Diffuse panniculitis in a teenage male with ZZ α_1-antitrypsin deficiency

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To the Editor:

Diffuse panniculitis is an inflammatory condition of the subcutaneous fat associated with a multiplicity of aetiological factors and nosological conditions [1, 2]. Diffuse panniculitis commonly occurs spontaneously and presents with painful skin nodules occasionally evolving into skin-ulcerating lesions discharging oily, yellow exudate. Histology shows an inflammatory infiltrate with lobular, septal or combined distribution, depending on the subjacent entity and the timing of biopsy, consisting of neutrophils, lymphocytes, histiocytes or a combination thereof; moreover, foamy macrophages, multinuclear giant cells, granulomas, necrosis or vasculitis may be seen [3]. Lesions may heal spontaneously (albeit less commonly) or after appropriate treatment with atrophic scarring. Any part of the superficial body may be involved although upper and lower extremities are more commonly affected [3]. Occasionally, it presents as part of a systemic inflammatory syndrome involving several extra-skin tissues and organs, and associates with thrombosis, a life-threatening clinical scenario [2].

A 17-year-old patient, a current smoker with a body mass index of 33.2 $kg \cdot m^{-2}$, presented to the emergency department complaining of erythematous, painful, indurating skin nodular lesions and low-grade fever over the previous 2 weeks (figure 1a). His previous medical and family history were noncontributory. Lesions were located bilaterally in the axillary regions, at the right abdominal surface and in both glutei. Differential diagnosis included mostly erythema nodosum and autoimmune rheumatic disease. After dermatological evaluation, a diagnosis of diffuse panniculitis was proposed. From laboratory evaluation, abnormal values included high C-reactive protein (CRP) (65 $mg \cdot L^{-1}$), low folic acid (1 $ng \cdot mL^{-1}$), low vitamin B_{12} (138 $pg \cdot mL^{-1}$), low albumin (2.7 $mg \cdot dL^{-1}$), low total serum proteins (4.8 $mg \cdot dL^{-1}$) and high ferritin levels (447 $ng \cdot mL^{-1}$). Computed tomography (CT) of the thorax and abdomen disclosed only diffuse oedema of the subcutaneous fat in the affected areas. Empirical antimicrobial treatment was started initially with a β-lactam, then changed to combined meropenem and linezolid upon deterioration. Due to low vitamin and albumin levels, enteric malabsorption was suspected, but endoscopy of the upper and lower gastrointestinal tract and capsule endoscopy for the small intestine did not detect abnormalities. Surgical biopsy of subcutaneous fat showed septal panniculitis with many histiocytes (figure 1b–d). Serology for autoimmunity, testing for HIV, hepatitis B virus and hepatitis C virus, and Quantiferon test were all negative. While lesions located in the glutei and the left axillary region became ulcerated, leaking oily, yellow exudates (figure 1a), the right abdominal wall lesion subsided spontaneously. New painful lesions appeared in concomitance with excessive subcutaneous oedema on the arms, scrotum and thighs. The lesions in the right arm and thighs ulcerated. Exudate cultures for common and specific pathogens including fungi and mycobacteria proved sterile. The patient continued to be febrile and his general clinical condition deteriorated. Due to excessive oedema of the arms and high D-dimer values, CT pulmonary angiography was performed, excluding pulmonary embolism. In the next few days and while lesions on the right upper arm appeared to subside, an insidious subcutaneous emphysema developed.

In the course of diagnostic work-up, serum α_1-antitrypsin (α_1-AT) levels were found to be extremely low (0.3 $g \cdot L^{-1}$, normal values 0.9–2.0 $g \cdot L^{-1}$) and the diagnosis of α_1-antitrypsin deficiency (α_1-ATD)-associated diffuse panniculitis as part of a systemic inflammatory syndrome was established; isoelectric focusing and genotyping confirmed the ZZ genotype/phenotype. Pulmonary function testing

Shareable abstract (@ERSpublications)
Diffuse panniculitis is a rare manifestation of α_1-ATD, albeit perhaps the most fulminant and life-threatening complication, associated usually with ZZ phenotype. Intravenous α_1-AT treatment is lifesaving. https://bit.ly/3EDmCzT

