A rare case of granulomatous slack skin associated with rheumatoid arthritis

Sir,

Granulomatous slack skin is a rare clinico-pathologic variant of cutaneous T-cell lymphoma and is distinct from granulomatous mycosis fungoides. It is characterized by hardened and erythematous plaques that mainly affect flexural areas with cutaneous sagging after some years. The distinctive clinical appearance results from elastolysis, mediated by giant cells in the infiltrate.[1] Chronic polyarthritis can rarely be associated with cutaneous T-cell lymphoma with unknown pathogenetic mechanisms.[2] We report a case of granulomatous slack skin associated with rheumatoid arthritis developing six years after the diagnosis of granulomatous slack skin.

A 29-year-old male presented with erythematous, loose atrophic patches on the shoulder and hip and violet erythematous papules and striae in the inguinal region. He was diagnosed with granulomatous slack skin in 2012 [Figures 1a-d and 2]. Histologic sections from the lesions showed diffuse granulomatous infiltrate composed of atypical lymphohistiocytes and giant cells in the dermis (Fig 1a). On higher magnification, there were evident epidermotropism of the atypical lymphocytes (fig 1b). There were multinucleated giant cells within the infiltrate that showed emperipolesis and elastophagocytosis (Fig 1c).

Immunohistochemistry studies showed increased CD3 and CD4 positivity and decreased CD5, CD7, CD8 and CD68 positivity. With all these findings, the patient had been diagnosed with granulomatous slack skin syndrome.

Inguinal lymph node biopsy had shown dermatopathic changes. Ultraviolet A phototherapy with psoralen (psoralen ultraviolet A) and interferon alpha-2a (3 × 3 mU/week) therapies was given for four years. Following this treatment, prominent lax skin and pendulous plaques in the axillary and inguinal folds were noted [Figures 3a-3c]. Extracorporeal photopheresis for two consecutive days per month was added to the previous therapies (interferon α-2a + psoralen ultraviolet A). The skin lesions continued to progress under the combination therapy. Psoralen ultraviolet A therapy was stopped and oral bexarotene was added at a dosage of 300 mg/m^2 to interferon α-2a and extracorporeal photopheresis. After one year, the patient developed swelling on both his elbows, wrists, knees and ankles, accompanied by morning stiffness that lasted for 30 min daily [Figure 3d]. Physical examination showed swelling and tenderness on palpation in both metacarpophalangeal joints, wrists, the right knee and both ankles. There was no erythema. The range of motion in the affected joints was minimally restricted. Serology revealed elevated C-reactive protein 15.7 mg/L (0–5), rheumatoid factor 32 IU/mL (0–14) and anti-cyclic citrullinated peptide <1 RU/mL (0–5); antinuclear antibody was negative. Magnetic resonance imaging of the hands and feet revealed severe inflammatory erosive polyarthritis [Figures 4 and 5]. Synovial fluid aspiration from the right knee joint showed a mild increase of white blood cells, 1125/μL (normal range: 0–1000/μL), tuberculosis and other microbial cultures were negative. The patient was diagnosed with human leukocyte antigen DR-B1+, rheumatoid factor + EP. After the diagnosis of rheumatoid arthritis, interferon therapy was stopped and the therapy regimen was adjusted to include

How to cite this article: Sanli HE, Akay BN, Atak MF, Kutlay S, Tas ND, Heper AO, *et al*. A rare case of granulomatous slack skin associated with rheumatoid arthritis. Indian J Dermatol Venereol Leprol 2021;87:535-9.

Received: May, 2020 Accepted: October, 2020 Published: June, 2021

DOI: 10.25259/IJDVL_483_20 PMID: ***

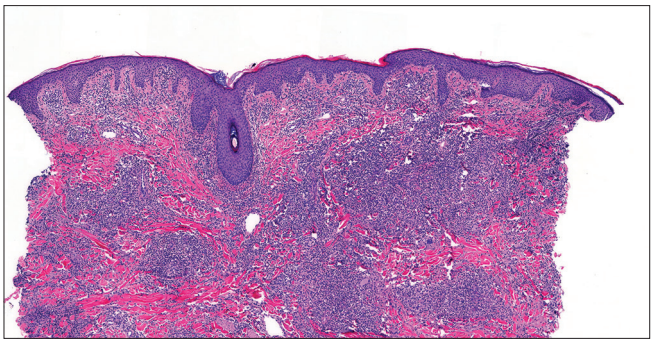

Figure 1a: Diffuse granulomatous infiltrates composed of atypical lymphocytes, histiocytes and giant cells (H and E, ×6.4)

