Diffuse skin thickening, myalgias and joint stiffness in a 41-year-old man

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A 41-year-old man presented with a history of myalgias and diffuse skin thickening that affected his arms, legs and abdomen. The patient was previously healthy, with no major medical illness of note. About a year before his presentation, he developed a flu-like illness and ankle edema. This was followed by a sensation of skin tightness in the antecubital fossae, inner aspects of thighs and legs, chest and abdominal wall. His hands, feet, neck and back were spared. He attributed his diffuse myalgias, and an 8.2 kg weight loss in the previous four months, to vigorous exercise. As symptoms progressed, he stopped weightlifting and running. Over the next few months, as his skin tightness progressed, joint contractures developed. While playing basketball, he had difficulty raising his arms above his head. Elbow contractures led to inability to fully extend his arms. He also complained of some muscle weakness and joint stiffness, but not of joint pain or swelling. He was on omeprazole 40 mg daily for his chronic heartburn, but did not have dysphagia, symptoms of Raynaud phenomenon, digital pits or ulcers, fever, dyspnea or cough. He also said he did not smoke, drink alcohol or use nutritional supplements.

On examination, the patient weighed 91.8 kg (body mass index 28.33), his heart rate was 95/min and blood pressure was 154/97 mm Hg. His skin was indurated with a *peau d'orange* (orange peel–like) appearance involving his upper arms (Figure 1A), forearms, lower abdomen, inner thighs and lower legs. His hands were not puffy, and there was no sclerodactyly, nor tendon friction rubs. He had somewhat limited active and passive range of motion of his shoulders, but there was no clinical evidence of proximal myopathy. Furrows along the superficial veins of his raised forearm are shown in Figure 1B. Nail-fold capillaroscopy was normal. Examination of his heart and lungs were unremarkable.

What is the most likely diagnosis?

a. Diffuse cutaneous systemic sclerosis
b. Diffuse fasciitis with eosinophilia
c. Scleredema diabeticorum
d. Nephrogenic systemic fibrosis
e. Scleredema associated with paraproteinemia

The main conditions to be considered in the differential diagnoses of a patient with diffuse skin tightening are as follows: diffuse cutaneous systemic sclerosis, scleredema, nephrogenic systemic fibrosis, diffuse fasciitis with eosinophilia (formerly eosinophilic fasciitis) and scleromyxedema (Box 1).[1] In this patient, there were no distinguishing features of diffuse cutaneous systemic sclerosis (Raynaud phenomenon, sclerodactyly, digital ulcers or pits, tendon friction rubs and nail-fold capillary abnormalities). Hence, (a) is unlikely. Scleredema is another sclerosing skin condition, with three subtypes.[1] Type 1 is more commonly seen in girls and young women, characterized by a febrile illness associated with a viral or bacterial infection, followed by rapid onset of skin hardening. It is frequently self-limited and resolves within months to a few years. Type 2 is a chronic and progressive condition associated with a paraproteinemia, particularly of the immunoglobulin G kappa type. Type 3 (scleredema diabeticorum) is seen in patients with long-standing uncontrolled diabetes mellitus, more often in men. The distribution and nature of skin induration in our patient were not characteristic of scleredema, which typically involves the nape of the neck, interscapular region, upper back and face. In addition, unlike in our patient, it usually spares the abdomen and the lower extremities. Thus, (c) and (e) are unlikely in this patient.

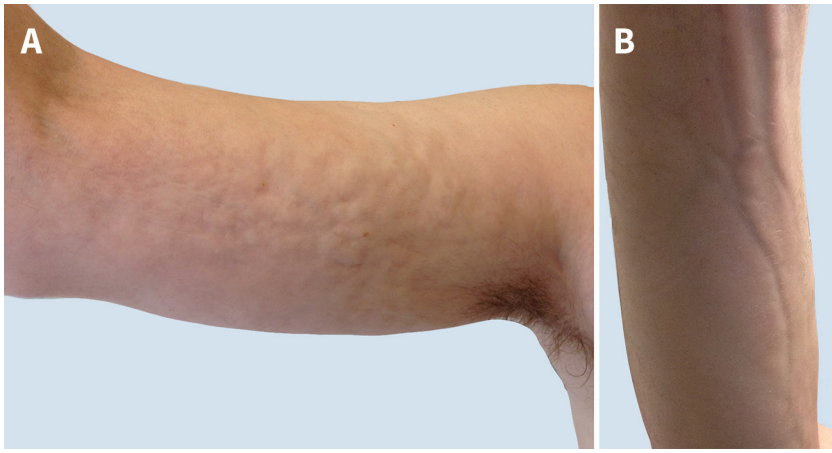

Figure 1: (A) Skin induration with a *peau d'orange* appearance in the right arm of a 41-year-old man with a one-year history of skin tightening. (B) Furrows along the superficial veins of the patient's raised right forearm.

