VIA MEDICA

QUIZ

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Hardening of the skin of the trunk and upper extremities without Raynaud's phenomenon — a quiz

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CASE REPORT

A 64-year-old Caucasian male with a history of chronic obstructive pulmonary disease was admitted to the Department of Dermatology, Venereology and Allergology in Wroclaw because of a 7-month history of progressive symmetrical skin thickening of the shoulders, forearms, chest and lateral sides of the trunk and lower limbs. Due to suspicion of systemic sclerosis the patient was hospitalized in the Department of Rheumatology and Internal Medicine in Wrocław. At that time the patient demonstrated skin hardening of the trunk and upper extremities (Fig. 1), however, without involvement of the face and hands. In addition, contractures and movement restriction in the elbow and shoulder joints without any signs of arthritis were noted. Nor Raynaud's phenomenon neither other systemic findings were observed. Laboratory examination revealed accelerated erythrocyte sedimentation rate (ESR) of 55 mm/h, peripheral blood eosinophilia (0.74×10^3/μL, N: < 0.6) and high C-reactive protein (CRP) concentration in the serum (41.44 mg/l, N: < 5.0). Nailfold capillaroscopy was normal and rheumatoid factor (RF) was not present. The patient started the treatment with azathioprine (100 mg/d *p.o.*) in combination with methylprednisolone (4 mg/d *p.o.*), however, no improvement was observed. Four months later, because of a lack of clinical improvement, the patient was hospitalized for the second time in the Department of Rheumatology and Internal Medicine. The laboratory examination revealed a decrease of biochemical markers of inflammation (ESR — 34 mm/h, CRP — 4.25 mg/L), as well as normalization of blood eosinophilia (0.06×10^3/μL). During this stay the dose of azathioprine was increased to 150 mg/d,

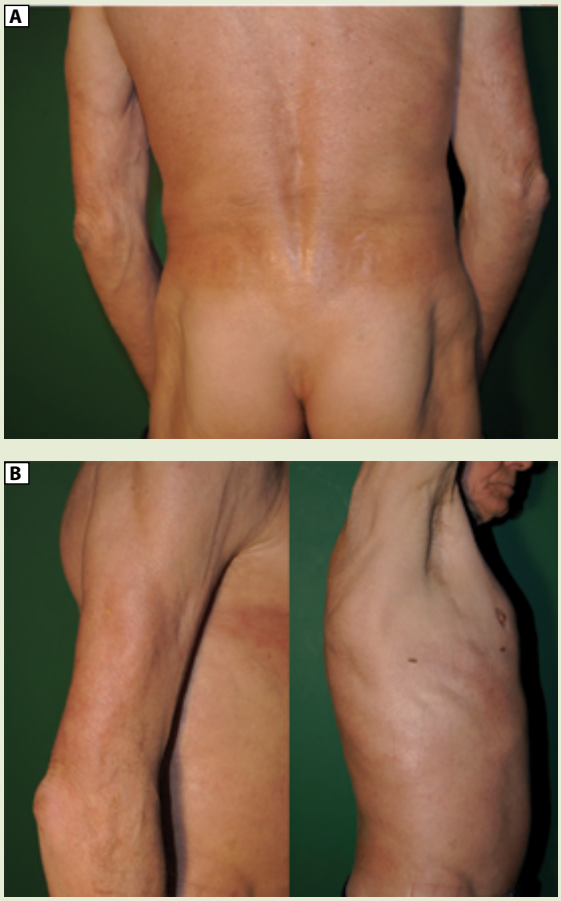

Figure 1A and 1 B. Clinical presentation of the patient

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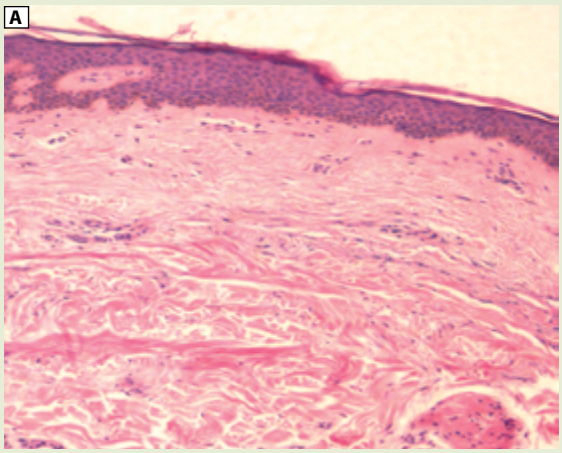

