27-year-old male had been diagnosed as XLA when he was 19 years old because of recurring episodes of sinopulmonary infections and hypogammaglobinaemia. The patient had a history of recurrent otitis media in childhood which was accompanied by perforation of tympanic membrane. He had experienced one episode of septic arthritis of hip joint at the age of two years old and was hospitalized several times for recurrent bacterial pneumonia since the age of 17 years old. He was referred to immunology clinic at the age of 19 years old for evaluation of immune function. Immunoglobulin levels at the time of diagnosis revealed agammaglobulinemia; IgG: 46mg/dl, IgM: 13.3 mg/dl and IgA: 20 mg/dl. Moreover, flow cytometric analysis of peripheral blood lymphocytes showed normal T-cell counts and absence of CD19, CD20 and CD21. Mutation in BTK (Bruton tyrosine kinase) gene (P.Aeg525Glu) was detected. Due to agammaglobulinemia and absence of B cells on several occasions and genetic confirmation of XLA, treatment with Intravenous Immunoglobulin (IVIG) was started as regular monthly infusions. He experienced no serious events following starting and continuing of replacement therapy. Ideal IgG level considered 800 mg/dl and the dose of IVIG adjusted accordingly.

At the age of 27 years old, the patient experienced mild fatigue associated with muscle pain following an episode of diarrhea. Symptoms were fluctuating for more than a month until fever was added to other symptoms. During the first visit, he underwent COVID-19 PCR and lung CT scan. No new pathological findings were seen on the chest CT-scan and PCR testing for COVID19 was negative. Laboratory tests including CBC, Diff, ESR and CRP were within normal limits but increased liver enzymes levels were detected. No improvement of symptoms seen with symptomatic treatment and even a 2 week empiric antibiotic and fever persisted. Therefore, he admitted for work-up of fever of unknown origin. In addition, the differential diagnosis included usual infections with unusual presentation. Unusual infections which are expected to occur in an immunodeficient patient e.g. chronic enteroviral CNS infections, malignancies and collagen vascular disorders. According to these differentials, laboratory and imaging studies were performed in addition to a detailed daily physical examination. Repeated CBC, DIFF, ESR, CRP, thyroid and renal function tests, electrolytes, urine and stool analysis were within normal ranges. Moreover, blood, urine and stool cultures were negative on several occasions. However elevated SGOT, SGPT, CPK and LDH mandated a meticulous malignancy work-up. Therefore, mild hepatosplenomegaly found imaging studies including abdominopelvic ultrasonography and CT scan ordered which showed non-significant paraaortic and inguinal lymph nodes for which biopsy was not possible as they were too small. CT scan of chest and neck were normal. Whole body PET scan showed no abnormal uptake.

Bone marrow aspiration was negative for hematologic malignancies, hemophagocytosis. Furthermore, cultures in Castaneda's medium were negative as the patient used non-pasteurized dairy as routine. Colonoscopy was performed and biopsy specimens were analyzed for PCR of common viruses responsible for diarrhea in hypogammaglobulinemic patients, such as norovirus, rotaviruses, adenoviruses and CMV, and no pathologic findings were found. Serum PCR for CMV, EBV and HIV were also negative. A complete auto antibody panel including ANA, RF, anti CCP, anti-ds-DNA was all negative as expected in agammaglobulinemia.

He was discharged with no diagnosis, and re-admitted after one month for continuous fever. Gradually, tense and non-pitting edema of the limbs and trunk was added to other symptoms and sensory neural hearing loss developed and progressed to complete bilateral hearing loss without any known etiopathology. Polymyalgia and increased muscle enzymes associated with muscle weakness rendered us to evaluate other differential diagnoses such as dermatomyositis, scleroderma and eosinophilic fasciitis. Skin and muscle biopsy and muscle MRI were performed to confirm the initial diagnosis of dermatomyositis/polymositis complex. Skin biopsy revealed mild basket weave hyperorthokeratosis and partial atrophy of epidermis with flattening of rete ridges. Upper dermis was unremarkable. Mid and deep dermis were mildly sclerotic and revealed perivascular and periadnexal infiltration of chronic inflammatory cells including lymphohistiocotes and few mast cells extending to subcutaneous fat septa and fibro connective tissue below fat eosinophils are rare. These pathologic findings are highly compatible with early inflammatory stage of scleroderma and morphea. Besides, Evidences in favor of scleroderma were seen on skin biopsy, myositis on muscle biopsy and fasciitis on MRI. Analysis of stool and PCR for Enteroviruses in blood, CSF and muscle biopsy specimen was all negative. In this study, the patient was treated with a diagnosis of scleroderma under observation of rheumatologist and during about two years of follow-up he is doing well. Cochlear implantation was performed for the patient and the results have been promising.