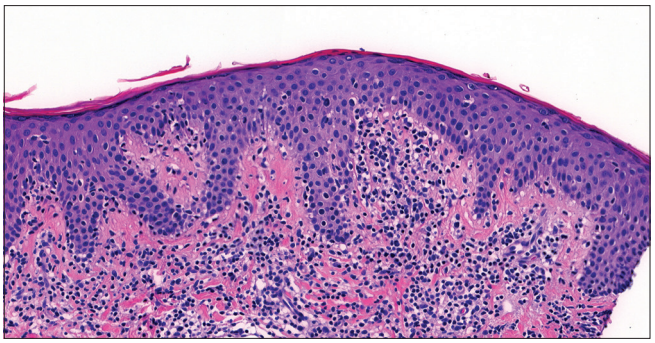

Figure 1b: Epidermotropism of the atypical lymphocytes (H and E, ×28.5)

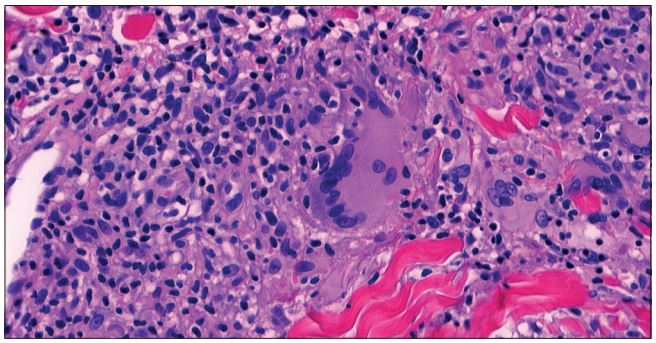

Figure 1c: Multinucleated giant cells showing emperipolesis and elastophagocytosis (H and E, ×59.1)

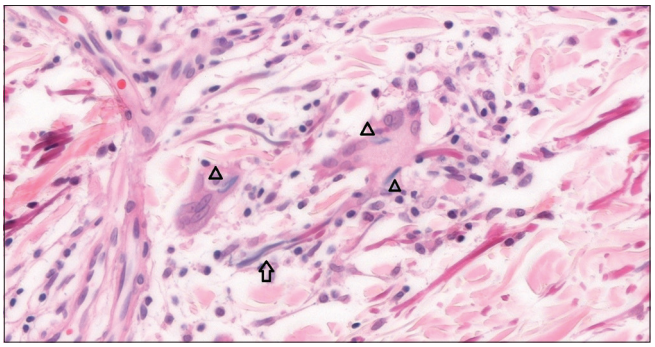

Figure 1d: Small fragments of basophilic elastic fibers (arrowhead) can be noted in the cytoplasm of multinuclear giant cells. Another free elastic fiber (arrow) can be seen outside of the giant cells (H&E, ×53.2)

prednisolone 15 mg/day and oral methotrexate 20 mg/week along with extracorporeal photopheresis and bexarotene. The prednisolone dose was tapered over several weeks. Methotrexate was continued in the same dosage. Despite the treatment, his joint symptoms improved partially; however, patient's pendulous skin lesions have progressed.

The patient was rescanned for systemic involvement of mycosis fungoides in 2019. Ultrasonography showed enlargement in the right inguinal lymph node and excisional biopsy showed nodal involvement. The patient was referred to the hematology department for further treatment options and brentuximab vedotin therapy has been planned.

Granulomatous slack skin is an extremely rare subtype of cutaneous T-cell lymphoma with indolent clinical behavior. The main differential diagnosis is with granulomatous mycosis fungoides: granulomas can be found in both entities, however, elastic fiber loss is less and focal in granulomatous mycosis fungoides. A denser subcutaneous cellular infiltrate and prominent lymphophagocytosis are more common in granulomatous slack skin. Despite these differences, granulomatous mycosis fungoides may show histopathologic overlap with granulomatous slack skin. The primary distinction between these two entities is made according to the clinical presentation.[3] Granulomatous mycosis fungoides primarily demonstrate widespread erythematous patches and plaques coexisting with typical mycosis fungoides lesions. On the contrary, granulomatous slack skin lesions become pendulous due to the loss of elastic tissue and the prognosis is better in granulomatous slack skin.

