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Case report

Shulman disease (eosinophilic fasciitis) in X-linked agammaglobulinemia

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X-linked agammaglobulinemia (XLA) diagnosed in the first year of life is an immunodeficiency with a life-long indication for substitution of immunoglobulins, due to lack of B lymphocytes in the periphery. The decrease of bacterial infection frequency and severity is an effect of immunoglobulin replacement. However, in the majority of patients bronchiectasis and chronic sinusitis with an overgrown mucous membrane develop despite regular substitution. Autoimmune diseases as co-existing diseases in XLA are noted in a few patients presenting symptoms associated with arthritis, scleroderma and myositis. Our patient was diagnosed with XLA in the first year of life, followed by regular substitution of immunoglobulins. The symptoms of pain, edema of muscles of the right shank with skin edema and discoloration after mild injury were noted in a 13-year-old boy. Shulman disease was diagnosed after 6 months of symptoms, based on histopathology of muscle and skin biopsy. Before the diagnosis, non-steroid anti-inflammatory drugs (NSAID) were used with a transient effect. After the diagnosis, therapy included steroids, immunoglobulins in a high dose and immunosuppression, with improvement of clinical symptoms. During methotrexate (MTX) therapy the patient developed two episodes of pneumonia, so mycophenolate mofetil (MMF) was used, with a similar effect. Now, with this therapy, the symptoms are mild and stable without progression.

Key words: agammaglobulinemia X-linked, eosinophilic fasciitis, diagnosis, therapy.

Introduction

X-linked agammaglobulinemia (XLA) is a primary humoral immunodeficiency caused by the *btk* mutation, leading to lack of B cells in the periphery and, in consequence, lack of immunoglobulins and specific antibody production. The first symptoms of immunodeficiency are noted after 4 months of life, when the maternal IgG level decreases. Recurrent bacterial infections, with a good response to antibiotics, are typical and, together with lack of tonsils in the boy, suggest agammaglobulinemia. Moreover, in a minority of patients, the lack of B lymphocytes (below 1% of peripheral blood mononuclear cells assayed with flow cytometry) is associated with a low number and reduced activation of NK cells [1, 2, 3, 4, 5]. In these patients the study of T cells showed a low number of memory CD4 T cells (CD4+CD45RO and CD4+CD45RO+CXCR5+). The total number of T cells, the CD8 subpopulation and regulatory T cells were comparable to healthy controls. The study of T lymphocyte function showed a Th1 response as the T cell profile in XLA patients [6, 7]. Standard treatment of XLA patients is based on regular substitution of immu-

noglobulin (intravenous or subcutaneous form as home therapy), supporting a stable IgG level in serum (no less than 5.0-5.5 g/l). It is believed that this level is sufficient to prevent bacterial infections [8, 9]. The occurrence of rheumatoid arthritis, dermatomyositis, and inflammatory bowel disease in XLA patients is difficult to explain [10, 11, 12, 13, 14]. One hypothesis suggested survival of self-reactive receptors on a few circulating B cells due to signaling by self antigens, which overcame the blocked signaling route through the *btk* mechanism [12]. From the study of XLA patients with rheumatoid arthritis the predominance of CD8+ T lymphocytes within infiltrations of synovial tissue and subcutaneous nodules indicated the role of these cells in the pathomechanism of rheumatoid erosive changes [13]. Other studies suggested the occurrence of Th1 oriented diseases such as arthritis and diabetes type 1 in XLA patients due to T cell activation (in the absence of CD30 signaling) not deleted by the CD95-dependent cross-tolerance mechanism. It leads to uncontrolled proliferative potential of autoreactive T cells [7].

The therapy of autoimmune disease in XLA patients is similar to patients without immunodeficiency, with one exception – regular substitution of immunoglobulins in XLA patients. There are suggestions for substitution in a higher dose (0.8 g/kg b.w.) to maintain a higher level of IgG than usual (about 8.0 g/l) [14]. In rheumatoid arthritis, methotrexate was used in therapy, but the clinical improvement was supported by an increased IgG level [13]. Recurrent infections with specific pathogens, e.g. *Mycoplasma pneumoniae*, were shown to be associated with arthritis in XLA patients, similar to *Mycoplasma*-induced arthritis in otherwise healthy people [14]. The association of XLA and scleroderma, dermatomyositis, and myositis is noted, but the explanation for this association is unknown [11]. The lack of autoantibody production, as well as various and unspecific clinical symptoms due to immunoglobulin substitution, show the difficulties of diagnosis and explain the delay in diagnosis of autoimmune disease in XLA patients. The therapy is even more difficult and problematic because steroids and immunosuppression increase the risk of severe infections in immunodeficient patients.

