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The enigmatic fascia: eosinophilic fasciitis

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Abstract: This case report highlights the potentially unrecognized subtype of unilateral eosinophilic fasciitis (EF) in a 28 year old man. With fewer than 300 reported encounters to date, EF is a rare disease that eludes clinicians by presenting as a scleroderma like syndrome. As EF remains a clinical diagnosis, biopsy results may be nonspecific, and the disease can easily be misdiagnosed (or missed entirely) if a full thickness biopsy is not reviewed by a dermatopathologist. The authors also emphasize the importance of internationally accepted diagnostic criteria, of which at least two different sets exist.

Keywords: biopsy; dermatology; dermopathology; diagnosis; eosinophilic fasciitis; scleroderma; Shulman syndrome.

With fewer than 300 reported encounters to date, Shulman syndrome (or eosinophilic fasciitis, EF) is a rare entity with an etiology that has continued to elude clinicians as a scleroderma like syndrome [1, 2]. The clinical presentation highlights the fascial involvement and typically begins with pain and edema of the affected area, rapidly progressing to fibrosis and induration. It generally has a symmetrical distribution, is associated with peripheral eosinophilia, and is preceded by strenuous physical activity in 30% of cases [1, 2]. The absence of Raynaud's phenomenon and internal organ involvement distinguishes this condition from systemic connective tissue diseases such as scleroderma [2]. There has been no genetic, geographic, or gender predisposition described in the literature, as sample size remains a limiting factor [1]. Early diagnosis is critical to prevent joint contractures, peripheral polyneuropathy, compartment

syndrome, and to recognize potential paraneoplastic syndromes [3, 4]. We present an atypical presentation of this rare disease with uncommon unilateral extremity involvement and an absence of traditional laboratory findings.

Case description

A 28 year old man employed as a mechanical engineer in the US Air Force presented to his primary care physician in September 2016 with a 2 year history of limited range of motion in all directions of the right hand and wrist. He had a prominent flexion contracture in the right elbow and reduced internal rotation of his right shoulder. His physical exam revealed hyperpigmentation over the anterior axilla. Skin topography was found to have increased thickening, induration, and roughness from the axilla extending to the forearm, consistent with a “woody” appearance (Figure 1). The application of hand pressure to this area demonstrated increased muscle tension and resistance to free movement of the muscle. There was no external involvement distal to the wrist.

Figure 1: Physical exam demonstrated hyperpigmentation (measuring 4 × 6 cm) over the medial proximal right upper extremity near the axilla in a 28 year old man. Tissue texture was described as “ropey” with a nontender, cord like feel. This photograph was obtained following a punch biopsy of the area.

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Laboratory analysis revealed a negative antinuclear antibody titer and a positive ribonucleoprotein extractable nuclear antibody. Magnetic resonance imaging of the right elbow, forearm, and wrist was unremarkable. Deep tissue biopsy of the affected forearm (Figure 2) and punch biopsy of the anterior shoulder (Figure 3) with direct immunofluorescence exhibited interstitial and perivascular inflammatory infiltrate. The presence of fibrosis and lymphocytes in the deepest portions indicated EF rather than scleroderma. Although this patient's pathology demonstrated rare eosinophils and EF is associated with eosinophilia in the blood, the inflammation in the tissue can have few to no eosinophils (Figure 4), especially in chronic lesions [5]. With an absence of visceral involvement and no history of Raynaud's phenomena, the diagnosis of EF was supported.

A multidisciplinary approach of systemic corticosteroids (oral prednisone 60 mg) with concomitant occupational and physical therapy to increase range of motion was prescribed in January 2017. The techniques provided to the patient included resistance training, opposition stretching, and restorative wrist therapy exercises to include Theraputty (CanDo Theraputty) and soft hand exercise ball (TheraBand). Marked improvements with grip strength, flexion and extension of the right wrist, and internal rotation of the right shoulder were appreciated in March 2017, 2 months after implementing the multidisciplinary approach. The patient's right wrist extension improved from 36° to 50°, right wrist flexion improved from 42° to 52°, and right shoulder internal rotation improved from 71° to 80°. Doubling of grip strength from 21 to 41 pounds was achieved using a digital

Figure 2: Deep fascial biopsy of the right forearm (×10 magnification) revealed interstitial and perivascular inflammatory infiltrate composed of lymphocytes and plasma cells.

Figure 3: Punch biopsy of the right anterior shoulder (×4 magnification) showed middermal sclerosis with lymphocytic perivascular inflammation.

Figure 4: Punch biopsy of the right anterior shoulder (×40 magnification) demonstrated an eosinophil.

dynamometer. Given these improvements, the patient's oral prednisone dose was slowly tapered by 10 mg weekly beginning in March 2017. Oral methotrexate 15 mg weekly

was initiated as a steroid sparing agent during prednisone tapering. Around that time, the patient experienced a subjective plateau in improvement; however, he did not experience progression of disease. In May 2017, he withdrew from military service, though his medical condition was unrelated. He remained on stable doses of 15 mg of methotrexate weekly and 20 mg of prednisone daily. Prednisone was dose reduced to 10 mg once per week starting March 13, 2017. The dose was at 20 mg on April 17, 2017, which was the last date of follow-up with us. The patient remained on those doses until he established care with an off base rheumatologist. The patient continued to receive medical care in civilian practice outside our network. Since his separation, he has continued to remain on low doses of methotrexate with folic acid supplementation without further progression. The patient separated from our care in early May 2017 and he now sees a rheumatologist every 6–12 months as needed.

