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Early View

Research letter

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Diffuse panniculitis in a teen male

with ZZ alpha$_1$-antitrypsin deficiency

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Take home message: Diffuse panniculitis is rare manifestation of AATD, albeit perhaps the most fulminant and life-threatening complication associated usually with ZZ phenotype. Intravenous AAT treatment is life-saving.

Key words: Diffuse panniculitis, inflammatory syndrome, alpha1 antitrypsin deficiency, ZZ, augmentation therapy, plasmapheresis

To the Editor

Diffuse panniculitis is an inflammatory condition of the subcutaneous fat associated with a multiplicity of etiologic factors and nosologic conditions [[i], [ii]]. Diffuse panniculitis commonly occurs spontaneously and presents with painful skin nodules occasionally evolving in 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 [[iii]]. 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].

Case presentation

A 17-year-old patient, current smoker, BMI of 33.2 kg/m2 presented at the emergency department complaining for erythematous, painful, indurating skin nodular lesions and low-grade fever over the previous two weeks [Figure 1a]. His previous medical and family history were non-contributory. 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 CRP (65 mg/L), low folic acid (1ng/ml), low B12 (138 pg/ml) low albumin (2.7 mg/dl), low total serum proteins (4.8 mg/dl) and high ferritin levels (447 ng/ml). Computerized Tomography (CT) of the thorax and abdomen disclosed only diffuse edema of subcutaneous fat in the affected areas. Empiric antimicrobial treatment was started initially with a beta-lactam 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 GI 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, 1c, 1d]. Serology for autoimmunity, testing for HIV, HBV, HCV, 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 edema 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 edema of the arms and high d-dimers 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, AAT serum levels were found extremely low 0.3 g/L [normal values 0.9-2.0 g/L] and the diagnosis of AAT deficiency (AATD) associated diffuse panniculitis as part of a systemic inflammatory syndrome was established;

isoelectric focusing and genotyping confirmed the ZZ genotype/phenotype. Pulmonary function testing was normal except a DLCO% predicted of 68% (systemic inflammatory syndrome with pleural effusions, obesity). Dapsone not being available for use, doxycycline was initiated, a course of plasmapheresis was performed and sequentially intravenous augmentation infusion with AAT was started at a dosage of 100 mg/kg after authorization 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 normalization of the laboratory tests followed. The patient was discharged, smoking cessation was recommended and the next administration of augmentation treatment was scheduled. At the day of readmission (the 10th day) a mild reactivation of the disease was evident rapidly responding to the next AAT iv administration.

Discussion

Diffuse panniculitis associated with AATD is an extremely rare, underdiagnosed systemic manifestation, potentially severe or even lethal, associated usually with ZZ genotype [[iv], [v]]. AAT is the most abundant serum and tissue circulating antiprotease produced mainly by liver hepatocyte [[vi]]. AAT acts as a protease inhibitor, targets preferentially excessive human neutrophil elastase and by protecting lungs connective tissue prevents early-emphysema development. AATD is one of the most common genetic conditions and the Z variant in homozygous state accounts for the 1-2% of all pulmonary emphysemas. Low or absent plasma levels and/or dysfunctional AAT molecules, including mutant Z molecules in the form of polymers, increase the risk to develop early- pulmonary emphysema, liver disease and rarely other systemic

manifestations including diffuse panniculitis and systemic vasculitis [vii]. Cigarette smoking is considered the major additional risk factor for emphysema development [viii]. Warter J and coworkers in 1972 first described the association between diffuse panniculitis and AATD [ix]. Since then, more than one hundred patients have been described mostly associated with the ZZ phenotype [4].

AAT 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, AAT is a very potent systemic anti-inflammatory molecule able to regulate neutrophilic chemotaxis, activation and degranulation and affects immune response, autoimmunity and apoptosis through its interactions with IL-8, LTB-4 and TNF-α [x]. Severe deficiency alleles, such as PiZ, $PiS_{siiyama}$, PiM_{Malton} and PiK_{kings} present low AAT serum 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 [xi]. Circulating polymers of the mutant protein not only lose any antiprotease and anti-inflammatory function but acquire a new and potent pro-inflammatory action responsible at sensible sites of the body (lung, liver, sub-cutis and vessels) to induce, sustain and increase inflammation and provoke tissue damage [xii]. This combined mechanism, loss of plasma antiprotease potential due to the serum AAT 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 [[xiii]]. This putative mechanism is further confirmed by the prompt and excellent response that augmentation therapy with iv AAT provides in almost all patients; offering of a fresh pool of wild, highly anti-inflammatory molecules sovereigns local inflammation and restores tissue damage [4, [xiv]]. In our patient immediately after the confirmation of the diagnosis of diffuse panniculitis related to the AATD 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 AATD, albeit perhaps the most fulminant and life-threatening complication of AATD in adults with the ZZ and much more rarely with the SZ and MZ phenotype. Biopsy of the lesions, serum AAT levels with CRP and phenotyping/genotyping are indispensable to confirm the diagnosis. In the setting of a high CRP associated with the inflammatory syndrome in diffuse panniculitis sometimes the AAT levels may increase at higher levels further emphasizing the need for genotyping or phenotyping to make the diagnosis of AAT deficiency. The recognized treatment options include dapsone, tetracyclines, intravenous AAT, 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 acting by degrading AAT and Z-AAT messenger RNA, therefore able to reduce significantly Z-AAT protein synthesis in hepatocytes and therefore leakage of Z polymers in plasma and tissues may find its