Shulman disease – eosinophilic fasciitis (EF) – is a rare connective tissue disease in the scleroderma-like group of disorders. In Shulman's original description the skin and soft tissue inflammation noted in people in the 4th decade of life was symmetrical and chronic. Subsequently, the observations showed the occurrence of this disease with typical features in children [15, 16, 17]. The criteria of eosinophilic fasciitis included major swelling, induration and thickening of skin and subcutaneous tissue symmetrical (or not), diffuse or localized, fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration. The minor criteria helping in diagnosis are: eosinophilia in peripheral blood, hypergammaglobulinemia, muscle weakness, increased aldolase level and groove sign (mainly in adults) [16, 17, 18]. The course of disease is prolonged, with occurrence of skin and tissue changes, and visceral involvement in a few patients [19]. The clinical diagnosis is based on symptoms, typical changes in muscles (MRI) and typical cellular infiltrates in histology of affected tissues. Eosinophilia, noted in the majority of patients, is not a predictive factor for the course of disease, severity and progress [18]. Therapy is as for other autoimmune diseases: steroids, classical immunosuppression. Due to skin involvement, methotrexate (MTX) is suggested as the best choice, subsequently or together with steroids used in a high dose (intravenous pulses) at first [16, 17, 19, 20, 21]. Immunosuppression with azathioprine, cyclosporine, cyclophosphamide, immunomodulatory drugs, e.g. colchicines, and supportive techniques, e.g. PUVA, is suggested for patients with poor tolerance of steroids and MTX. In case of resistance to steroids and immunosuppressive therapy, anti-TNF monoclonal antibodies were used [17, 19]. In pediatric patients the best therapeutic results were obtained with steroids (pulses) and MTX prolonged therapy. The good effects of therapy in EF are noted after prolonged maintenance therapy, on average, for more than 3 years (37 months median, range from 6 to 115 months) [17]. The response to therapy was defined as complete remission (free of symptoms), remission (patients with disability without progression) and failure of therapy (progression of persistent symptoms and physical limitations) [17]. For children mycophenolate mofetil (MMF) as immunosuppression after first-line standard steroid therapy is another proposition of prolonged therapy. MMF was used with the hope of preventing fibrosis of affected skin [15].

The purpose of this case report is to show the problems of diagnosis and therapy of this autoimmune disease in a boy with XLA.

Patient

S.D., born 2002, was diagnosed with X-linked agammaglobulinemia at 9 months of age. Laboratory assays showed no trace of immunoglobulins (IgG, IgA and IgM) and lack of B lymphocytes. The respiratory infections were treated with antibiotics, with a good response. Pneumonia was the reason for hospitalization when the diagnosis of immunodeficiency was established. Substitution of immunoglobulins (in intravenous form) was introduced and after 4 months a stable level of IgG was achieved (> 5.0 g/l). During the following years of observation chronic sinusitis with overgrowing mucous membrane developed, although the respiratory tract infections subsided. The form of substitution was changed to subcutaneous in

Table I. Results of laboratory data during diagnosis and therapy of Shulman disease in XLA patient

Date	08.2013	12.2013	01.2014	03.2014	02.05.2014	04.05.2014	23.05.2014	06.2014	10.2014	12.2014	03.2015
Blood		ND					ND				
WBC (10^3/μl)	13.6		18.9	25.9	14.4	15.9		22.4	16.8	14.1	21.7
Neutro (%)	54.3		62.1	87.6	58.7	36.9		83.5	80.2	48.3	75.8
Limfo (%)	34.6		31.0	5.9	26.7	45.0		9.7	9.8	34.5	17.2
Mono (%)	9.0				13.2	17.0			8.7	12.3	6.7
Eos (%)	1.8				1.1	0.7			1.1	4.8	0.2
Biochemistry			ND								
protein (g/l)	61.7	66.5			60.4	ND	68.9	61.5	ND		64.1
CRP (mg/l)		44.0			62.3		ND	ND		69.6	55.1
Fe (μmol/l)					4.7		4.4	3.4			3.9
IgG (g/l)	6.16	8.61	6.72	7.21	ND	ND	12.2	8.14	7.15	7.26	7.12
SCIG (g/kg bw/mth)	0.37	0.37	0.37	0.37			from June again	0.33	0.33	0.4	0.4
Other symptoms and therapy		Pharyngitis antibiotic							increased weight bronchitis antibiotic	pneumonia antibiotics	pneumonia antibiotics
Symptoms of Shulman disease and therapy	swollen and painful muscles of crus after mild injury and effort	still pain and contraction of knee (mild)	biopsy of skin and muscle	MRI oedema and infiltrations of muscles and skin	hist.-path.: suggestion for Shulman disease		pain relief, reduced oedema, no contractions in join	mild pain and oedema of muscles, skin discoloration	stable – mild symptoms	stable – mild symptoms limitation of effort	stable – mild symptoms limitation of effort
	NSAID	NSAID and physicotherapy	NSAID	NSAID antibiotic	IVIG 0.5 g/kg bw steroids *i.v.* antibiotic	IVIG 0.5 g/kg bw steroids *i.v.*	steroid p.o. 0.5 mg/kg bw	steroids 0.2 mg/kg bw to 0.1 mg/kg	steroids 0.10 mg/kg MTX 20 mg/week	steroids 0.1 mg/kg MTX 15 mg/week	steroids 0.15 mg/kg MMF 25 mg/kg

