Dermatomyositis-like syndrome in x-linked agammaglobulinemia

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ABSTRACT

Primary immunodeficiencies (PIDs) encompass more than 250 different pathological conditions. X-linked agammaglobulinemia (XLA) has been occasionally associated with cutaneous and muscular manifestations resembling dermatomyositis, often termed dermatomyositis-like syndrome (DLS). This syndrome has been associated with cutaneous, muscular and central nervous system manifestations, accompanying a persistent infection by an Echovirus. According to sixteen previously reported cases, this syndrome has a poor prognosis. We report the case of a 27-years old male, with XLA and DLS, successfully treated with 6 cycles of human immunoglobulin and methotrexate. Clinical symptoms improved dramatically with a complete resolution of the musculoskeletal manifestations. Despite this clinical response, prognosis should remain reserved. The evolution of this syndrome remains unpredictable and therapeutic options are limited. To the best of our knowledge, there are only a few reports of similar cases which have survived so many months after the diagnosis.

Keywords: Dermatomyositis-like syndrome; X-linked agammaglobulinemia; Immunoglobulin; Primary immunodeficiencies

INTRODUCTION

Primary immunodeficiencies (PIDs) encompass more than 250 different pathological conditions. X-linked agammaglobulinemia (XLA) is a primary humoral deficiency due to defects in a signal transduction molecule – Bruton tyrosine kinase – which is expressed in every stages of the $CD19^+$ B cell maturation process. An accurate estimate of the incidence or prevalence of XLA is difficult to obtain because the disease is uncommon. However, a minimal estimate of approximately 1 in 379,000 live births was provided from a national registry[1]. Typically, XLA patients present lymphoid hypoplasia, almost complete absence of $CD19^+$ B cells in the peripheral blood, severe hypogammaglobulinemia with severe antibody deficiency and increased susceptibility to infection. The most common clinical manifestations of XLA are recurrent and chronic infections (bacterial - encapsulated pyogenic bacteria, viral, fungal or parasitic). More rarely, some malignancies, sensorineural hearing loss and auto-immune manifestations have been associated with XLA. In 1956, Janeway et al. reported a syndrome with cutaneous and muscular manifestations resembling dermatomyositis in patients with XLA[2]. Since then this condition has been termed dermatomyositis-like syndrome (DLS).

This rare association of conditions is usually progressive and fatal and is characterized by erythema, edema and induration of the skin, muscle weakness, and flexion contractures of the extremities[2-4].

This syndrome is typically accompanied by central nervous system manifestations associated with persistent infection by an Echovirus. The involvement of Echovirus at the onset of the cutaneous and muscular manifestations has also been suggested[5].

CASE REPORT

We report the case of a 27-years old male with XLA, whose medical history included xerophthalmia, decreased visual acuity, repeated conjunctivitis, severe dental caries, chronic obstructive pulmonary disease (with a forced expiratory volume in 1 second (FEV1)=38,4% and a spirometry/FEV1 relationship of of 51,3), cylindrical bronchiectasis with *Haemophilus*

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influenza colonization, pansinusitis, peptic esophagitis, *Giardia lamblia* gastrointestinal infection and low height and weight. He also described progressive sensorineural hearing loss requiring placement of auditory prostheses. XLA had been confirmed several years before by demonstration of 16 and 18 exons deletion of Bruton Tyrosine Kinase (BTK) gene.

The patient presented to the Rheumatology Department due to persistent symmetric polyarthritis evolving over the last 5 years, associated with proximal muscle weakness and paresthesia of both feet over the past 2 years. The patient was receiving naproxen, analgesics, 19 mg of prednisolone-equivalent and "replacement" doses of human immunoglobulin (according to serum levels) for his XLA. At first observation, he was 166cm tall, he weighted 49 Kg and the cardiopulmonary sounds were normal. We observed a pronounced proximal muscular atrophy of the lower limbs (Figure 1) and the presence of erythematous cutaneous lesions bilaterally on the 2nd, 3th and 4th metacarpophalangeal joints (Figure 2). Limited range of motion was present in the elbows, wrists, hips, knees and ankles. Swelling and tenderness of several metacarpophalangeal and proximal interphalangeal joints was documented. Distal strength of both upper and lower limbs was notably normal, but reduced muscle strength of the pelvic girdle was observed (3+ in a five grade scale).

Laboratory results showed no significant abnormalities, namely in the inflammatory parameters and muscle enzymes. The electromyogram revealed signs of muscle fibers lesion in the right iliopsoas muscle. Following electromyography the patient started complaining of involuntary muscle contractions (mainly in the right lower limb, where the exam had been performed). Muscle biopsy was performed in the right deltoid muscle and demonstrated abundant inflammatory infiltrate in muscle fibres (mainly CD3+, CD4+ and CD8+ T cells) with evident perifascicular atrophy suggesting dermatomyositis.

