Juvenile eosinophilic fasciitis: three case reports with a review of the literature

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ABSTRACT

Objective. *Eosinophilic fasciitis is an uncommon scleroderma-like disorder characterised by induration and thickening of skin and soft tissue, usually associated with peripheral eosinophilia, poorly characterised in childhood.*

Methods. *We report 3 paediatric cases of eosinophilic fasciitis showing unusual clinical and histopathological features with a review of the literature.*

Results. *All cases presented progressive motility impairment started from upper limbs with no skin abnormalities. All cases showed systemic inflammatory involvement and 2 patients had acute complications. Two patients developed disabling outcomes despite appropriate treatments.*

Conclusion. *Eosinophilic fasciitis may present unusual clinical and histopathological features during childhood and requires early recognition in order to prevent acute complications and disabling outcomes.*

Introduction

Eosinophilic fasciitis (EF), also called Shulman's syndrome or fasciitis-panniculitis syndrome, is an uncommon scleroderma-like disorder of unknown etiology, characterised by induration and thickening of skin and soft tissue, usually associated with peripheral eosinophilia. Firstly described by Shulman in 1974 (1) and initially considered a variant of localised scleroderma (2), EF has now been regarded as autonomous clinical entity (3). While clinical features in adults have recently been reviewed (4), juvenile EF (jEF) is poorly characterised.

Patients and methods

Patient 1

A 3-year-old female developed a progressive motility limitations of fingers, wrists, hips and knees after an upper respiratory infection effectively treated with oral antibiotics (Fig. 1). Laboratory investigations revealed increased CRP (2.4 mg/dl) with hypereosinophilia (11670/mm^3), whereas muscle enzymes were normal. Serology for *Borrelia, Echinococcus, Trichinella* and *Toxocara*, allergy tests, and autoantibody assay were all negatives. Abdominal echo-scan disclosed hepatosplenomegaly with mesenteric lymphadenopathy. Oral prednisone (1 mg/kg/day) was started with resolution of hepatosplenomegaly and mesenteric lymphadenopathy, laboratory tests and improvement of joint contractures within 3–4 days.

When steroid treatment was discontinued, she dramatically relapsed: open rhinolalia appeared with inability to swallow. On whole body magnetic resonance imaging (WB-MRI), STIR sequences revealed fascial thickening and hyperintensity at lower limbs. A skin-to-muscle biopsy was performed showing fibrosis and inflammatory infiltration of muscular fascia (Fig. 1).

After 3 intravenous pulses of methylprednisolone (30 mg/kg/day), oral prednisone and cyclosporine (4 mg/kg/day) were started with an intensive physiotherapy programme. Despite progressive improvements, knee and tibiotarsal joint contractures persist after three years.

Patient 2

A female was well into her 4 years of age when suddenly presented asthenia, low-grade fever and severe stiffness at upper limbs. The patient's paediatrician observed joint contractures of fingers, wrists and elbows. Laboratory tests showed eosinophilia (4890/mm^3), hypergammaglobulinaemia (2.1 g/dl) and increased CRP (2.1 mg/dl). Because of positive *Mycoplasma pneumoniae* IgM, a course of antibiotic therapy was performed without benefit.

At admission to our Institute, she complained diffuse myalgia and cutaneous hyperesthesia. The girl was unable to stand up or to walk alone. Subcutaneous fat layer was reduced. Axillary lymphadenopathy, splenomegaly and severe hepatomegaly were also present. Laboratory tests confirmed hypereosinophilia (2600/mm^3). Plasma triglycerides ranged from up to 830 mg/dl to normal values. Serology for *Borrelia burgdorferi* and autoantibodies assay were negatives, except for anti-glutamate decarboxylase antibodies (4.77 U/ml). During hospitalisation, she developed chest pain with tachycardia and appearance of third heart sound.

