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CLINICAL PATHOLOGY CONFERENCE

Anti-neutrophil Cytoplasmic Antibody (c-ANCA) Positive Recurrent Eosinophilic Fasciitis Responsive to Cyclophosphamide

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Abbreviations

ANA	Antinuclear antibodies
c-ANCA	Cytoplasmic antineutrophil cytoplasmic antibody
CRP	C-reactive protein
CS	Corticosteroids
CT	Computed tomography
CYC	Cyclophosphamide
EF	Eosinophilic fasciitis
EMS	Eosinophilia-myalgia syndrome
HES	Idiopathic hypereosinophilic syndrome
HIV	Human immunodeficiency virus
IgM, IgG, IgA	Immunoglobulin M, G, A
IL	Interleukin
IV	Intravenous
IVIG	Intravenous immunoglobulins
MAC	Membrane attack complex
MPO	Myeloperoxidase antibody
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
p-ANCA	Perinuclear antineutrophil cytoplasmic antibody
PDGFRA	Platelet-derived growth factor receptor alpha
PR3	Proteinase 3 antibodies
PUVA	Psoralen plus ultraviolet A
ROM	Range of motion
sIgMD	Selective Immunoglobulin M Deficiency
TGF β	Transforming growth factor-beta

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Case presentation

A 65-year-old white man who carried the diagnosis of eosinophilic fasciitis (EF) presented with worsening neck, shoulder, and back stiffness over the last 3 years. His symptoms started 8 years ago with abdominal muscle tightness and skin thickness, which progressed to upper and lower extremities within weeks. During this period, he also complained of exertional muscle pain, especially after prolonged exercise. Based on peripheral eosinophilia and a muscle biopsy, he was diagnosed with EF and treated successfully with high-dose corticosteroids (CS). However, each attempt to decrease CS dose below 20 mg resulted in worsening of his muscle tightness, especially around proximal upper extremities and neck muscles. Five years before the presentation, he used hydroxychloroquine for 8 months and methotrexate for another 8 months as steroid tapering agents, with no benefit. Three years before the presentation, he developed CS myopathy and thus CS was stopped. Six months before the presentation, he was restarted on hydroxychloroquine without any improvement.

At presentation, he complained of worsening diffuse muscle stiffness since stopping CS, in addition to the significant skin tightness of his upper extremities, neck and back, associated with limited range of motion, over the last year. His review of systems was negative except for extreme fatigue. He has been exercising regularly, although his exercise tolerance gradually diminished because of his muscle stiffness and muscle pain.

His past medical history was relevant for recurrent Herpes Simplex infections, sinus infections (five to six times a year since age 40) with low serum immunoglobulin M levels (IgM), findings consistent with a diagnosis of Selective Immunoglobulin M Deficiency (sIgMD), chronic fatigue syndrome, depression, and steroid-induced hypertension, cataracts, and hypercholesterolemia. He was also diagnosed with eosinophilic gastritis by gastric antrum biopsy at age 45, which was treated with omeprozole since then (of note, a gastrointestinal endoscopy with gastric antrum biopsy was normal 2 years prior). His family history was negative for hematological or rheumatologic diseases. He had four sinus surgeries in the past, and had no drug or environmental allergies.

His medications at presentation included monthly 25 g intravenous immunoglobulins (IVIG) for the last 12 years (that resulted in amelioration of his recurrent sinusitis), hydroxychloroquine 200 mg and omeprazole 20 mg twice a day, atorvastatin 10 mg and irbesartan 150 mg once a day, eszopiclone 0.75 mg and temazepam 30 mg every night. He had one time use of L-tryptophan 20 years ago for sleeping problems.

Significant physical examination findings at the presentation were livedo reticularis on his lower extremities, an erythematosus rash over his knees, and skin induration over the anterior thighs, shoulders, lower and upper back (Fig. 1). He had decreased range of motion of his neck in all directions, limited shoulder flexion and abduction caused by muscle stiffness, and decreased forward bending of the spine. There was no evidence of muscle weakness or tenderness. Neurological examination was normal except for symmetrically decreased deep tendon reflexes of his lower extremities and bilaterally positive straight leg raising.

