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EDITORIAL

Clinical guide to eosinophilic fasciitis: straddling dermatology and rheumatology

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"What's in a name?
That which we call a rose by any other name would smell as sweet"
Romeo and Juliet

1. Introduction

Eosinophilic fasciitis (EF) has originally been described by Shulman in 1974 as 'diffuse fasciitis with eosinophilia.' The two patients in the original observation provided a history of strenuous exercise a few days before the onset of the circumferential swelling and induration of the skin in the distal areas of the extremities. The patients had no Raynaud's phenomenon. En-bloc biopsies skin-to-fascia of the clinically involved tissues showed marked fascial thickening and inflammatory cell infiltration by lymphocytes and plasma cells. Peripheral eosinophilia in these patients was not matched by eosinophilic tissue infiltration. The patients responded well to oral corticosteroid therapy. Rodnan proposed for this disorder the name 'eosinophilic fasciitis,' the American College of Rheumatology proposed 'diffuse fasciitis with or without eosinophilia,' others used the label 'Shulman syndrome,' yet 'eosinophilic fasciitis' became the most widely accepted name for this disorder.EF begins with the acute or subacute onset of symmetrical erythema, edema, and induration of extremities, often also of the trunk, accompanied by elevated inflammatory markers. The lesions may progress to sclerosis of the subcutaneous tissue and fascia, complicating with flexion contracture of the fingers along with carpal tunnel syndrome. Visceral involvement is uncommon. Increased erythrocyte sedimentation rate may be present with disease activity.

2. Review

2.1. Etiology

An autoimmune mechanism is presumed to be involved in the pathophysiology of EF, initiated by diverse triggers. The relation to strenuous physical exercise, originally described by Shulman, has been de-emphasized in recent works [1,2]. Several possible etiologies came into attention such as drug toxicity (antituberculous medications, phenytoin, simvastatin, atorvastatin, infliximab, pembrolizumab) [1], infections [3], radiation therapy, insect bites, and malignant neoplasia (the EF behaving as a paraneoplastic syndrome) [4]. A holistic concept [5] has been proposed in describing the set of disorders characterized by chronic inflammation and fibrosis of the subcutaneous septa and muscular fascia, under the term 'fasciitis-panniculitis syndrome' (FPS). The authors reported on data of 32 consecutive patients with EF and related syndrome cared for during 10 years. There were 14 cases of idiopathic FPS, i.e. EF, FPS secondary to vascular in 6, initiated by infections in 6, paraneoplastic in 3 cases. One case each was caused by trauma, insect bites, and Sweet's syndrome. FPS had a sleeve-like shape in 20 cases, a plaque-like shape in 7, and combined in 5. Improvement was spontaneous in 4 cases. Under cimetidine monotherapy in five patients, complete remission was noticed in 3. The FPS notion gives prominence to the stereotypic tissue reaction pattern involving the subcutaneous septa and muscular fascia, emphasizes the etiologic and clinical diversity of the disorder, and notices the similar response to drug therapy in different clinical settings. The FPS concept is also supported by MRI studies showing that the hyperintense signal on MR T2-weighted images are not limited to the fascia but may extend to the adjacent adipose tissue and muscle fibers [6]. Furthermore, clinical and histological similarities are recognized between EF and morphea profunda: inflammation and sclerosis in the deep dermis, panniculus adiposus, fascia, and superficial muscle layers. EF and morphea profunda may occur in association, have similar autoimmune mechanisms, both have a 2–3-year course, and usually respond to corticosteroid treatment. Indeed, EF is often considered to belong to the severe side of the morphea spectrum [3].

2.2. Diagnosis

There are no generally accepted diagnostic criteria for EF. Pinal-Fernandez et al. [7] proposed the criteria for diagnosis and classification of EF. Two major criteria are: a. swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetrical or nonsymmetrical, diffuse (involving extremities, the trunk, and abdomen), or localized (involving the extremities), b. fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin). Five minor criteria are: a. eosinophilia >0.5 × 10 9 /L,

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b. hypergammaglobulinemia >1.5 g/L. c. muscle weakness and/or elevated aldolase levels, d. groove sign and/or peau d'orange, e. hyperintense fascia on MR T2-weighted images. Accordingly, two major or one major and two minor criteria are consistent with EF diagnosis.

2.3. Differential diagnosis

EF is distinguished from *systemic sclerosis* by the absence in EF of three typical findings in systemic sclerosis – sclerodactyly, Raynaud's phenomenon, and nailfold capillary changes, as well presence of anticentromere, anti- topoisomerase I, and anti-RNA polymerase III antibodies. In distinction, the face, hands, and feet are spared in EF [1,3]. *Morphea profunda* holds clinical and histological similarities with plaque-like EF [3,5]. While isomorphic morphea occurs in areas of skin friction (not so EF), the symmetrical morphea variant is distributed on the trunk and extremities alike EF and may be confused with EF. Moreover, EF and morphea may overlap. The *toxic oil syndrome*, caused by ingestion of adulterated rapeseed oil 1981 in Spain, was characterized by morphea-like skin lesions affecting the face, trunk, and extremities, along with myopathy, peripheral neuropathy, and arthralgia [8]. The *eosinophilia–myalgia syndrome*, which had epidemic proportions in 1989 was caused by ingestion of the dietary supplement L-5-hydroxytryptophan, unfortunately contaminated. Patients complained of severe myalgias. Morphea-like lesions were conspicuous. Visceral involvement was occasionally present. Blood eosinophilia was a frequent attribute [9]. *Nephrogenic systemic fibrosis* is a progressive multiorgan fibrosing condition developing 2 to 75 days after exposure to gadolinium-based contrast agents used for magnetic resonance imaging. Patients with advanced renal insufficiency are at higher risk. Prominent findings on physical examination are indurated papules and plaques, on the extremities, buttocks, and trunk, sparing the face [10]. Other fibrosing disorders, easily distinguished on physical examination from EF, are *myxedema, scleredema, and palmar fasciitis*. Pretibial myxedema is a cutaneous manifestation of Graves' disease presenting as yellowish-brown papules, nodules and plaques on both shins; it may be refractory to control of underlying thyroid disease. Scleredema of Buschke is characterized by stiffness and hardening of the subcutaneous tissues on the upper back and posterior surface of the neck. Palmar fasciitis is a paraneoplastic syndrome manifesting as a painful swelling of the hands, caused by inflammation and sclerosis of the palmar fascia, tendon sheaths, small joints of the fingers, and flexion contractures.