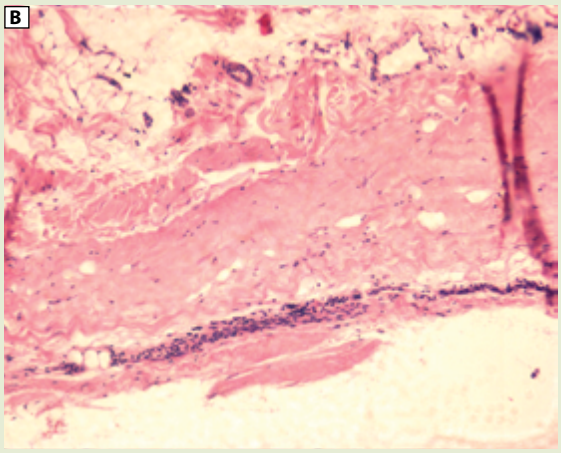

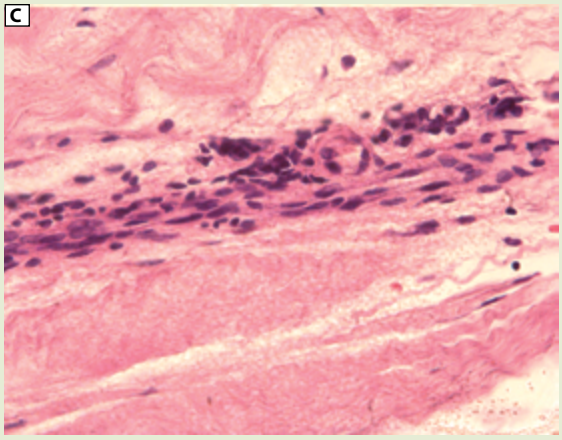

Figure 2. Histological examination. A. A very mild eosinophilic infiltration around the small vessels in the dermis, plain dermo-epidermal junction, and otherwise normal histology of epidermis and dermis; B. A dense inflammatory infiltrate of the deep fascia with scattered eosinophils; C. Larger magnification of inflammatory infiltrate of the fascia

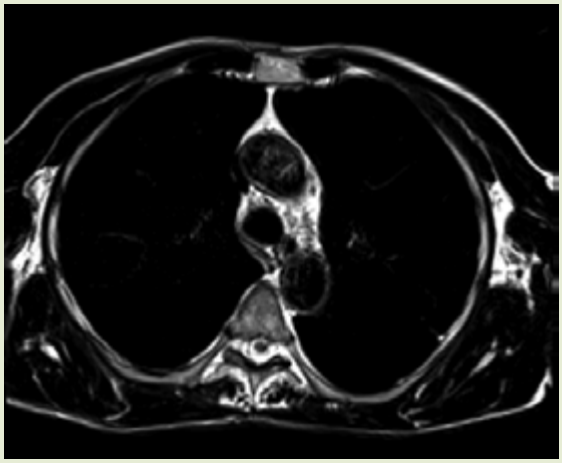

Figure 3. Magnetic resonance imaging of the chest of the presented patient. Please note thickening and irregularity of the fascia on the right site

and the dose of methylprednisolone was maintained. However, dermatological consultation was also reco mmended. According to the suggestion of consulting dermatologist, a deep skin biopsy was performed. Histological examination of the specimen revealed a mild eosinophilic infiltration around the small blood vessels of the dermis and thickened fascia surrounded by a dense inflammatory infiltrate (Fig. 2). Magnetic resonance imaging (MRI) of the chest discovered subcutaneous hyperintense bands from the superior to inferior margin of the scapula suggestive of edema and inflammatory changes in the superficial part of the fascia (Fig. 3).

WHAT IS YOUR DIAGNOSIS?

See next page for answer.

EOSINOPHILIC FASCIITIS

On the basis of the clinical and histological findings the diagnosis of Shulman syndrome was established and systemic prednisone therapy was initiated at a dose of 0.5 mg/kg/day, which resulted in a significant improvement of clinical condition of our patient. An in-depth diagnostic did not reveal any underlying condition, which might be related to observed symptoms.

Eosinophilic fasciitis (EF), also known as Shulman syndrome or diffuse EF, is a rare inflammatory and fibrosing disorder of the skin and fascia. Described in 1974 by Lawrence Shulman, this distinctive entity, has yet to unlock the many mysteries, including the etiology and pathophysiology. Since its discovery, EF has been reported in over 300 cases [1]. EF tends to predominate in Caucasians but reports have also been made in Asians, African Americans and Africans [1]. Women are more often affected than men [1]. The age of the patients at the disease onset is widely varied and ranges from 1 to 88 years with the most cases being recognized at from the third to the sixth decade of life [1].