Initial significant laboratory findings are shown in Table 1. Liver and kidney functions were normal. Antinuclear (ANA), antidouble stranded DNA, antiphospholipid, anticentromere, antitopoisomerase I, antiribonucleoproteins, anti -Jo-1, anti-Ro, anti-La, and anti-Smith antibodies were negative. Cytoplasmic antineutrophil cytoplasmic antibody (*c*-ANCA) was persistently positive (at the initial visit to 6 months after presentation), with negative proteinase 3 antibodies (PR3). Perinuclear antineutrophil cytoplasmic antibody (*p*-ANCA) and myeloperoxidase antibody (MPO) were negative. Cryoglobulins, Lyme test, rheumatoid factor, serum/urine electrophoresis, hepatitis B and C antibodies, and cytomegalovirus and human immunodeficiency virus (HIV) tests were all negative. Serum lysozyme (a nonspecific antigen that can cause a *c*-ANCA pattern) was negative. Serum vitamin B12, tryptase, interleukin (IL)-5, IL13, and IL4 levels were normal; platelet-derived growth factor receptor alpha (PDGFRA) fusion gene mutation was negative.

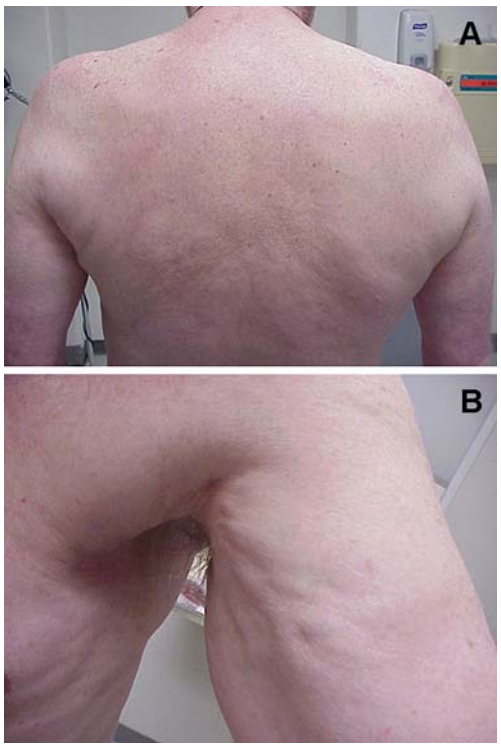

Fig. 1. Physical examination at presentation: A) skin induration over the shoulders and upper back; B) Groove sign on the medial aspect of the right axillary area

Radiological findings

The magnetic resonance imaging (MRI) of the thoracic spine (Fig. 2a) demonstrated skin thickening, diffuse edema, and stranding in the subcutaneous soft tissues extending along the fascial planes and mild diffuse abnormal signal in the posterior paraspinal muscles. The MRI of the pelvis and thighs (Fig. 2b, inversion recovery axial scan of thighs) showed nearly symmetric edema-like signal in the regional muscles and fascial planes (more pronounced along the

Table 1. Laboratory findings at presentation

Test (Normal Value)	Results
Hemoglobin (13–17 g/dL)	15.2
White blood cell count (3.5–10.7×10^9/L)	8.76
Eosinophils, % (0–7)	11.4 %
Absolute eosinophil count (0–0.8×10^9/L)	1
Platelet count (160–400×10^9/L)	356
Erythrocyte sedimentation rate (0–12 mm/h)	3
C-reactive protein (0–1 mg/dL)	2.4
Aldolase (0–7 U/L)	7.4
Myoglobin (0–116)	54.4
Complement C3 (79–152)	114
Complement C4 (16–38)	20
Total complement activity CH50 (31–66)	63
Thyroid stimulating hormone (0.49–4.60 mIU/L)	1.78
Vitamin B12 (200–1,100) pg/ml	464
Tryptase (1.9–13.5) μg/l	2.5
Immunoglobulin A (85–453 mg/dL)	548
Immunoglobulin G (751–1,560 mg/dL)	1,820
Immunoglobulin M (46–304 mg/dL)	36.7