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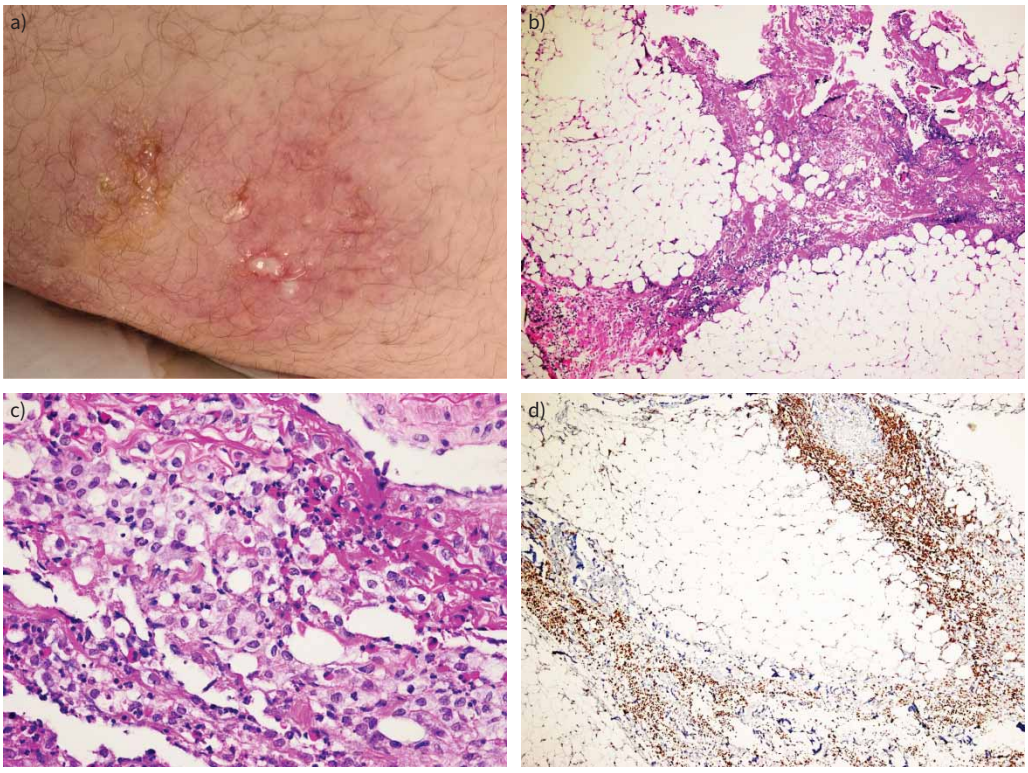

FIGURE 1 a) Erythematous, painful, indurating skin nodular lesions, partly ulcerated and leaking oily, yellow exudate. b) Panniculitis with inflammation mainly centring on fibrous septa (septal type) (haematoxylin and eosin (H&E) stain, 40× magnification). c) Histiocytic predominance in the inflammatory infiltrate (H&E stain, 40× magnification). d) Immunostaining for CD68 (PGM-1 clone) confirming histiocytic predominance (40× magnification).

was normal except a diffusing capacity of the lung for carbon monoxide of 68% predicted (systemic inflammatory syndrome with pleural effusions and obesity). Dapsone not being available for use, doxycycline was initiated, a course of plasmapheresis was performed and sequentially, intravenous augmentation infusion with α_1-AT was started at a dosage of 100 $mg \cdot kg^{-1}$ after authorisation was obtained. The day after the initiation of the augmentation therapy, the patient presented remarkable improvement of his general condition. Rapid remission of the inflammatory lesions and normalisation of the laboratory tests followed. The patient was discharged, smoking cessation was recommended and the next administration of augmentation treatment was scheduled. On the day of readmission (the 10th day), a mild reactivation of the disease was evident, rapidly responding to the next *i.v.* α_1-AT administration.

