Evolution of one systemic rheumatic disease into another: scleroderma evolving to eosinophilic fasciitis with myositis

Sirs,

A 33-year-old woman developed systemic sclerosis (SSc) six years ago manifesting initially with puffy hands, Raynaud's phenomenon, fingertip ulcers and small hand joints arthritis. Subsequently, progressive skin thickening of fingers/hands (sclerodactyly), face, limbs and abdomen ensued along with facial and chest wall telangiectasias and oral aperture reduction. Furthermore, the last three years incipient pulmonary fibrosis was diagnosed. From diagnosis anti-nuclear antibodies (ANA, 1:1280, nucleolar pattern) and rheumatoid factor (RF, 150IU/ml, normal range (n.r.) <15IU/ml) were present while anti-Scl70 antibody was negative. She was treated with methotrexate s.c. (20mg/week) and occasionally low dose oral methylprednisolone. Sildenafil 20mg t.i.d. was given during winter months to combat digital ulcers. Six months ago, during her last scheduled evaluation, the patient complained of myalgias, without preceding intense physical activity. Clinical examination revealed an intense *peau d'orange* appearance of skin of both brachial areas, thighs and abdomen. Muscle strength was normal, while sclerodactyly of hands and feet had remarkably regressed. Laboratory tests showed peripheral eosinophilia (820/μL), diffuse hypergammaglobulinaemia (γ-globulins 20%) and elevated serum CPK 1397U/L (n.r.<192U/L), AST 115U/L (n.r.<35), ALT 86U/L (n.r.<43) and LDH 704U/L (n.r.<214U/L). Acute phase reactants (C-reactive-protein, erythrocyte-sedimentation-rate) and thyroid hormones were within normal range, while the presence of anti-Pm/Scl75 and anti-Pm/Scl100 positivity was found for the first time.

With the suspected diagnosis of eosinophilic fasciitis (EF) with muscle involvement, a full-thickness wedge biopsy, including skin, subcutis, fascia and muscle, from the inner side of one arm was obtained.

The biopsy showed typical skin histological findings of scleroderma, including marked thickening of dermal collagen, loss of periadnexal fat, compression of adnexal structures as well as thickening and luminal narrowing of small vessel (Fig. 1A). In the deeper layers, perivascular inflammation along with fascial thickening and accumulation of lymphocytes and macrophages was seen (Fig. 1B); findings compatible with EF. In the muscular layer inflammation with lymphocytic infiltration, phagocytosis, necrotic fibres and perifascicular atrophy (Fig. 1C-D), was evident, histological findings suggestive of myositis. Methotrexate was discontinued and oral prednisolone (0.5mg/kg body-weight/day) and azathioprine (2.5mg/kg body-weight/day) were initiated. One month later, clinical and laboratory improvement was noticeable.