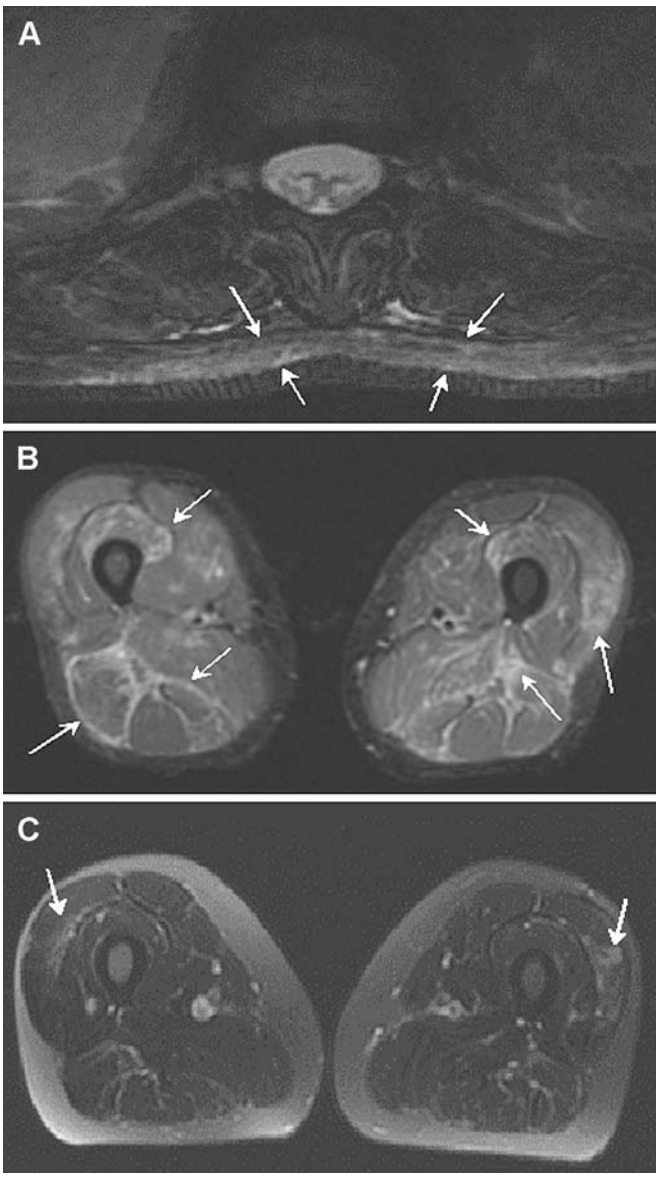

Fig. 2. Magnetic Resonance Imaging: A) Inversion recovery (IR) axial thoracic spine demonstrates skin thickening and edema signal in subcutaneous tissue (arrows); B) axial IR bilateral thigh muscles before cyclophosphamide (CYC) with bilateral edema-like signal in the muscles and fascia (arrows); C) axial bilateral thighs fat suppressed T2 weighted images after 6 months of CYC demonstrates near complete resolution of the edema signal, with mild residual signal in the vastus lateralis (arrows)

biceps femoris, vastus intermedius, and vastus lateralis muscles) without muscle atrophy. A chest radiography and computed tomography (CT) of the chest, abdomen, and pelvis were normal. An electromyography revealed mild sensory axonal degenerating neuropathy of the lower extremities.

Pathological findings

A deep-needle biopsy of the left thigh demonstrated a slightly fibrotic dermis, thickened fascia with fibrin deposition, a non-necrotizing vasculitis of the small blood vessels, and inflammatory findings consisting of macrophages, plasma cells, neutrophils and lymphocytes in the skin, perimysial connective tissue, perivascular area, and, to a lesser degree, within the skeletal muscle (Fig. 3). Eosinophils were absent. The immunofluorescent studies demonstrated the presence of a weak membrane attack complex (MAC) C5b-9 complex, IgG, IgA, and C3 staining, within and around the individual muscle fibers.