position also in the treatment of AATD-related diffuse panniculitis [xv] in combination with contemporaneous treatment with intravenous AAT.

FIGURE LEGENDS

Figure 1a). Erythematous, painful, indurating skin nodular lesions, partly ulcerated leaking oily yellow exudate.

Figure 1b). Panniculitis with inflammation mainly centering on fibrous septa (septal type), H&E stain x40.

Figure 1c). Histiocytic predominance in the inflammatory infiltrate, H&E stain, x40

Figure 1d). Immunostaining for CD68 (PGM-1 clone) confirming histiocytic predominance x40.

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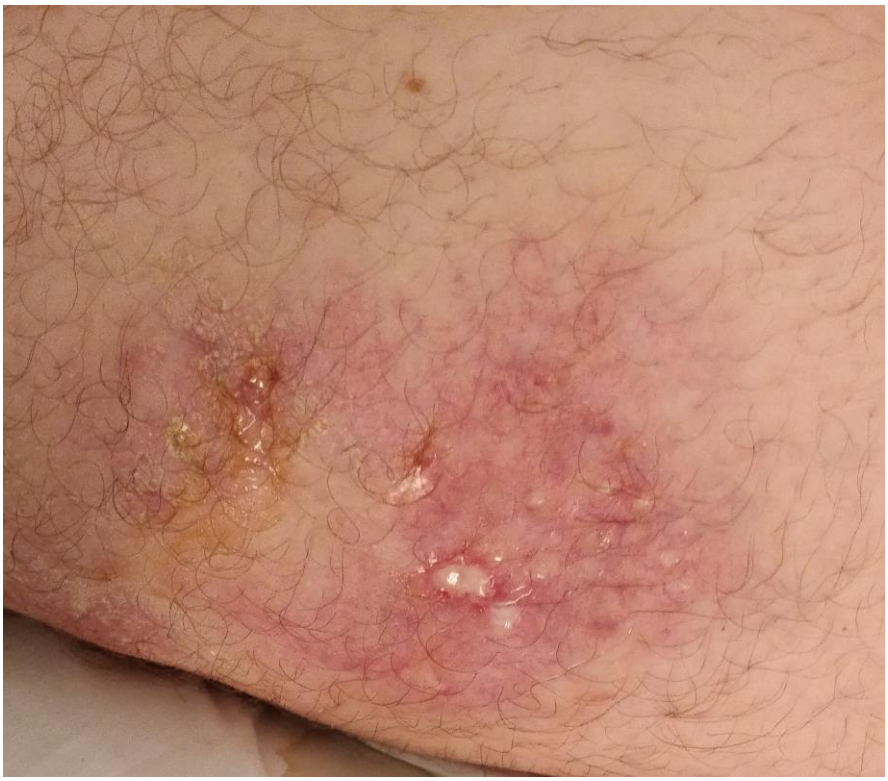

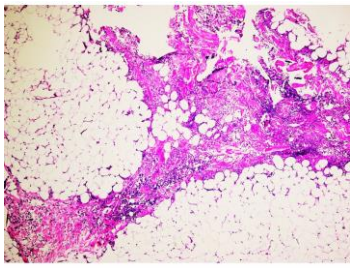

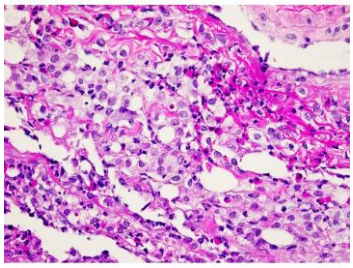

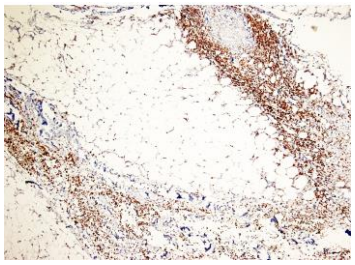

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