Nephrogenic systemic fibrosis is a sclerosing skin disorder seen in patients with severe renal insufficiency, often with end stage renal disease.[1] In 2006, its association with exposure to gadolinium-based contrast agents was established.[1] This relatively healthy patient had no history of chronic kidney disease and there was no mention of prior exposure to gadolinium-based contrast agents. Therefore, (d) is also unlikely.

Option (b) is the most likely diagnosis. Diffuse fasciitis with eosinophilia is suggested by the history of abrupt onset of skin induration with *peau d'orange* changes (Figure 1A), "groove sign" on this patient's raised forearm (furrows along the superficial veins, Figure 1B), and recent history of heavy physical activity.

What investigations should be ordered next?

a. Antitopoisomerase I (Scl-70) and anti-RNA polymerase III antibodies
b. Fasting blood glucose and glycated hemoglobin (HbA_{1c})
c. Monoclonal protein in blood and urine
d. A full-thickness incisional skin biopsy
e. Spirometry, transfer factor and transthoracic echocardiogram

The commonly encountered antibodies in systemic sclerosis are anticentromere antibody, seen in limited cutaneous systemic sclerosis, in which skin tightness is confined only to the distal extremities and face (unlike our patient), and anti-Scl-70 and anti-RNA polymerase III antibodies, seen in subsets of diffuse cutaneous systemic sclerosis, in which skin tightness is more generalized, including the trunk. However, in the absence of the characteristic clinical features of diffuse cutaneous systemic sclerosis mentioned above, ordering these antibodies (a) would not be indicated. Likewise, screening for interstitial lung disease associated with diffuse cutaneous systemic sclerosis, with pulmonary function testing and for pulmonary hypertension with echocardiogram (e) would also not be justified. Also, as the distribution and nature of skin induration is not characteristic of scleredema, looking for its associations, such as diabetes mellitus (b) or a paraproteinemia (c), would not be appropriate. Establishing a diagnosis of diffuse fasciitis with eosinophilia requires a full-thickness skin biopsy including subcutaneous fat, fascia and underlying muscle, which is the preferred course of action in this case (d).

Laboratory studies showed normal hemoglobin and platelet count. White blood cell count was 9.2 x 10^9/L, with 60.1% neutrophils, 8.6% lymphocytes and 23.3% eosinophils. Comprehensive metabolic panel and thyroid function tests were normal. Erythrocyte sedimentation rate was 10 mm/h, C-reactive protein was 43 mg/L, creatine phosphokinase was 31 U/L and aldolase was 7.3 U/L. Antinuclear antibody was positive at 1:40 (homogeneous pattern) but, as expected, antibodies to extractable nuclear antigens including anticentromere, anti-Scl-70 and anti-U1 RNP were negative.

Box 1: Differential diagnoses of the main diffuse sclerosing skin conditions[1]

Condition	Key features
Diffuse cutaneous systemic sclerosis	Sclerodactyly, skin tightness affecting the extremities, face, and eventually the trunk; hyperpigmentation, salt and pepper skin; telangiectasias; calcinosis; Raynaud phenomenon; nail-fold capillary abnormalities, digital pits or ulcers; interstitial lung disease; pulmonary hypertension; dysmotility affecting the gastrointestinal tract; joint contractures; scleroderma renal crisis. Positive antinuclear antibodies; positive anti-Scl-70 or anti-RNA polymerase III antibody. Other systemic sclerosis–specific antibodies are less common.
Scleredema	Skin tightness affecting nape of neck, interscapular region, upper back and face; usually spares hands, lower trunk and lower extremities. In children, there may be a history of preceding streptococcal infection; in adults, it is associated with poorly controlled diabetes mellitus or a paraproteinemia. Diagnosis can be confirmed on skin biopsy.
Nephrogenic systemic fibrosis	History of exposure to gadolinium-based contrast agents for magnetic resonance imaging scan, typically in patients with severe renal insufficiency. Initially there is cutaneous erythema and edema, followed by symmetric skin thickening over the extremities, which moves from distal to proximal but usually spares the face and head; ultimately painful patches, papules or nodules coalesce to form indurated, dermal plaques with a "cobblestone," "woody" or *peau d'orange* appearance. Sclerodactyly is common; loss of skin appendages, hyperpigmentation and severe fixed joint contractures may develop. Raynaud phenomenon is absent and nail-fold capillaroscopy is normal. Diagnosis is confirmed on skin biopsy.
Diffuse fasciitis with eosinophilia	Starts with edema and erythema in the extremities, along with myalgias and arthralgias, soon followed by woody induration; associated with a *peau d'orange* appearance (Figure 1A). "Groove sign" is characteristic (Figure 1B). Sclerodactyly is uncommon. Peripheral blood and tissue eosinophilia decreases rapidly with treatment. Elevated erythrocyte sedimentation rate and C-reactive protein; polyclonal hypergammaglobulinemia. Creatine kinase is usually normal, but aldolase is often elevated before therapy. A full-thickness excisional biopsy from skin to muscle confirms the diagnosis (Figure 2).
Scleromyxedema	Associated with a benign monoclonal gammopathy. Cutaneous mucin deposition results in multiple flesh-coloured lichenoid papules, 2–3 mm in diameter, producing a typical "cobblestone" appearance, often on the glabella, neck, behind the ears, dorsum of the hands and the fingers (causing sclerodactyly), but sparing the palms. Over time, skin-fold thickening can lead to a leonine "mask-like" facies. Other features include Raynaud phenomenon, dysphagia, proximal myopathy, cardiopulmonary complications, and mild neurologic complications. Of untreated patients, 10% develop "dermato-neuro syndrome," a potentially fatal complication characterized by fever, seizures and coma.