We started treatment with methotrexate in gradual increase (10 mg per week until 15 mg per week), associated with human immunoglobulin (400 mg/Kg/ /day during 5 days, each month, for 6 months). The clinical symptoms improved dramatically, including a complete resolution of the articular manifestations, paraesthesia and muscle involuntary contractions. Muscle weakness was gradually improved over a few months and the grading scale for assessment of function in patients with myositis[6] evolved from 19/30 to 28/30. Currently, 9 months after starting the immunoglobulin, the patient remains well under this treatment of methotrexate, 15 mg per week, orally, prednisolone, 10 mg per day, orally, and monthly re-

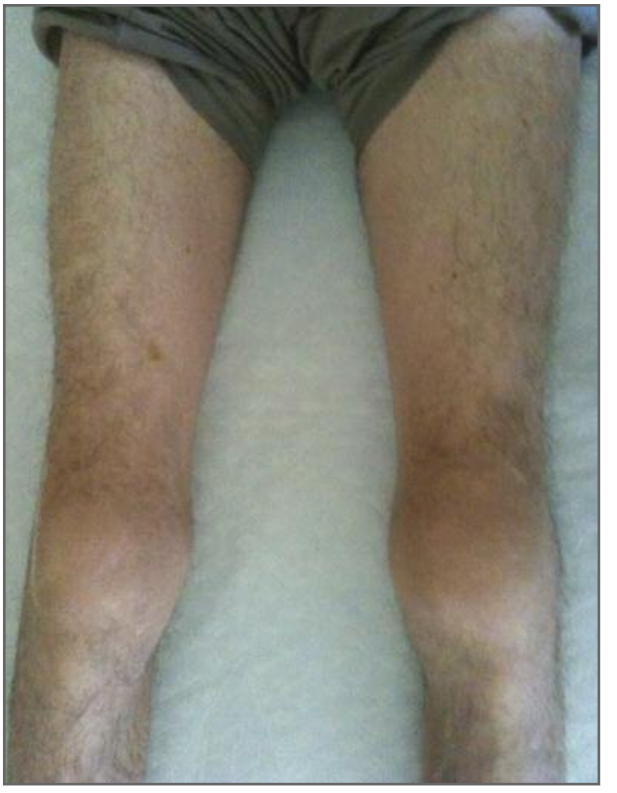

FIGURE 1. Pronounced proximal muscular atrophy of the lower limbs

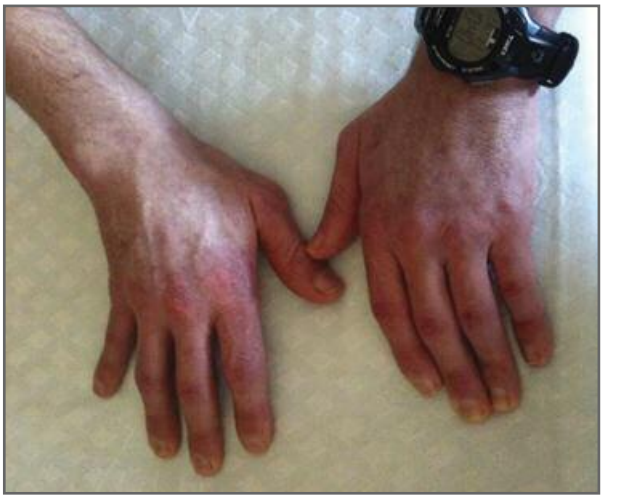

FIGURE 2. Erythematous cutaneous lesions overlying the 2nd, 3th and 4th metacarpophalangeal joints

placement doses of human immunoglobulin (doses according to serum levels), to control XLA.

DISCUSSION

The hypothesis usually proposed for the pathogenesis of this syndrome is persistent viral infection, namely by an Echovirus. In some cases presented on literature, viruses were isolated usually from the cerebrospinal fluid but also occasionally from muscle. Typically a single type of Echovirus is found, although an Echovirus--Adenovirus combination or an association of two Echoviruses have been described[7]. It should be mentioned that neurologic signs are often usually mild, particularly at the onset, and can even be completely absent[8]. The Echovirus infection had been associated with meningoencephalitis and with DLS. However, it is not clear if the persistent viral infection has to be present in the central nervous system or in other tissue, namely muscle. In our case report, there were no neurological signs that could justify a lumbar puncture to search for the presence of an Echovirus. We did not search for viruses elsewhere, because, based on available evidence, their identification would not change the therapeutic approach.