The etiology of Shulman syndrome is unknown, but researchers have proposed some possible triggers and associations. The hypothesis of an abnormal immune reaction has been formulated based on the presence of hypergammaglobulinemia and antinuclear antibodies (ANA) in some patients [2, 3]. Some researchers believe that EF is a subtype of scleroderma due to the characteristic hardening of the skin while others believe it falls in the category of fasciitis-panniculitis syndromes due to its characteristic hardening and thickening of the skin on the basis of chronic inflammation [2]. Triggers that have been implicated with this disorder include drugs, such as simvastatin or phenytoin, and other environmental factors such as *Borrelia burgdorferi* infection, excessive exercise in subjects who are usually not very physically active, prolonged exposure to a cold environment and trauma. These triggers are thought to an abnormal response leading to an accumulation of eosinophils and other leukocytes in different areas of the body [2]. Some cases might have been related to L-tryptophan as the epidemic of EF was seen in 1982 [2].

The onset of EF is usually sudden, developing in a range of days to weeks, while less common variants may be more gradual. Both share an initial presentation of symmetrical pain, inflammation and non-pitting edema affecting the arms and forearms more commonly than the thighs and legs. On rare occasions the face, neck, buttocks, abdomen and chest may be involved as well. One may see venous grooving, a shallow furrow seen from the underlying veins, as the skin begins to change as well as *peau d'orange*. In its natural course, the disease initially presents with features of acute skin inflammation such as erythema and warmth of the affected area. It is followed by skin induration and finally skin fibrosis is observed. If the disease progresses, dermatogenic contractures may develop affecting the quality of life (QoL). Some patients may present with malaise, asthenia, arthritis and myalgia. Carpal tunnel syndrome (CTS) has also been documented due to the compression of the median nerve. Internal organ involvement, usually of mild severity, is an uncommon feature of EF [2]. The characteristic features of Shulman syndrome are described in Table 1.

Table 1. Features of eosinophilic fasciitis (Shulman syndrome)

Symmetrical hardening of the skin and subcutaneous tissue
Peripheral and tissue eosinophilia
Hypergammaglobulinemia
Elevation of erythrocyte sedimentation rate
Inflammation and fibrosis of the fascia with eosinophilic, lymphocytic and plasmacytic infiltrate

Peripheral blood eosinophilia is seen in about 61–83%, hypergammaglobulinemia in 18–67% and elevated ERS in 29–70% of the affected individuals [1]. RF and ANA are usually absent, but may be present on rare occasions. Tissue inhibitor of metalloproteinase 1 (TIMP-1) is a new serological marker found in patients with active disease [1]. The imaging method of choice is MRI. The characteristic findings on MRI include fascial thickening with abnormal signal intensity and contrast enhancement with gadolinium [1, 4]. To establish the definitive histological diagnosis, deep incisional biopsy containing skin, fatty tissue, fascia and superficial muscles is necessary. Histopathological hallmarks are inflammation, thickening, edema and sclerosis of the fascia. Other findings include infiltration of the deep fascia from plasma cells, lymphocytes, eosinophils and histiocytes as well as hyalinized collagen bands running parallel to the fascia [1].

Treatment depends on the severity of the disease. In some cases, EF resolves spontaneously. However, in most patients high-dose prednisone gradually tapered is considered as the first line treatment [5]. Other therapies such as surgical decompression of CTS, surgical release of the contracture and non-steroidal anti-inflammatory drugs for analgesia should be considered if necessary [2]. Unfortunately, in certain cases, the disease may be refractory to the corticosteroid therapy [5]. As an alternative, other immunosuppressive drugs like mycophenolate mofetil or methotrexate should be considered [5]. Of note, Khanna et al. [6] documented a very good effect of a therapy with monoclonal TNF-alpha inhibitor, while Bukiej et al. [7] showed significant improvement of steroid-resistant EF after cyclosporine A course. Furthermore, Lebeaux et al. [5] described positive results of treatment with methotrexate, azathioprine and rituximab. Considering the current insights on disease's pathogenesis, it seems reasonable to determine the efficacy of treatment

with interleukin-5 inhibitors such as mepolizumab, benralizumab or reslizumab [8, 9].

Summarizing, the main rationale for our case presentation was a relatively small number of EF descriptions found in the literature. In the described case the lack of internal organ involvement and the absence of Raynaud's phenomenon were helpful differentiation features from systemic sclerosis. We hope that, with the surging advancement of understanding of Shulman syndrome, early recognition, adequate therapeutic management and patient education may prolong the remission, decrease the risk of comorbidities and improve the patients' QoL.

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