Table I. Differences between juvenile and adult eosinophilic fasciitis. All cases with onset of eosinophilic fasciitis before 18 years of age in PubMed-MEDLINE were reviewed: complete data were available for 16 cases only. These cases are compared to the present series and the adult form.

Characteristics	Juvenile EF (present series)	Juvenile EF (literature) ref 5,8,10-16,20-25	Adult EF (literature) ref 4,6,17,18
Number of patients	3	16	> 300
Sex (female:male)	3:0	10:6	1:1
Age of onset (median, range), y	4 (3,4-4,4)	8 (1-17)	40-50 (18-88)
History of trauma or intense physical exertion	0	0	30-46%
History of infections	1 (33%)	5 (31%)	-
Cutaneous manifestations (swelling and induration, groove sign, peau d'orange)	1 (33%)	8 (50%)	>90%
Articular manifestations (joint contractures, tendons retractions, prayer sign)	16 (100%)	16 (100%)	>40%
Visceral manifestations	2 (66%)	4 (25%)	rare
Relapse/resistance to treatments or disabling outcomes	2 (66%)	9 (56%)	rare (less than 10-30%)

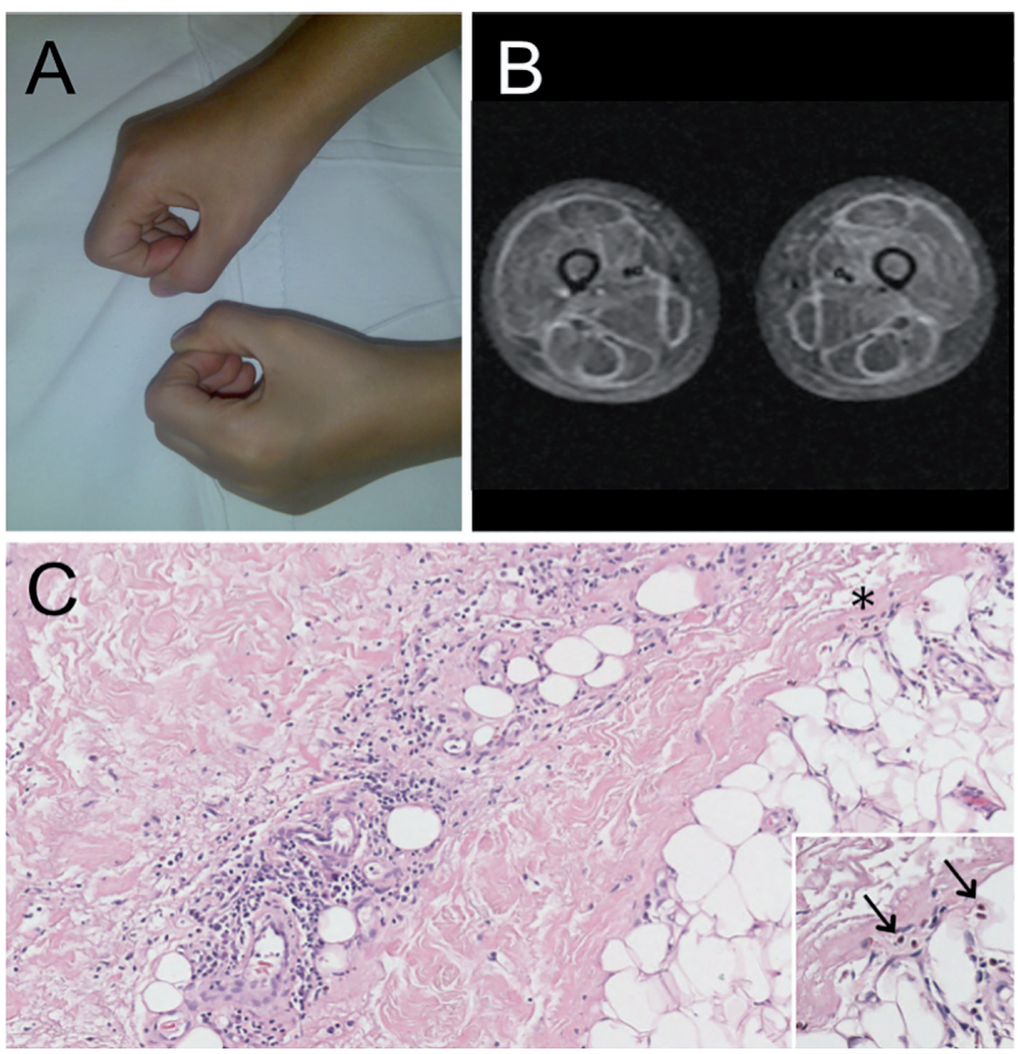

Fig. 1. Major features of juvenile eosinophilic fasciitis. The photo shows joint contractures of fingers in a child at disease onset (**A**). Axial MRI STIR image shows hyperintensity and thickening of both superficial and deep fascia (**B**). Microscopic examination shows fascial fibrosis and inflammatory infiltrate containing lymphocytes, plasma cells, mast cells and some eosinophils (**C**; eosinophils are shown at highest magnification and indicated with arrows).

Echocardiogram revealed pericardial effusion. WB-MRI (STIR sequences) showed fascial hyperintense signal at limbs (Suppl. Fig. 1). A full-thickness biopsy showed marked inflammatory infiltration of fascia, septa of hypodermis, and perimysium by macrophages and T lymphocytes. A perivascular and perineural infiltration was also present (Suppl. Fig. 2).

She was treated with oral prednisone (2 mg/kg/day), cyclosporine (4 mg/kg/day) and intensive physiotherapy, with rapid normalisation of biological markers and progressive recovery of her motility. Five months later, blood exams and MRI were normal (Suppl. Fig. 1): steroid therapy was stopped and replaced by ibuprofen (10 mg/kg/day). After two years, a slight morning stiffness persists.