In 1985, Lederman et al[9], performed an analysis of 96 patients with XLA. DLS was observed in 6 patients, all of which had meningitis/encephalitis. Five of these patients also had arthritis. Five of the six patients had disseminated Adenovirus infection. All six patients died. One patient had DLS at diagnosis of XLA and the

TABLE I. XLA AND DLS (16 LITERATURE CASES AS OF 1990)[6]

Nº	Clinical manifestations	Neurologic manifestations	Viral cultures	Evolution
1	Erythema, edema, muscle infiltration	Meningoencephalitis	Echovirus, adenovirus	Died
2	Erythema, edema, muscle infiltration	Meningoencephalitis	Echovirus	Died
3	Erythema, edema, muscle infiltration	Seizures, headache, altered mental status	Not performed	Died
4	Erythema, edema, polymyositis	Confusion, loss of memory	Echovirus	Died
5	Cutaneous atrophy, edema, polymyositis	Headaches, nuchal rigidity	Echovirus	Died (10 weeks)
6	Polymyositis	Deafness	Echovirus	Died (2,5 years)
7	Erythema, polymyositis	No signs	Echovirus	Died (7 months)
8	Erythema, edema, polymyositis	Headaches, seizure	Echovirus	Died (29 months)
9	Erythema, edema, polymyositis	Seizures, confusion	Echovirus	Died (3 years)
10	Polymyositis	No signs	Echovirus	Alive (4 years)
11	Cutaneous atrophy, polymyositis	Nerve VI + VII, paresis, ataxia, deafness	Echovirus	Died (4 years)
12	Polymyositis, edema	Lethargy	Echovirus	Alive (5,5 years)
13	Polymyositis, edema	Seizures, deafness	Echovirus	Died (2 years)
14	Erythema, edema, polymyositis	Seizures, confusion	Echovirus	Died (1 year)
15	Cutaneous atrophy, edema, polymyositis	Cranioencephalic computed tomography (CE-CT) alterations	Echovirus	Died (1 month)
16	Erythema, polymyositis	Seizures	Negative	Died (2 years)

TABLE II. XLA AND DLS (17TH CASE REPORTED)

Nº	Clinical manifestations	Neurologic manifestations	Viral cultures	Evolution
17	Polymyositis, polyarthritis	Deafness	Not performed	Alive (2 years)

others developed it while on gamaglobulin prophylaxis[9]. A case report of a successful treatment of this syndrome with intravenous immunoglobulin therapy in a patient with XLA was described[10].

In 1990, Thyss et al[7], made a review of the literature and found 16 reported cases of DLS associated with XLA. The most interesting results of that review are shown in the Table I. The majority of patients have a conjugation of the following symptoms: erythema, edema, muscle infiltration, cutaneous atrophy and polymyositis. Most of them had neurological manifestations, the Echovirus was found in 14 (viral cultures were performed only in 15) and the prognosis was dramatic (14 of 16 died within 5.5 years). In Table II we perform a similar classification of the case we report herein. Since 1990, several cases of a dermatomyositis-like syndrome were described, but none was reported in association to XLA.

The patient reported in this paper had a good response to high-dose immunoglobulin treatment. Wagner et al[11], described a patient with XLA and growth hormone deficiency who developed an Echovirus-associated meningoencephalitis and DLS while being treated with intramuscular gammaglobulin (replacement dose) and human growth hormone. Initiation of high-dose intravenous gammaglobulin resulted in resolution of the clinical symptoms and the patient remained asymptomatic over 55 months.

Another reported case of treatment with gammaglobulin, methotrexate and corticosteroids (case 14, Table I), who had a poor prognosis, was found in the literature[12]. In our case, an off-label immunomodulator treatment was added to the immunoglobulin therapy as well. Our patient had a clinical relevant peripheral polyarthritis and a monthly intense treatment with immunoglobulin was interpreted has a transitory situation. Hence, regarding the existence of no recent reports of infections on this patient, and the expectancy that a sustained reduction on the immunoglobulin therapy frequency could be done without clinical flares of the myositis, methotrexate was added. On the other hand, the prednisolone dose was gradually tapered until a smaller dose could be reached, regarding the infectious risks concerns.

We describe an additional case of excellent response to high-dose intravenous immunoglobulin, at least in the short term. Besides the viral cultures for Echovirus were not performed, it was possible to identify and successfully treat this rare syndrome. Although the presence of an Echovirus was observed in most of the clinical cases described in literature, there is no evidence to associate the presence of this virus with clinical manifestations, recommended treatment or outcome. Given the rarity of these conditions, no clinical trials are expected in the near future, thus underlining the importance of sharing clinical experience.

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