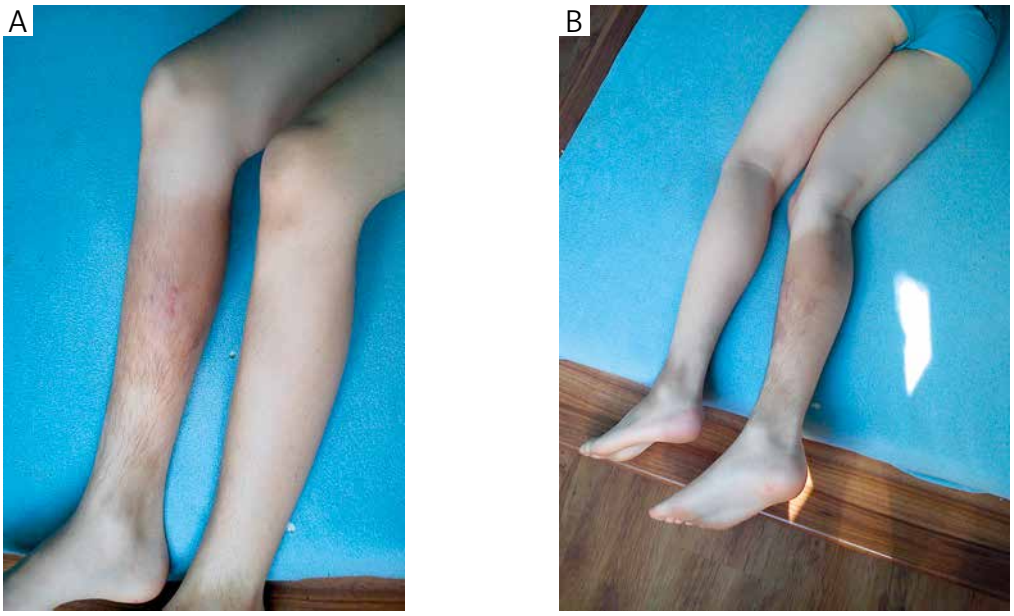

Fig. 1. Skin changes and swollen muscles of right sheen after initial therapy with non-steroid anti-inflammatory drugs (NSAID)

2011 without any problems. At this time, high-resolution computed tomography (HRCT) of the lungs showed a few bronchiectases in both lungs. The physical development was normal and the boy was attending school. He participated in sport activities with the exception of swimming due to sinusitis. In autumn of 2013 the boy reported pain and cramps of the right shank after a small injury during cycling. The skin was erythematous, swollen, firm and painful (Fig. 1). The first line therapy with anti-inflammatory drugs (NSAID) was successful for a short time. After exercises and/or effort such as walking or brief cycling, pain and skin changes recurred. In physical examination, the skin was swollen, very firm and muscles (bicipital muscle, especially the medial part) were "rock hard" in palpation. There was no groove sign and no general symptoms, but knee contraction was noted. The subsequent therapy included anti-inflammatory drugs again, physiotherapy (massage) and laser therapy with a transient effect. After the next exacerbation, deep skin and muscle biopsy was performed. Based on clinical symptoms and histology of muscle infiltrates, the diagnosis of eosinophilic fasciitis (Shulman disease) was established. Steroids (intravenous pulses) and a high dose of immunoglobulins were used with a good response after 4 months (mild symptoms without pain, without contractions of knee, but still with limitation of effort), followed by low doses of steroids and methotrexate (MTX) as a maintenance schedule. After episodes of pneumonias, MTX was changed to MMF with similar results. The boy is living normally and attending school activities with limitation of extra efforts. Anti-pain drugs are used sporadically, often after effort (e.g. long walk, cycling). The subcutaneous immunoglobulin is continued in a dose of 0.3-0.4 g/kg bw/month.