2.4. Therapy

The rarity of EF precluded performing randomized controlled trials of treatment for EF. Historically, monotherapy with prednisone 0.5–2.0 mg/kg/day was the first-line treatment for EF. Partial or complete response was reported in about 60% of patients and cure may take up to 4 years; relapse rate is high [11]. Superior response rates were reported in combining a corticosteroid medication with methotrexate 15–25 mg/week. (3,12,13,). In a retrospective review from a single institution, from 1997 to 2016, of 89 patients with EF, prednisone treatment was supplemented with methotrexate in 79% of cases, with hydroxychloroquine in 45% of cases, mycophenolate mofetil in 18%, azathioprine in 8%. No single immunosuppressant agent was associated with a superior response during treatment. Complete response rate was 60% at 3 years [12]. All the latter studies are retrospective and prone to confounding. Other treatments for EF are infliximab, azathioprine, sulfasalazine, cyclosporine, cyclophosphamide, rituximab, tocilizumab, sirolimus PUVA, immunoglobulins, and bone marrow transplantation, referred in case series or single case reports [3,13]. The long-term prognosis of EF is generally good, but relapse can occur after discontinuation of treatment [3,12,14,15].

2.5. Conclusion

In conclusion, a comprehensive rather than the exclusive concept is our understanding of the EF, comprising a gamut of disorders, from a variety of causes, having analogous clinical and pathological features, similar disease course and comparable response to therapy.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Luzar B, Calonje E. Idiopathic connective tissue disorders. McKee's Pathol Skin. 2020;17:771–825.
2. Chan KK, Magro C, Shoushtari A, et al. Eosinophilic fasciitis following checkpoint inhibitor therapy: four cases and a review of literature. Oncologist. 2020;25(2):140–149.
3. Mertens JS, Seyger MMB, Thurlings RM, et al., Morphea and eosinophilic fasciitis: an update. Am J Clin Dermatol. 18(4): 491–512. 2017.
•• **The article is of considerable importance in providing up-to-date information on major issues.**
4. Haddad H, Sundaram S, Magro C, et al. Eosinophilic fasciitis as a paraneoplastic syndrome, a case report and review of the literature. Hematol Oncol Stem Cell Ther. 2014;7(2):90–92.
5. Naschitz JE, Boss JH, Misselevich I, et al., The fasciitis-panniculitis syndromes clinical and pathologic features. Medicine (Baltimore). 75(1): 6–16. 1996.
• **Another, unconventional, view of the topic.**

6. Kirchgesner T, Dallaudière B, Omoumi P, et al. Eosinophilic fasciitis: typical abnormalities, variants and differential diagnosis of fasciae abnormalities using MR imaging. Diagn Interv Imaging. 2015;96 (4):341–348.
7. Pinal-Fernandez I, Selva-O' Callaghan A, Grau JMK. Diagnosis and classification of eosinophilic fasciitis. Autoimmun Rev. 2014;13(4–5):379–382.
8. Posada de La Paz M, Philen RM, Borda IA. Toxic oil syndrome: the perspective after 20 years. Epidemiol Rev. 2001;23(2):231–247.
9. Uitto J, Varga J, Peltonen J, et al. Eosinophilia-myalgia syndrome. Int J Dermatol. 1992;31(4):223–228.
10. Wilson J, Gleghorn K, Seigel Q, et al. Nephrogenic systemic fibrosis: a 15-year retrospective study at a single tertiary care center. J Am Acad Dermatol. 2017;77(2):235–240.
11. Lakhanpal S, Ginsburg WW, Michet CJ, et al. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Semin Arthritis Rheum. 1988;17(4):221–231.
12. Mango RL, Bugdayli K, Crowson CS, et al., Baseline characteristics and long-term outcomes of eosinophilic fasciitis in 89 patients seen at a single center over 20 years. Int J Rheum Dis. 23(2): 233–239. 2020.
•• **Data of a single center study over two decades.**
13. Erez D, Shoenfeld Y, Natour A, et al. Clinical experience with biologic treatment in resistant eosinophilic fasciitis: case reports and review of the literature. Medicine (Baltimore). 2021;100(13): e25359020. 23:233-9.
14. Mazori DR, Femia AN, Vleugels RA. Eosinophilic fasciitis: an updated review on diagnosis and treatment. Curr Rheumatol Rep. 2017;19 (12):74.
15. Jinnin M, Yamamoto T, Asano Y, et al., Diagnostic criteria, severity classification and guidelines of eosinophilic fasciitis. J Dermatol. 45 (8): 881–890. 2018.
• **This article provides criteria and guidelines important for future studies.**