Patient 3

A 4-year-old female developed a progressive and painless motility impairment started from fingers and wrists, leading to inability to grasp in only six weeks. No previous infections, physical stresses, trauma or medications were referred. The diagnosis of juvenile idiopathic arthritis was proposed by patient's own physician. We evaluated the girl 5 months later. A small indurated skin lesion was present at trunk. Hepatomegaly and axillary lymphadenopathy were also present. Laboratory investigations showed hypereosinophilia (1850/mmc), hypergammaglobulinemia (1.7 g/dl) and increased ERS (26 mm/h). ANA were slightly positive (titer 1:80, speckled pattern). Research for helminths in stool, serology and allergic tests were negative. On WB-MRI, STIR sequences revealed fascial hyperintense signal at upper and lower limbs. A full-thickness biopsy confirmed the diagnosis of jEF. Oral prednisone (2 mg/kg/day), intramuscular methotrexate (20 mg/m^2/week), and intense physiotherapy were started. Four months later, steroid treatment was stopped, while intramuscular methotrexate is still administered. Two years later, she is asymptomatic without any disabling outcomes.

Discussion

In the study we describe 3 cases of jEF recently diagnosed at our Department between 2011 and 2014. The disease hallmarks are: i) very early onset (all cases occurred between 3-4 years of age), ii) rapidly progressive joint contractures, iii) hypereosinophilia, iv) fascial hyperintense signal on WB-MRI (STIR sequences), and v) fascial mononuclear-cells inflammatory infiltrate at the biopsy of the involved limbs (Fig. 1, Suppl. Table I).

In contrast with EF commonly described in adults, jEF is characterised by a very early onset (5). An association with trauma is missing, while history of infection was reported. The clinical presentation is dominated by a severe articular involvement that is prevalent in respect to the typical skin changes observed in adults. A systemic involvement (hepatosplenomegaly, lymphadenopathy) is more frequently present. Moreover, disease course appears to more severe in children (Table I).