Discussion

Common characteristics of EF include symmetrical swelling and skin induration of the distal extremities [1, 6, 7]. It has rarely been reported to have unilateral involvement [8]. Typically, EF presents with pain and edema of the affected area that rapidly progresses to fibrosis and woody induration with a scleroderma like appearance [1]. Although this is a deeper fascial process, it has been reported that there can be some overlying hyperpigmentation over the affected area [1]. Groove sign, a characteristic finding of EF, consists of a depression along the course of the superficial veins, more marked on elevation of the affected limb [9]. Because the upper dermis and epidermis are spared by the fibrotic process and the connective tissue around the veins is relatively immobile, the superficial layers of skin can bow inward as the peripheral venous pressure falls, producing this characteristic sign [9]. The disease commonly progresses rapidly from initial edema to fibrosis [1]; however, our patient exhibited an insidious course. Scleroderma patients present with similar cutaneous involvement, making distinction between these two diseases difficult [1]. In EF, the skin of the hands and feet are generally spared and there is an absence of findings suggestive of scleroderma to include Raynaud's phenomenon and involvement of the internal organs [1]. Such distinction is important, as EF remains a clinical diagnosis and biopsy results may be nonspecific, as in this case. This presentation is under recognized and can easily be misdiagnosed or missed altogether if a full thickness biopsy is not reviewed by a dermatopathologist [9].

Another unique aspect of this case was a lack of typical laboratory findings that have been previously cited in the literature [2]. In the clinical course of 52 cases of EF observed at Mayo Clinic, peripheral blood eosinophilia was noted in 33 of 52 patients (63%), hypergammaglobulinemia was noted in 17 of 49 patients (35%), and elevated erythrocyte sedimentation rate (ESR) was noted in 15 of 52 patients (29%) [10]. Peripheral blood eosinophilia, elevated ESR, CRP, aldolase, and hypergammaglobulinemia, which are traditionally observed [1, 2], were all absent in our patient. It is possible that our patient's laboratory values may have normalized by the time of diagnosis.

This patient's absence of classic history, physical examination, and traditional laboratory findings highlight the importance of an internationally accepted diagnostic criteria; currently, at least two different criteria exist according to a review of the literature by Wollina et al. [11]. These include criteria proposed by Pinal-Fernandez et al. [12] and a diagnostic criteria from Jannin et al. [13]. According to the criteria proposed by Pinal-Fernandez, major criteria include: (1) swelling, induration, and thickening of the skin and subcutaneous tissue, diffuse or localized; or (2) fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration on full thickness biopsy [12]. Minor criteria include peripheral eosinophilia $>0.5 \times 10^9/L$, hypergammaglobulinemia $>1.5 \text{ g/L}$, muscle weakness and/or elevated aldolase levels, groove sign and/or peau d'orange appearance of skin, and hyperintense fascia on magnetic resonance T2-weighted images [12]. Ultimately, the diagnosis of EF relies upon the combination of characteristic clinical, laboratory, imaging, and histologic findings, as there is no universally accepted international criteria [11, 12]. Our patient exhibited two major criteria as described by Pinal-Fernandez et al. [12], including physical examination findings of thickening and induration of the skin in conjunction with biopsy findings that demonstrated the presence of fibrosis with lymphocytes in the deepest portions of the skin. There was an absence of minor criteria, which may be attributed to his late presentation and subsequently delayed diagnostic evaluation.

This case reminds physicians to consider the potential employment of osteopathic manipulative treatment (OMT). As physical therapy is essential to prevent joint contractures that may develop in nearly half of all patients, OMT may play a role in enhancing mobility of the tissue [11]. Our patient was not provided with formal OMT but did receive aggressive occupational therapy to improve grip strength and range of motion for his right wrist and shoulder. In addition to therapy, early treatment with corticosteroids is integral to avoid progression of the disease to the surrounding joints, nerves, and muscle compartments [3, 4]. As mentioned, there is significant similarity regarding the

pathophysiology of both scleroderma and EF, particularly in the areas of cutaneous manifestations and musculoskeletal involvement. Research has evaluated the efficacy of both physical and occupational therapy as a treatment regimen to enhance clinical outcomes. These have demonstrated substantial benefit to patients afflicted with scleroderma but are, unfortunately, often underutilized [14]. Tissue mobilization and mobility exercises have demonstrated meaningful interval change for mobility and functional status [15]. Given this disease's involvement in the deepest layers of the fascia, a key area of OMT investigation would be soft tissue technique. This modality has been cited to increase circulation and range of motion [16]. Additionally, reduced fascial tension, improved edema, and enhanced lymphatic drainage have been recognized as potential benefits of soft tissue OMT [16]. A limiting variable of EF is the rarity of this disease, but treatments including the soft tissue technique should be encouraged as an area of future investigation.

Conclusions

This case highlights the challenging display of dermatological syndromes and the importance of recognizing clinical patterns. Moreover, a thorough musculoskeletal exam was essential in the setting of incongruent biopsy and serological findings in this particular patient. The case sheds further light on the potential under recognized subtype of unilateral eosinophilic fasciitis that may go undiagnosed. Acknowledgment of this subtype is of tremendous importance given the vast difference in prognosis of EF and other scleroderma variants. Such distinction is vital for the early employment of corticosteroids and manipulative therapy.

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