Erosive polyarthritis in mycosis fungoides or other types of cutaneous T-cell lymphoma is very rare and the pathogenesis is unclear. In the presence of mycosis fungoides, direct invasion of the synovium by malignant clonal T cells has been described.[4] In patients with genetic susceptibility, malignant T cells can migrate through the joint and increase inflammation by producing cytokines such as interferon-γ and interleukin-2.[5] Regardless of the former explanations, rheumatoid arthritis and mycosis

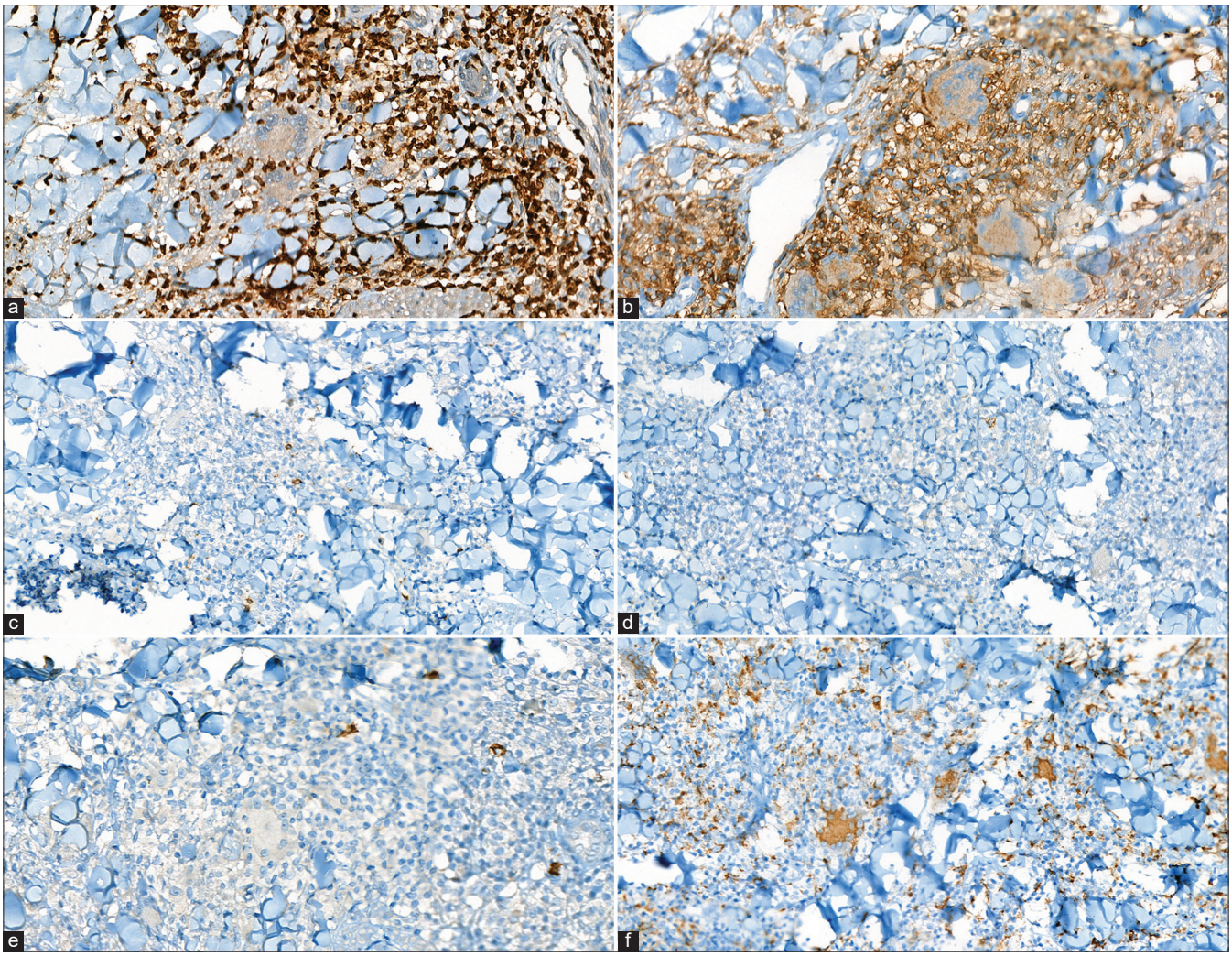

Figure 2: (a) Immunohistochemistry showing increased CD3 positivity (×39.6). (b) increased CD4 positivity (×39.6). (c) decreased CD5 positivity (×33). (d) decreased CD7 positivity (×33). (e) decreased CD8 positivity (×47.5). (f) decreased CD 68 positivity (×33)

fungoides can coexist independently. Paraneoplastic joint involvement can also occur in mycosis fungoides and the severity of lymphoma correlates with joint involvement, as depicted in our case.[6] Contrary to our case, mycosis fungoides patients with joint involvement reported in the literature presented with rheumatoid factor negative erosive arthritis.[7]