Treatment plan and further follow-up

The patient was started on pulse CS (1,000 mg for 3 days) followed by oral CS (40 mg to 0 over the next 4 months). There was a considerable improvement in the patient's stiffness and fatigue after the pulse steroids. At the same time, intravenous cyclophosphamide was started and administered for 6 months (monthly doses ranging between 1,000 and 1,400 mg). In addition to the medical treatment, he was started on extensive physical therapy consisting of soft tissue mobilization, functional mobilization, stretches utilizing contract/relax, and combination of isotonic techniques for

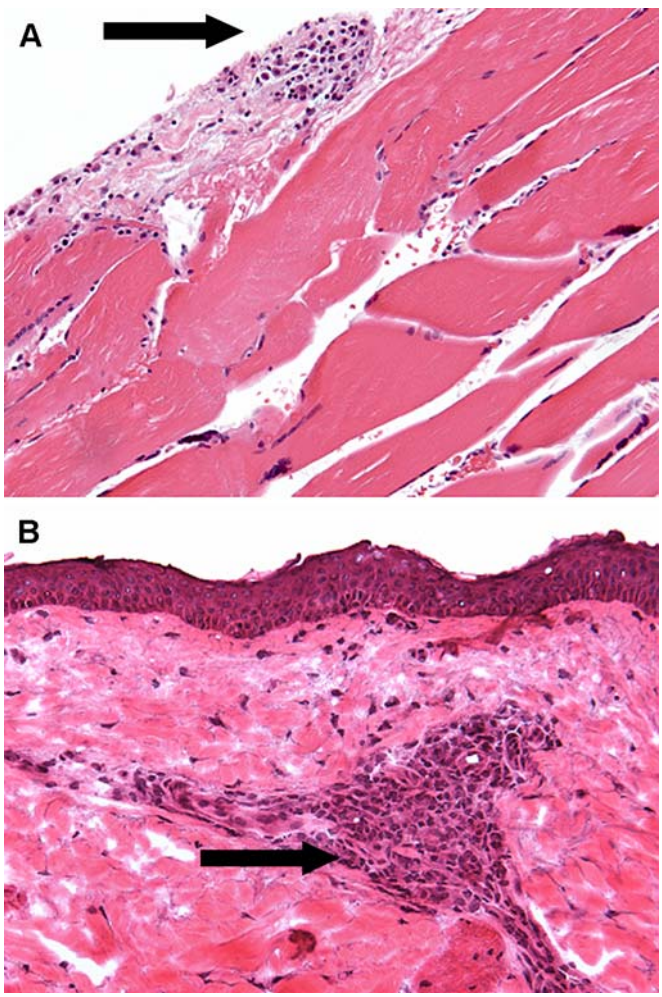

Fig. 3. Deep needle biopsy of the left thigh: A) mononuclear cell infiltrates localized predominantly in the connective tissue (arrow) with minimal muscle involvement; B) vasculitic mononuclear cell infiltrates around a capillary artery at dermo-hypodermal junction

scapular mobility. Cervical retraction range of motion (ROM) and upper thoracic extension mobilization were done to improve forward head posture. Serratus anterior, mid/lower trapezius, and rotator cuff strengthening were incorporated to improve the scapulohumeral rhythm.

After 6 months of treatment, the patient had significant improvement in skin tightness and in neck and shoulder myofascial mobility (Fig. 4). The skin rolling that was not possible at presentation (because of the adherence to the underlying structures) was gained in a large portion of his trunk. Eosinophil count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were normal, and the *c*-ANCA test was negative. His pelvis and thigh MRI showed improved edema in the soft tissues (Fig. 2c).

After 12 months of follow-up, he continued to have clinical improvement (Fig. 4) with normal eosinophil count, ESR, and CRP and a negative *c*-ANCA test. His skin tightness was only limited to a small area over the thoracic spine.

Clinical discussion

We present a patient with recurrent EF and persistent *c*-ANCA positivity who had persistent response to IV cyclophosphamide. However, because of the atypical features at the presentation and the steroid-dependent nature of the disease, there were many diagnostic and therapeutic challenges. The broad differential diagnosis in our patient included eosinophilia-myalgia syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, systemic sclerosis, and nephrogenic fibrosing dermopathy.