The laboratory data and clinical symptoms before and during the therapy of Shulman disease are shown in Table I.

Imaging diagnosis

USG – obliterated structure of medial part of bigastric muscle of the right sheen, thicker and changed structure of subcutaneous tissue with decreased microcirculation.

MRI – the area of swelling with enhanced contrast binding in head region of medial part of bigastric muscle of the sheen. Tendon with normal signal and preserved continuity, swelling of adjacent adipose tissue.

Histopathology of muscle biopsy

The samples contain fibrous connective tissue (it is probably a thickened epimysium) and a fragment of skeletal muscle. In both components of the biopsy material numerous outgrowths of unspecific granulation tissue with abundant lymphocytic-macrophagic inflammatory infiltrate with an admixture of neutrophils and eosinophils are seen (Fig. 2).

Periodic acid-Schiff and Grocott stains to reveal unspecific pathogens including fungi were both negative. Immunohistochemical stains with antibodies against CD3 and CD20 showed almost total absence of CD20-positive cells (which corroborates the diagnosis of agammaglobulinemia) and that the inflammatory infiltrates were limited to T lymphocytes (including both helper CD4+ cells and cytotoxic CD8+ cells) and to CD68+ macrophages.

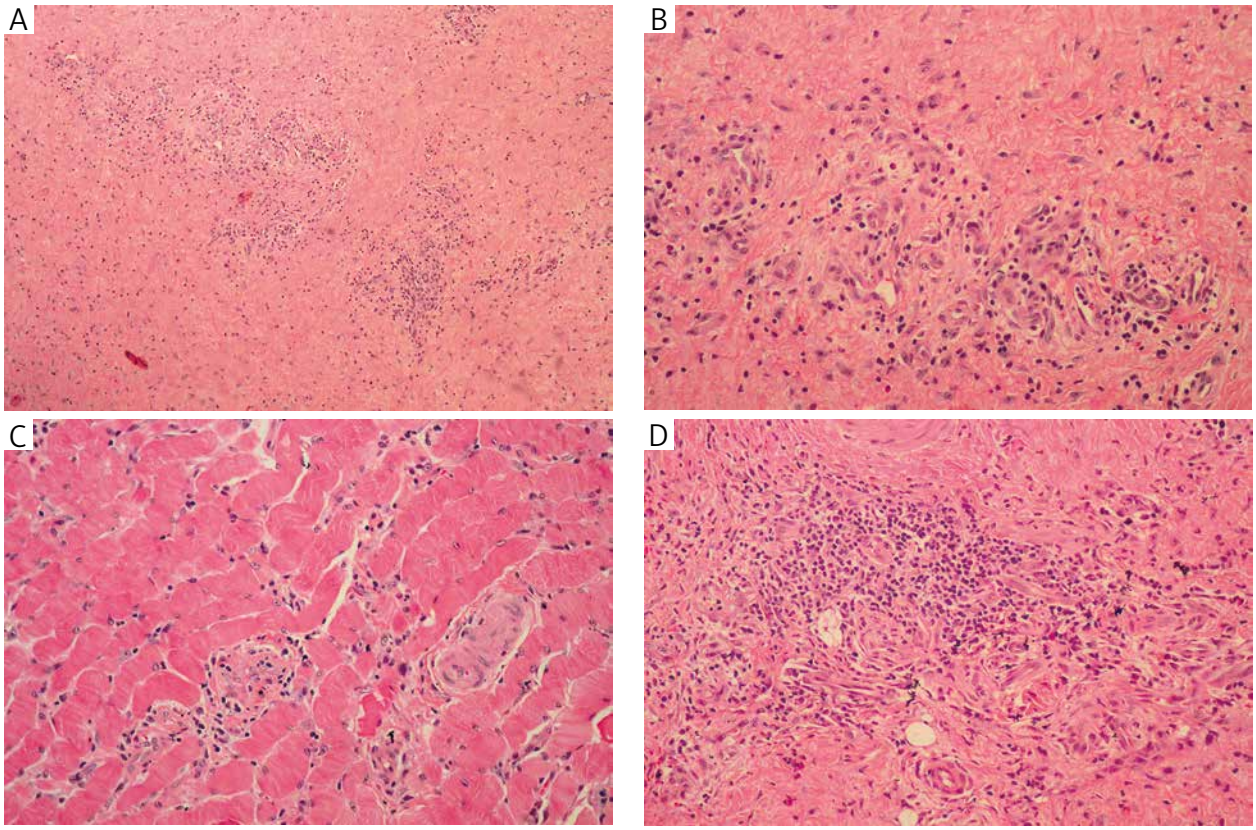

Fig. 2. Histopathology of muscle biopsy showing lymphocytic infiltrations and presence of eosinophils (A–D)