Treatment options in granulomatous slack skin are interferon α-2a, psoralen ultraviolet A, bexarotene, surgery and radiotherapy. Many of these were given to our case without adequate response. Brentuximab vedotin was planned due to the progression of skin lesions and lymph node involvement. Our patient's joint symptoms resolved under brentuximab therapy after remission

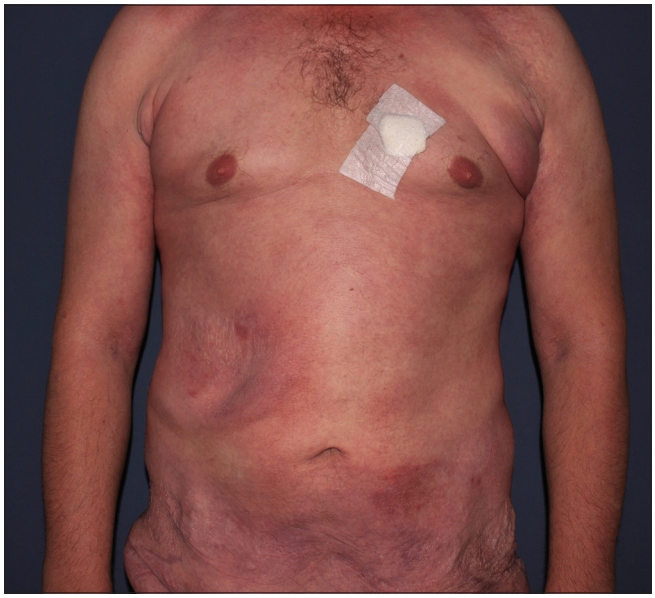

Figure 3a: Presentation of lax/atrophic skin or pendulous plaques in the lower part of abdomen