Diffuse panniculitis associated with α_1-ATD is an extremely rare, underdiagnosed systemic manifestation, this is potentially severe or even lethal, associated usually with ZZ genotype [4, 5]. α_1-AT is the most abundant serum and tissue circulating antiprotease, produced mainly by liver hepatocytes [6]. α_1-AT acts as a protease inhibitor preferentially targeting excess human neutrophil elastase and, by protecting lungs connective tissue, prevents early emphysema development. α_1-ATD is one of the most common genetic conditions and the Z variant in the homozygous state accounts for the 1–2% of all pulmonary emphysemas. Low or absent plasma levels and/or dysfunctional α_1-AT molecules, including mutant Z molecules in the form of polymers, increase the risk of developing early pulmonary emphysema, liver disease and, rarely, other systemic manifestations, including diffuse panniculitis and systemic vasculitis [7]. Cigarette smoking is considered the major additional risk factor for emphysema development [8]. Warter *et al.* [9], in 1972, first described the association between diffuse panniculitis and α_1-ATD. Since then, >100 patients have been described, mostly associated with the ZZ phenotype [4].

α_1-AT is an effective inhibitor of several serine proteinases in addition to neutrophil elastase (its main target), such as cathepsin G, trypsin, chymotrypsin, plasminogen activator and serine proteinase-3 [6]. In addition, α_1-AT is a very potent systemic anti-inflammatory molecule able to regulate neutrophilic

chemotaxis, activation and degranulation, and affecting immune response, autoimmunity and apoptosis through its interactions with interleukin 8, leukotriene B_4 and tumour necrosis factor α [10]. Severe deficiency alleles, such as PiZ, $PiS_{Siiyama}$, PiM_{Malton} and PiK_{Kings}, present low serum α_1-AT levels not by reducing synthesis in the liver hepatocytes but by its excessive degradation in the endoplasmic reticulum in a great proportion and by the intracellular formation of polymers of the mutant protein [7]. The accumulation of the above, because of their toxicity (gain of function), relates to neonatal hepatitis syndrome, early-life cirrhosis and hepatocellular carcinoma. Milder deficiency alleles such as the PiS, PiI and PiQueen's form polymers but at a slower rate [11]. Circulating polymers of the mutant protein not only lose any antiprotease and anti-inflammatory function but acquire a new and potent proinflammatory action at sensitive sites of the body (lung, liver, subcutis and vessels) to induce, sustain and increase inflammation, and provoke tissue damage [12]. This combined mechanism, loss of plasma antiprotease potential due to the serum α_1-AT levels (loss of function) and increase of protease burden due to Z polymers' action on neutrophilic local inflammation (gain of function) are considered the pathogenetic mechanism of tissue damage in diffuse panniculitis [13]. This putative mechanism is further confirmed by the prompt and excellent response that augmentation therapy with *i.v.* α_1-AT provides in almost all patients; offering of a fresh pool of wild, highly anti-inflammatory molecules reduces local inflammation and restores tissue damage [4, 14]. In our patient, immediately after the confirmation of the diagnosis of diffuse panniculitis related to the α_1-ATD ZZ phenotype, doxycycline was initiated mainly for its anti-inflammatory and immune-regulatory actions, plasmapheresis in an attempt to eliminate polymers of the Z mutant protein from blood and tissues, and augmentation therapy in order to offer targeted anti-inflammatory action.

To conclude, we describe a rare manifestation of α_1-ATD, albeit perhaps the most fulminant and life-threatening complication of α_1-ATD in adults with the ZZ and, much more rarely, with the SZ and MZ phenotype. Biopsy of the lesions, serum α_1-AT levels with CRP and phenotyping/genotyping are indispensable to confirm the diagnosis. In the setting of a high CRP level associated with the inflammatory syndrome in diffuse panniculitis, sometimes the α_1-AT levels may increase to higher levels, further emphasising the need for genotyping or phenotyping to make the diagnosis of α_1-ATD. The recognised treatment options include dapsone, tetracyclines, intravenous α_1-AT, plasmapheresis (low case numbers) and liver transplant (low case numbers) [4, 5]. So far, augmentation therapy is life-saving treatment [4]. In perspective, new drugs like fazirsiran (an RNA-interfering molecule that acts by degrading α_1-AT and Z-α_1-AT mRNA, thereby significantly reducing Z-α_1-AT protein synthesis in hepatocytes and, therefore, leakage of Z polymers in plasma and tissues) may find a place in the treatment of α_1-ATD-related diffuse panniculitis [15] in combination with contemporaneous treatment with intravenous α_1-AT.

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