Eosinophilic fasciitis (EF) or Shulman syndrome, first described in 1974, is a fibrosing disorder of unknown etiopathogenesis [1, 2], usually responsive to corticosteroids. Patients present with scleroderma-like skin induration and peripheral eosinophilia; the disease can be triggered by simvastatin [3], atorvastatin [4], phenytoin [5], borreliosis [6, 7], or trichloroethylene exposure [8]. Approximately 30% of the EF patients have a preceding history of physical exertion or trauma [6–9]; it can be associated with hematological conditions such as aplastic anemia or myeloproliferative disorders [10–12]. The diagnosis of EF is confirmed by a deep biopsy, skin to muscle, which shows fibrosis of the fascia and an infiltrate of lymphocytes, histiocytes, plasma cells, and eosinophils localized within the dermis, fascia, epimysium, perimysium or endomysium. Of note, eosinophils are not required for the diagnosis of EF; eosinophilic infiltration and peripheral eosinophilia may be absent at the chronic stage of the disease [13], or after CS treatment [14], as most likely was the case with our patient. Membrane attack complex C5b9 deposits, described in our patient's muscle biopsy, are usually seen in dermatomyositis and point toward an immune-based myopathy. However, the muscle biopsy in dermatomyositis shows mononuclear inflammation localized to perivascular areas or in the connective tissue, but not in the muscle. Furthermore, in dermatomyositis, punched-out areas of myofiber damage occur secondary to ischemia and perifascicular atrophy, none of them seen in our patient. To our knowledge, membrane attack complex C5b9 deposits have not been described in EF patients until now. Of interest, it was demonstrated in dermatomyositis patients the long-term use of IVIG decreases the MAC C5b9 deposits [15], which can explain the weak staining in our patient. Magnetic resonance image can assist with the diagnosis of EF, guide the choice of the biopsy site, and be a marker of response to treatment [16, 17]. There are a variety of disorders that can present with edema-like signal, such as an infectious myopathy, a fibrotic tissue process, an active inflammatory myositis associated with inflammatory findings along the fascia; however, the presence of peripheral eosinophilia, woody induration of the skin and subcutaneous tissues, extensive fascial involvement, and the lack of muscle

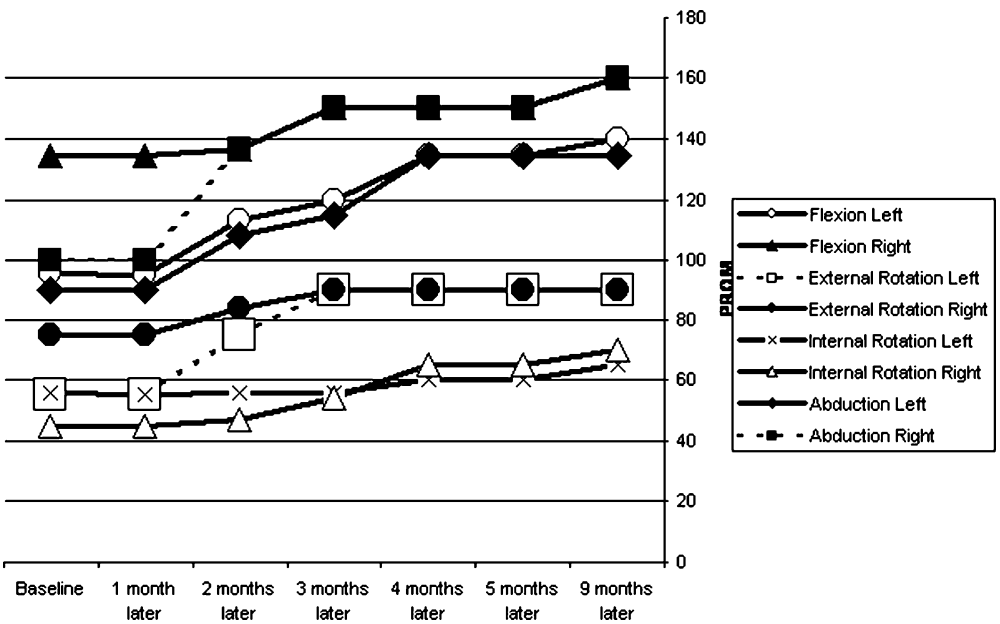

Fig. 4. Significant improvement of the shoulder passive range of motion (PROM) with cyclophosphamide therapy and physical therapy

weakness and atrophy in our patient made the diagnosis of EF more likely.