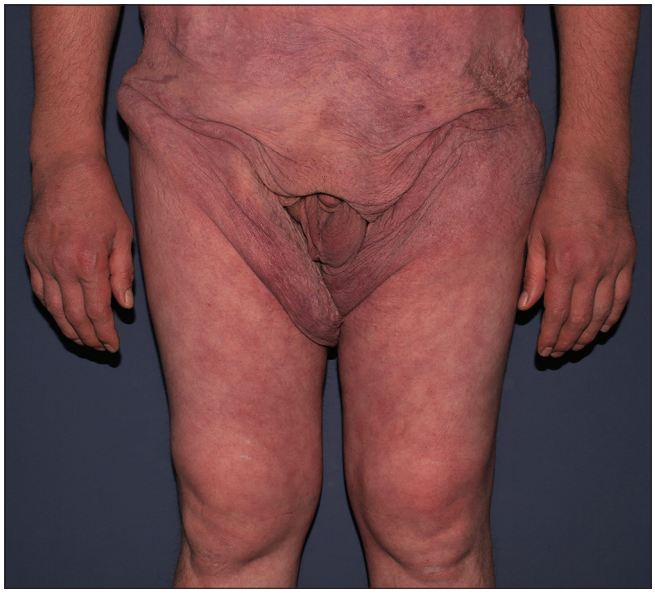

Figure 3b: Prominent pendulous skin in the inguinal folds

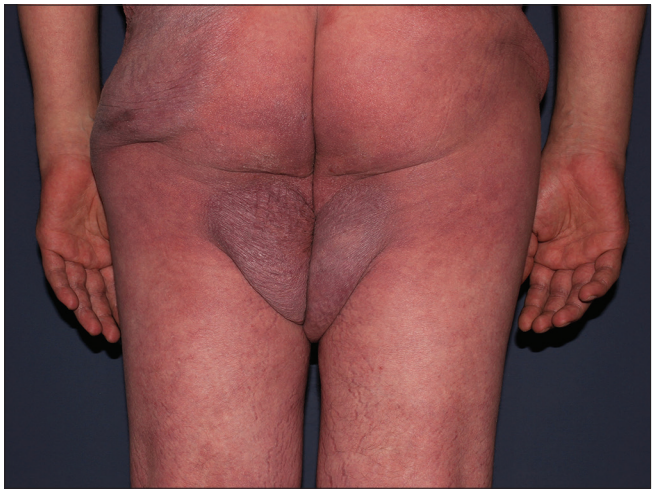

Figure 3c: Pendulous skin lesions in the posteriomedial aspect of thighs

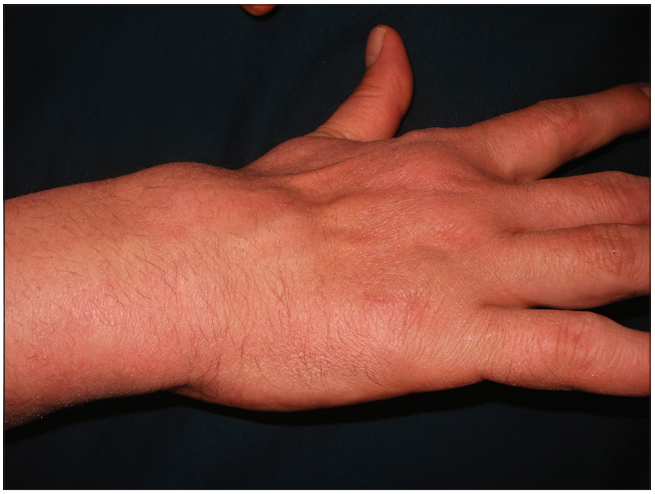

Figure 3d: Multiple cystic structures seen on the dorsal side of the left the wrist and boutonniere deformity of the thumb is observed

of the granulomatous slack skin syndrome. Thus, we concluded that the involvement was paraneoplastic in our patient.

In conclusion, granulomatous slack skin and rheumatoid arthritis association are rarely described and the pathogenesis is poorly understood. Dermatologists should be aware of this rare association and it should be kept in mind that interferon therapy can exacerbate joint symptoms. Further investigation is recommended for patients diagnosed with mycosis fungoides presenting with joint symptoms.

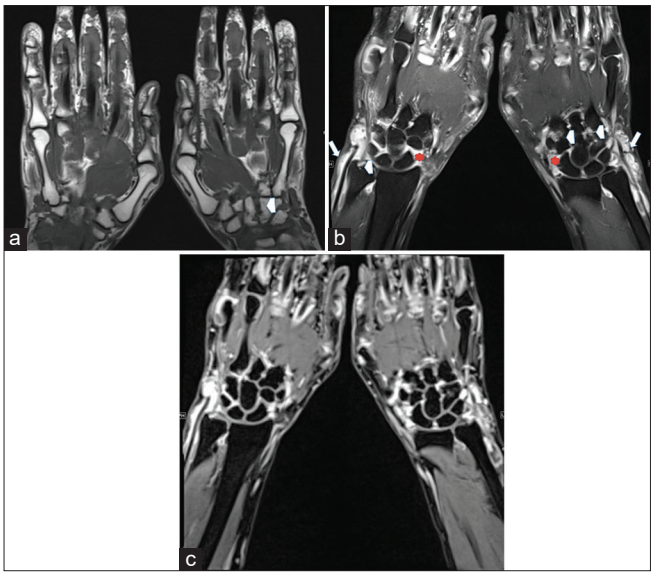

Figure 4: Magnetic resonance imaging of both hands demonstrates diffuse tenosynovial soft-tissue thickening and hyperintense inflammatory changes involving all extensor and flexor tendons, particularly in bilateral extensor carpi ulnaris tendon sheath (arrow) and shows intense contrast enhancement in the postcontrast examination, the tendons themselves appear normal. There is marked pannus and inflammation (*) around the wrist articulations and erosions in the distal ulna, right 3rd, and 4th metacarpal bases, left hamatum and 4th metacarpal bone (arrowheads). (a) Precontrast coronal T1-weighted magnetic resonance image, (b) Coronal T2-weighted fat-saturated magnetic resonance image, (c) Postcontrast coronal T1-weighted fat-saturated magnetic resonance image

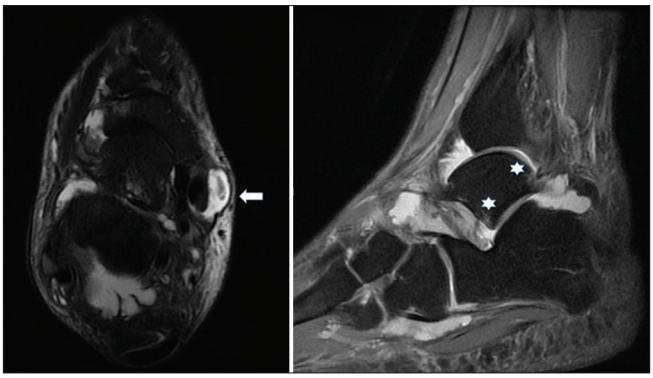

Figure 5: Marked fluid distension and synovial thickening with distension of the common peroneal tendon sheath into the peroneus brevis and peroneus longus sheaths (arrow), reactive subcortical bone marrow edema along the anterior and posterior aspect of the talus (*) and intraarticular effusion. Sagittal (left) and axial (right) T2-weighted fat-saturated magnetic resonance image

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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