All our patients presented without skin manifestations typically reported in adult EF, grooves sign or *peau d'orange*, that has been suggested as major diagnostic criterion (4). Only patient 3 showed a small indurated skin area at trunk. As already described, morphea-like lesions have been reported in about one-third of patients with adult EF (6). Several reports stress that EF may be misdiagnosed as scleroderma (7, 8) and some cases of jEF who later developed scleroderma have also been reported (9, 10). This findings suggest that EF and scleroderma may be parts of continuum (11). Conversely, in the jEF, cutaneous manifestation are usually absent at disease onset (12-16), as observed in our cases. 2 of our patients presented an early and isolated involvement of fingers, with severe disability to grasp: this feature seems to characterise jEF, since "*en griffe*" fingers are usually reported as a late complication in adult EF (4, 12, 13).

Another relevant distinct feature of jEF is the presence of a systemic involvement. All of our patients showed a generalised activation of reticuloendothelial system, with hepatosplenomegaly and lymphadenopathy, that is uncommon in adult EF (4, 6, 17, 18). Moreover, patient 1 presented a open rhinolalia with inability to swallow and patient 2 developed an acute pericarditis, that required steroid administration. Patients 2 also developed a severe muscular-cutaneous hyperalgesia associated to a concomitant loss of subcutaneous fat layer and a persistent elevation of acute phase reactants. The histopathology revealed an inflammatory infiltrate extended from muscular fascia to the fibrous septa of subcutaneous tissue, resulting in a septal panniculitis, and to perimysium and perineurium: this latter finding may likely justify the unusual hyperalgesia. Moreover, an inflammatory infiltration of the adventitia of the vessels was also present.

MRI is considered an excellent imaging modality to study soft tissue. On STIR sequences, most pathologic tissues – including muscular fascia with inflammatory involvement – are particularly proton rich and have prolonged T1 relaxation and T2 decay times, resulting in high signal intensity. Nevertheless, this finding is non-specific and the diagnosis of jEF still requires a full-thickness skin-to-muscle biopsy. Furthermore, MRI can also direct the surgeon to the optimal location for biopsy and play a role as a marker of disease activity, identifying response to therapy and relapse (19).

Our patients showed severe and progressive clinical picture that led us to treat them with oral steroid and intensive physiotherapy. A complete remission without disabling outcomes was obtained in patient 3 only, in whom methotrexate was started early. The effect of methotrexate has already been described in adult EF (4). Conversely, patient 1 relapsed during steroid tapering, requiring intravenous pulses of methylprednisolone. Despite the use of oral cyclosporine, she developed disabling outcomes. Two years after disease onset, patient 2 complains slight joint pain despite the steroid treatment. In literature, an early and aggressive treatment has been recommended to reduce the risk of relapse and to shorten the overall duration of therapy in adult EF (4). Recently 2 cases of steroid-resistant jEF have been treated with infliximab with benefit (20, 21).

In conclusion, we report three cases of jEF that show an unusual onset of this rare disease, usually described in adults. Despite some similarities with the adult form (peripheral eosinophilia and mononuclear-cells infiltration at biopsy), jEF present a number of distinctive features, such as the very early onset, the prevalence of a severe articular involvement on skin manifestations at disease onset and, as describe in the present report, a more pronounced systemic involvement. These data support the possibility that jEF could be considered as a distinct entity (Table I). In this respect, the very early onset and the severe course of the disease in association with the description of anecdotal cases of familial EF (22, 23) might support the hypothesis of a possible genetic cause of this rare condition.

A progressive motility impairment started from the extremities in a previ-

ously healthy child, should prompt physicians to suspect a fasciitis, especially when CPK is normal, even without cutaneous signs. When severe eosinophilia allows the diagnostic suspicion of jEF, WB-MRI STIR sequences should be performed, aiming to check the site to perform a full-thickness biopsy to confirm the diagnosis. Our cases show that jEF requires early recognition and appropriate treatments, because the disease may develop a systemic inflammatory involvement and worsen rapidly, causing acute complications or leaving long-term disabling outcomes.

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