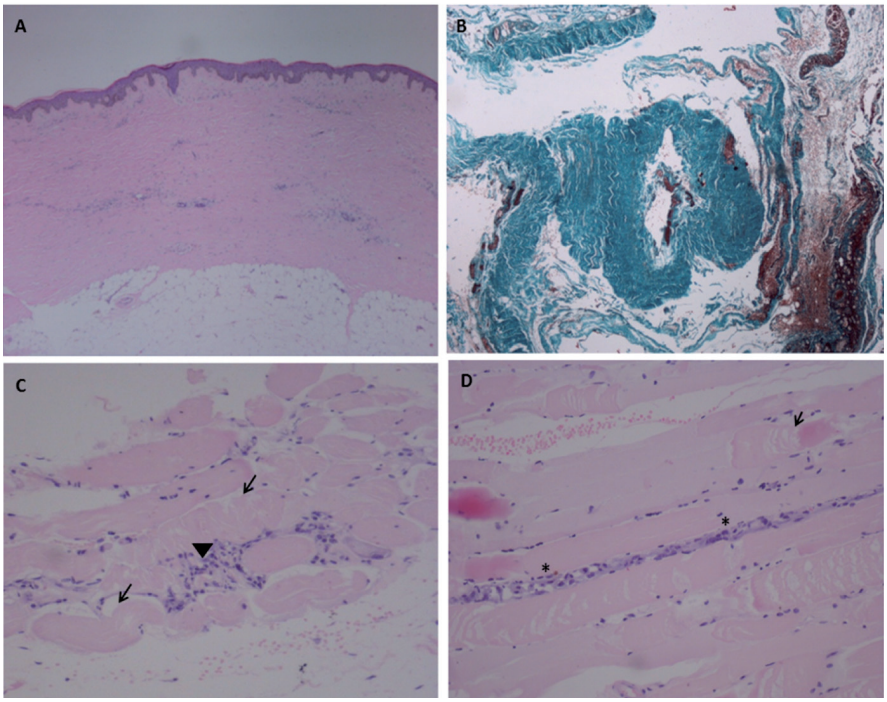

Fig. 1. Full-thickness wedge biopsy, including skin, subcutis, fascia and muscle, of the inner side of the right arm. (**A**) The epidermis is thin and atrophic. The middle and lower dermis show a marked thickening of dermal collagen with overall paucity of adnexal structures, loss of periadnexal fat as well as thickening and luminal narrowing of small vessel blood vessels (H&E, X40). (**B**) In the deeper layers, fascial thickening and inflammation, perivascular inflammation along with accumulation of lymphocytes and macrophages is seen, findings suggestive of eosinophilic fasciitis (Masson's Trichrome, X40). (**C, D**) In the muscle layer, inflammation with muscle fibres invaded by lymphocytes (arrowhead), vacuolar muscle fibres (arrows), necrotic fibres with phagocytosis (asterisks), and perifascicular atrophy are evident, findings suggestive of myositis (H&E, X200).

We present this case firstly because evolution or overlap of SSc with EF and subjacent myositis has been described exceedingly rarely in the literature (1), and to point out how a systemic autoimmune disease may evolve into another through sequential involvement of different organs/systems (2). Systemic autoimmune rheumatic diseases can present with at times erratic clinical phenotype. In some patients the disorder can run a mild, subclinical course, while in others it can be a severe, life-threatening disorder. Furthermore, some patients can initially present with the clinical phenotype of one disorder, as our patient, and after a disease course of some years they may manifest characteristics of other rheumatic disorders.

EF is an uncommon scleroderma-mimicking disease entity characterised by symmetric swelling of the extremities and the trunk progressing to sclerosis of the mid and deep dermis, subcutaneous fat and fascia.

Internal organ involvement is exceptionally rare and induration typically spares the digits, features distinguishing EF from SSc (3-5). SSc and EF are both inflammatory skin fibrotic disorders. Although the phenotypic end-stage of these two diseases is ultimately the same, namely fibrosis, patients present with different clinical features. To date it is not known whether these diseases share a common pathogenic pathway. There are however few gene expression microarray studies performed on skin or fibroblasts from patients with SSc and EF suggesting that gene expression of the skin biopsy from EF patients is clustered close to diffuse proliferative SSc (6), which could be a possible explanation of the observed sequential autoimmune reaction towards similar molecular targets.

E. Zampeli[1], *MD, PhD*
A. Pantelidaki[2], *MD*
H.M. Moutsopoulos[1,3,4], *MD, FACP FRCP(hc), Master ACR*

[1]Institute for Autoimmune Systemic and Neurological Diseases, Athens;
[2]Pathologist, Michalakopoulou 42, Athens;
[3]Academy of Athens;
[4]Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Greece.

Please address correspondence to:
Dr Evangelia Zampeli,
Institute for Systemic Autoimmune and Neurological Diseases,
M. Asias 75, 11527, Athens, Greece.
E-mail: zampelieva@gmail.com

Competing interests: none declared.

References

1. DROSOS AA, PAPADIMITRIOU CS MOUTSOPOULOS HM: An overlap of diffuse fasciitis with eosinophilia and scleroderma. *Rheumatol Int* 1984; 4: 187-89.
2. KARAGIANNI P, ZAMPELI E, MOUTSOPOULOS HM: Evolution from one autoimmune disorder to another. Epitope spreading? *Scand J Immunol* 2018; 87: e12657.
3. MOUTSOPOULOS HM, WEBBER BL, PAVLIDIS NA, FOSTIROPOULOS G, GOULES D SHULMAN LE: Diffuse fasciitis with eosinophilia. A clinicopathologic study. *Am J Med* 1980; 68: 701-9.
4. PINAL-FERNANDEZ I, SELVA-O' CALLAGHAN A GRAU JM: Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* 2014; 13: 379-82.
5. FETT N, ARTHUR M: Eosinophilic fasciitis: Current concepts. *Clin Dermatol* 2018; 36: 487-97.
6. LIMPERS A, VAN ROYEN-KERKHOF A, VAN ROON JA, RADSTAKE TR, BROEN JC: Overlapping gene expression profiles indicative of antigen processing and the interferon pathway characterize inflammatory fibrotic skin diseases. *Expert Rev Clin Immunol* 2014; 10: 231-41.