Discussion

Diffuse fasciitis with eosinophilia is an uncommon fibrosing disorder, first described by Lawrence E. Shulman in 1975.[2] White men are most commonly affected.[1] The exact etiology of diffuse fasciitis with eosinophilia is unknown. Reported triggers include intense physical exercise or preceding trauma.[3] Certain drug exposures, arthropod bites and *Borrelia burgdorferi* infection have been implicated.[3] In addition, chronic cutaneous graft-versus-host disease has also been associated with this disorder.[4]

The earliest phase of diffuse fasciitis with eosinophilia is often characterized by edema and erythema in the extremities, soon followed by woody induration, frequently associated with a *peau d'orange* appearance, as seen in our patient. Elevation of an affected extremity leads to reduction of the distending venous pressure, causing indentation along the course of the superficial veins — the characteristic "groove sign" shown in Figure 1B. Myalgias, arthralgias and peripheral neuropathies are common. Muscle wasting and joint contractures may result from periarticular fascial involvement, but usually there is no overt muscle weakness. Sclerodactyly, as seen in systemic sclerosis, is distinctly uncommon.[3]

The diagnosis of diffuse fasciitis with eosinophilia is based on physical examination, laboratory testing, magnetic resonance imaging (MRI) and histopathologic examination. Patients develop eosinophilia, elevated inflammatory markers and polyclonal hypergammaglobulinemia.[5] However, both peripheral blood and tissue eosinophilia can be short lived, and tend to wane rapidly with the start of therapy. Hence, eosinophilia is not required for diagnosis.[1] Although creatine kinase is normal, serum aldolase is often elevated before therapy.[1] On MRI, fascial inflammation is shown by increased T_2 signal in the subcutaneous tissue and deep fascia and enhancement on postcontrast fat-suppressed T_1 images.[6] Other imaging modalities, such as ultrasound[7] and fluorodeoxyglucose–positron emission tomography/computed tomography[8] scans, can also show evidence of fascial inflammation.

The diagnosis of diffuse fasciitis with eosinophilia is confirmed on a full-thickness incisional biopsy from skin to muscle that enables adequate visualization of the pathological changes. Characteristic findings include lymphoplasmacytic inflammation along with histiocytes, mast cells and eosinophils infiltrating the deep dermis, fascia and superficial muscle. The inflammatory infiltrate does not usually involve the epidermis, papillary dermis and the adnexa. In addition, there is thickening of the deep fascia caused by sclerosis and fibrosis.[3] The specific skin biopsy findings differentiating the main diffuse sclerosing skin conditions are described in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.171012/-/DC1).

Glucocorticoids are the mainstay of therapy for this disorder; these are started in moderate to high doses (e.g., prednisone 20–100 mg/d).[1,3] Resolution of eosinophilia is rapid, but softening of skin and fascia and reversal of the joint contractures may take longer.[1] Although physical therapy can be beneficial, patients must be warned about the risks of rapidly resuming their predisease level of physical activity, because of the reported association of vigorous exercise and triggering of disease onset in some cases.[1] If response to therapy with glucocorticoids is inadequate, hydroxychloroquine[1,9] or methotrexate[1,10] can be added. Both spontaneous recovery and relapses can occur.[9] Patients should also be monitored for future development of hematologic disorders, such as aplastic anemia, leukemias and other blood dyscrasias, which occurs in about 10% of patients.[9]

Case revisited

A full-thickness incisional biopsy showed evidence of chronic fasciitis with subjacent muscle involvement (Figure 2). The patient's eosinophilia normalized within a few weeks after starting prednisone 60 mg daily, which was then reduced by 10 mg every 2 weeks, and finally maintained at 5 mg daily. Addition of hydroxychloroquine 200 mg twice daily induced further softening of skin and fascia, and his groove sign faded away in the next 6 months. He has stopped working out. No hematologic complications have developed so far.