Lymphocytic infiltrates invade muscle while endomysium invasion is obvious, although the true invasion of myofibers is not unequivocal. In contrast to the epimysium where granulation tissue and fibrosis are abundant, within the muscle these features are much less notable. There is no basis for suspicion of a neoplastic process of any kind.

Immunohistochemistry was performed for CD34, CD68, CD3, CD20, CD4, and CD8. Other stains used were periodic acid-Schiff and Grocott.

To summarize, the whole microscopic picture suggests focal myositis, granulomatous myositis (peri-epimyositis), and eosinophilic fasciitis. The clinical symptoms and basic disease together with histopathology indicate eosinophilic fasciitis, a disease from the scleroderma group, as the diagnosis.

Therapy

After establishing the diagnosis, the use of steroids in a high dose intravenously for the patient with XLA was a difficult decision. The first infusion (750 mg of methylprednisolone) resulted in resolution of pain and wooden-like swelling of skin. Within one month, infusion of methylprednisolone in the same dose was repeated 3 times during regular visits to hospital followed by steroids given orally. The infusion of high-dose immunoglobulins (1.0 g/kg bw) was performed, but the results were poor, so this therapy was discontinued. The low dose of steroids was associated with introduction of MTX (20 mg weekly) as immunosuppression. The symptoms were still present due to steroids dependence, so, despite visible side effects of steroids (increased weight, moon-like face), therapy with a low dose is being continued. Two episodes of pneumonia with prolonged course suggested modification of therapy, and MTX was changed to MMF (500 mg/day) under lipid and blood morphology control. The clinical results of this therapy are similar to previous therapy with MTX. Up to now, the parameters of blood morphology and triglycerides have been within normal values. The basic therapy of XLA with regular substitution of immunoglobulins in subcutaneous form is being continued together with immunosuppressive therapy of Shulman disease.

Discussion

The mechanisms of autoimmunity in XLA are unknown [11, 12, 13, 14]. Prevalence of rheumatoid diseases and autoimmune diseases from the scleroderma group are still an open question. In our patient, clinical symptoms of eosinophilic fasciitis seemed to be typical, but the diagnosis was delayed, due to absence of eosinophilia in peripheral blood, asymmetric swelling of skin and tissue, and migrating erythemas, which did not fulfill the criteria. The diagnosis was made after histopathology of muscle biopsy together

with clinical symptoms of prolonged inflammation and a poor response to NSAID therapy. The standard therapy of eosinophilic fasciitis is based a high dose of steroids given intravenously (pulses), but the described patients were adults and otherwise healthy. In XLA, despite the regular immunoglobulin substitution, the decision of steroids in a high dose is always difficult. The substitution of immunoglobulins prevents infection with common pathogens, but infections with other pathogens such as enteroviruses, fungi and bacteria including *Klebsiella*, *Proteus*, and *Pseudomonas* present a higher risk than in patients without immunodeficiency. This point of view increases the difficulties of the decision of any invasive procedures in XLA patients. In our patient, the scar after biopsy, after prolonged healing, is still thick and visible. Another problem for high-dose steroids in our patient was age, just at the beginning of puberty. Hopefully, the level of testosterone was normal and the boy developed normally during the observation period, without inhibition or delay. The typical side effects of steroids (overweight, diabetes, changes of face and skin appearance) were visible but mild, disappearing after lowering the steroid dose.

The good prognosis in Shulman disease is associated with prolonged steroid and immunosuppressive therapy, which is difficult even for adults to be so patient and persistent in therapy. The disease course shows better and worse periods, with occurrence of new or exacerbation of present symptoms. The limitations of physical effort are hard for an active school boy, so recurrent episodes of pain and edema were predicable. Moreover, the perspective of effective therapy within 2-3 years is very difficult for such a patient living with agammaglobulinemia and immunoglobulin substitution for life. Our patient showed all these problems, and psychological support for him and his family was required. We hope that continued therapy with steroids and immunosuppression will be effective, leading to complete remission of Shulman disease in our XLA patient.

The authors declare no conflict of interest.

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