Discussion

The primary immunodeficiency diseases (PIDs) are genetic abnormalities that affect different components of the innate and adaptive responses. On the other hand, Autoimmune Diseases (ADs) are a heterogeneous group of disorders which occur due to a loss of tolerance to self-antigens. Although PIDs and ADs are considered as separate categories, genetic advances and a greater understanding of the pathophysiological processes has clarified a close correlation between these two variables. As immune system is in charge of controlling autoimmunity in healthy individuals, therefore defective immune function may underlie unusual autoimmune manifestations, thus they are now accepted as interconnected processes (9). Patients with PIDs may be more susceptible to ADs, allergic diseases and malignancies in addition to unusual infections (10). In a previous study in our center, autoimmunity was detected in 23% of patients with common variable immunodeficiency (CVID) including juvenile idiopathic arthritis, systemic lupus erythematosus and lichen planus in 6. 2 and 2 percent respectively. No study in our center has addressed autoimmune manifestations in XLA yet (11). The mechanisms of autoimmunity in XLA are unknown. The association of XLA and scleroderma, dermatomyositis, and myositis is noted, but the reason for this association is also not yet completely understood (12). One hypothesis suggested survival of self-reactive receptors on few circulating B-cells due to signaling by self-antigens, which overcame the blocked signaling route through the BTK mechanism (13). Studies suggested that T-cell activation not deleted by the CD95-dependent cross-tolerance mechanism may lead to uncontrolled proliferative potential of auto reactive T-cells which in turn facilitate the occurrence of Th1 oriented diseases such as diabetes type1 in XLA patients (14).

Infection with enteroviruses can cause chronic meningoencephalitis in XLA which is sometimes associated with a dermatomyositis-like syndrome. In the current study, according to edema of the limbs, myalgia and increase in muscle enzymes and exclusion of differentials such as lymphoma, viral infections (with negative PCR), TB (by negative PPD and PCR) and other differential

diagnoses such as scleroderma and eosinophilic fasciitis were proposed.

Eosinophilic fasciitis is a scleroderma-like syndrome that is characterized by painful progressive swelling of fascia and subcutaneous tissue (7). Diagnosis is based on the combination of three findings; clinical features, serology and histological confirmation (15). In this case, to confirm the definitive diagnosis, skin and muscle biopsy performed following muscle MRI. Evidences in favor of scleroderma were seen on skin biopsy, myositis on muscle biopsy and eosinophilic fasciitis on MRI and biopsy. Both EF and morphea showed similar cutaneous sclerosis and immunopathogenesis and both of them are characterized with absence of sclerodactyly, visceral involvement and Reynaud's phenomenon. The inflammation of the fascia in EF can extend to the dermis and also the dermal inflammation of morphea extends to the fascia as in the pansclerotic variant (16). Our patient presented with clinical and histopathologic features of two subtypes of deep morphea: Eosinophilic fasciitis and generalized morphea. The simultaneous presentation indicates that EF and GM are closely related and may be disease entities that fall along a continuum. The patient was treated with prednisolone and cyclosporine which was switched to azathioprine because of cyclosporine induced hypertension. After a few days of treatment, there was a marked improvement in pain, muscle weakness and scleroderma. Eosinophilic fasciitis and generalized morphea overlapping are a rare manifestation in a patient with X-linked agammaglobulinemia, the concept that is not currently recognized in the present published data about autoimmunity in XLA.

Conclusion

Rheumatological diseases are relatively rare manifestations of XLA. Different types of connective tissue diseases are reported in XLA patient and the most commonly reported rheumatological diseases in such patients is dermatomyositis. Other connective tissue diseases are rarely reported as case reports. High index of suspicion and thorough follow up of each manifestation in primary immunodeficient patients is mandatory to diagnose the underlying disease and prompt medical management is necessary to prevent irreversible end organ damages.

Conflict of interest

The authors declare that there is no conflict of interest.

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