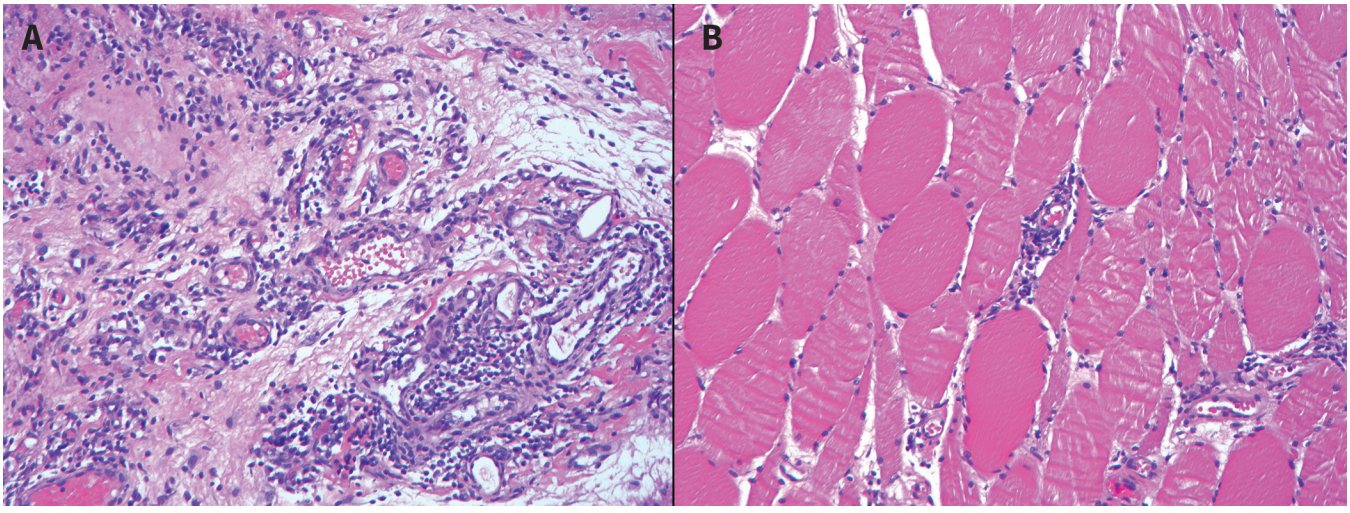

Figure 2: Full-thickness incisional skin biopsy including fascia and underlying left biceps muscle. (A) Histologic section showing a prominent chronic perivascular inflammatory cell infiltrate consisting primarily of benign-appearing lymphocytes involving the deep fascia and the soft tissue adjacent to the muscle, suggestive of chronic fasciitis. Hematoxylin and eosin stain (original magnification x 200). (B) The inflammatory infiltrate invades the subjacent muscle. There is mild muscle fibre atrophy, and a chronic, predominantly perivascular inflammation. Hematoxylin and eosin stain (original magnification x 200).

References

1. Morgan ND, Hummers LK. Scleroderma mimickers. *Curr Treatm Opt Rheumatol* 2016;2:69-84.
2. Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? *Trans Assoc Am Physicians* 1975;88:70-86.
3. Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after — what do we really know? Report of 11 patients and review of the literature. *Dermatology* 2006;213:93-101.
4. Ganta CC, Chatterjee S, Pohlman B, et al. Chronic graft-versus-host disease presenting as eosinophilic fasciitis: therapeutic challenges and an additional case. *J Clin Rheumatol* 2015;21:86-94.
5. Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. *Int J Dermatol* 2008;47:29-35.
6. Baumann F, Bruhlmann P, Andreisek G, et al. MRI for diagnosis and monitoring of patients with eosinophilic fasciitis. *AJR Am J Roentgenol* 2005;184:169-74.
7. Kissin EY, Garg A, Grayson PC, et al. Ultrasound assessment of subcutaneous compressibility: a potential adjunctive diagnostic tool in eosinophilic fasciitis. *J Clin Rheumatol* 2013;19:382-5.
8. Kim HJ, Lee SW, Kim GJ, et al. Usefulness of FDG PET/CT in the diagnosis of eosinophilic fasciitis. *Clin Nucl Med* 2014;39:801-2.
9. Lakhanpal S, Ginsburg WW, Michet CJ, et al. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. *Semin Arthritis Rheum* 1988;17:221-31.
10. Wright NA, Mazori DR, Patel M, et al. Epidemiology and treatment of eosinophilic fasciitis: an analysis of 63 patients from 3 tertiary care centers. *JAMA Dermatol* 2016;152:97-9.

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