Eosinophilia-myalgia syndrome (EMS), first recognized in 1989 in association with L-Tryptophan use, is defined by peripheral eosinophilia and myalgias. Our patient used L-Tryptophan only once, 12 years before his muscles problems started, so this would be an unlikely cause of his muscle problems. The acute phase of EMS starts with generalized myalgia, dyspnea, cough, fever, cutaneous hyperesthesia, rash, pruritus, and swelling of the extremities, symptoms that our patient did not have. The chronic phase presents with scleroderma-like cutaneous changes, and progresses to multiorgan system involvement. Eosinophilia-myalgia syndrome shares many clinical and histopathological features with EF, such as woody induration of the skin, inflammation of the fascia and muscle, peripheral eosinophilia; however, the lack of systemic features in our patient made the diagnosis of EMS less likely.

Idiopathic hypereosinophilic syndrome (HES) is characterized by peripheral eosinophilia and major organ involvement, commonly cardiac, pulmonary, and neurological. This disorder includes *a myeloproliferative form* with myeloid cell involvement (featuring interstitial chromosome 4q12 deletion, increased serum vitamin B12, increased tryptase levels, and response to tyrosine kinase inhibitor, imatinib mesylate [18]), and a *lymphocytic form* with lymphoid cell involvement, characterized by phenotypically abnormal T cells clonal proliferations that often overproduce interleukin 5 (IL-5). The consequence of interstitial deletion in the patients with myeloproliferative variant is an activated tyrosine kinase FIP1-like1- Platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA) [19]. Recently, the myeloproliferative form has been classified as chronic eosinophilic leukemia. Because of the presence of peripheral eosinophilia and history of eosinophilic gastritis in our patient, HES and chronic eosinophilic leukemia were diagnostic considerations. However, our patient tested negative for PDGFRA fusion gene mutation, he had normal serum levels of vitamin B12, tryptase, and cytokines, and had no signs of end-organ dysfunction.

Because of extensive skin fibrosis, EF was considered for many years to be a variant of systemic sclerosis, which is characterized by fibrosis of the skin, internal organs, and microvasculature. Our patient's responsiveness to CS therapy, the presence of peripheral eosinophilia, the lack of extracutaneous and vascular disease, and the absence of autoantibodies excluded this diagnosis. Nephrogenic fibrosing dermopathy is another systemic sclerosis-like fibrosing disease associated with renal insufficiency, and recently linked to gadolinium-based contrast agent use with MRI or magnetic resonance angiography (MRA) [20]. Our patient did not have any renal involvement, and his biopsy findings were not consistent with those found in this nephrogenic dermopathy, such as thickened collagen bundles with surrounding elastic fiber, fibroblasts, and mucin deposition [21]. Sclererderma of Buschke, scleredema diabeticorum, and scleromyxedema present with skin induration, but in these conditions the eosinophil count is normal and there is no evidence of inflammation on the biopsy.

Systemic corticosteroids are used as the first-line treatment for EF. Moderate to high doses of CS given early in the course of the disease can induce a complete remission in one-third of the cases [3]. Spontaneous recovery was also reported. Steroid-sparing immunosuppressive agents such as hydroxychloroquine, cyclosporine, azathioprine, methotrexate [22], or cyclophosphamide [14–23] alone or in combination with CS have shown some benefit in patients who did not respond to CS therapy alone [24, 25]. There are also reports of remission with hydroxyzine, cimetidine, and psoralen plus ultraviolet A (PUVA) bath photochemotherapy [26, 27]. We choose cyclophosphamide for our patient based on the non-necrotizing vasculitic component of the disease, *c*-ANCA positivity, and the history of methotrexate failure. Physical therapy is also extremely important in the management of EF patients as it improves joint range of motion, myofascial mobility, and also prevents joint contractures. The severity of our patient's soft tissue and myofascial restrictions decreased noticeably since his first session of physical therapy.

In conclusion, cyclophosphamide should be considered as a therapeutic and a steroid-sparing agent in patients with recurrent EF, especially when atypical features such as *c*-ANCA positivity and non-necrotizing vasculitis are present.

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