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Alpha-1 antitrypsin deficiency-associated panniculitis: a case report

Panikulitis pri pomanjkanju alfa-1 antitripsina: prikaz primera

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Abstract

Alpha-1 antitrypsin deficiency is a hereditary disorder with predominantly pulmonary but also extrapulmonary manifestations. In the skin, it is associated with panniculitis, a necrotizing neutrophilic inflammation in the subcutis. Clinically, it presents with tender, erythematous, oedematous, recurrent, and potentially ulcerative nodules, most often located on the extremities or the trunk. The entity is often unrecognized, though it can greatly affect the patient's quality of life and is potentially lethal. Clinical suspicion is supported by deep-skin biopsy, the concentration of alpha-1 antitrypsin in the serum, and electrophoresis, or, if possible, by genotype or phenotype characterization. Currently, the most widely accepted treatment options include dapsone, doxycycline, and augmentation therapy. We report a case of a young Caucasian man with alpha-1 antitrypsin deficiency that manifested with recurring and extremely painful nodules on his legs and gluteal area. The diagnosis was established based on the patient's history, a low serum level of alpha-1 antitrypsin, and the findings of the deep-skin biopsy, which were suggestive of neutrophilic panniculitis. Total remission was achieved with dapsone, and the therapy was well-tolerated.

Izvleček

Pomanjkanje encima alfa-1 antitripsina je dedna bolezen, ki največkrat prizadene pljuča, jetra, redkeje pa kožo, kjer pa se izrazi kot panikulitis. Panikulitis je nekrotizirajoče nevtrofilno vnetje podkožnega maščevja. Kaže se z bolečimi, eritemastimi in edemastimi vozliči na udih in trupu, ki se pogosto ponavljajo ter lahko ulcerirajo. Bolezen se pogosto spregleda oziroma se prepozna prepozno, čeprav pomembno vpliva na kakovost bolnikovega življenja in je lahko smrtna. Pri postavitvi diagnoze so v pomoč: histopatološki izvid globoke biopsije kože, določanje koncentracije alfa-1-antitripsina v serumu, elektroforeza serumskih beljakovin in genotipizacija ter fenotipizacija. Možnosti zdravljenja vključujejo: dapson, doksiciklin in intravensko nadomeščanje alfa-1-antitripsina. S kliničnim primerom predstavljamo mladega moškega s panikulitisom in znanim pomanjkanjem alfa-1-antitripsina. Diagnozo smo potrdili z znižano koncentracijo alfa-1-antitripsina v serumu in nevtrofilnim panikulitisom v patohistološki preiskavi biopta kože. Po uvedbi dapsona pa je prišlo do popolne remisije bolezni.

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Ključne besede: panikulitis; nevtrofilni panikulitis; alfa-1 antitripsin; pomanjkanje alfa-1 antitripsina; dapson

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1 Introduction

Panniculitis is an inflammation of the subcutaneous fat that presents non-specifically through various disorders (1). It is also a rare extrapulmonary manifestation of alpha-1 antitrypsin (AAT) deficiency (AATD). Panniculitis in AATD is estimated to affect 1 in 1000 individuals (2), although the actual prevalence remains unknown as it is often misdiagnosed (3,4). Epidemiological characteristics include European ancestry and female gender, with the condition most frequently occurring in the fourth decade of life (4-6). In general, panniculitis develops spontaneously and is less commonly triggered by trauma or iatrogenic procedures (2,4). Clinically, it presents with tender, red, oedematous, and potentially ulcerative subcutaneous nodules with oily discharge. The nodules often recur and predominantly appear on the extremities, though the abdomen, trunk, gluteal area, and face can also be affected (3,4,6,7). In the initial stages, skin lesions can mimic cellulitis and may later heal with atrophic scars (6,7). Histopathologically, panniculitis in AATD is neutrophilic. For a correct diagnosis, the distribution of the inflammatory infiltrate, potential septal thickening, and especially the type of fat necrosis need to be evaluated. The characteristic features include "floating fat" and neutrophil splaying (2,8). The biopsy findings should be considered in conjunction with the patient's clinical picture, history, and analytical data (6,7). Timely diagnosis is crucial, while improper management can be potentially life-threatening (9).

2 Case report

A 34-year-old Caucasian man presented with a 5 x 3 cm indurated, tender, dry, and non-fluctuating oedema in the left popliteal fossa. It was circumscribed by a 10 x 6 mm erythematous area and mimicked cellulitis (Figure 1). In addition, multiple tender, erythematous nodules appeared on the medial side of the right thigh and calf (Figure 2), as well as on the soles of both feet (Figure 3). The skin lesions developed simultaneously, acutely, and spontaneously without prior manipulation, injury, or insect bites to the affected sites. No systemic symptoms were present. Over the past six months, the patient has experienced several outbreaks of similar skin lesions on the lower extremities, sometimes accompanied by oral ulcers. He did not have any prescribed medications and was allergic to naproxen.

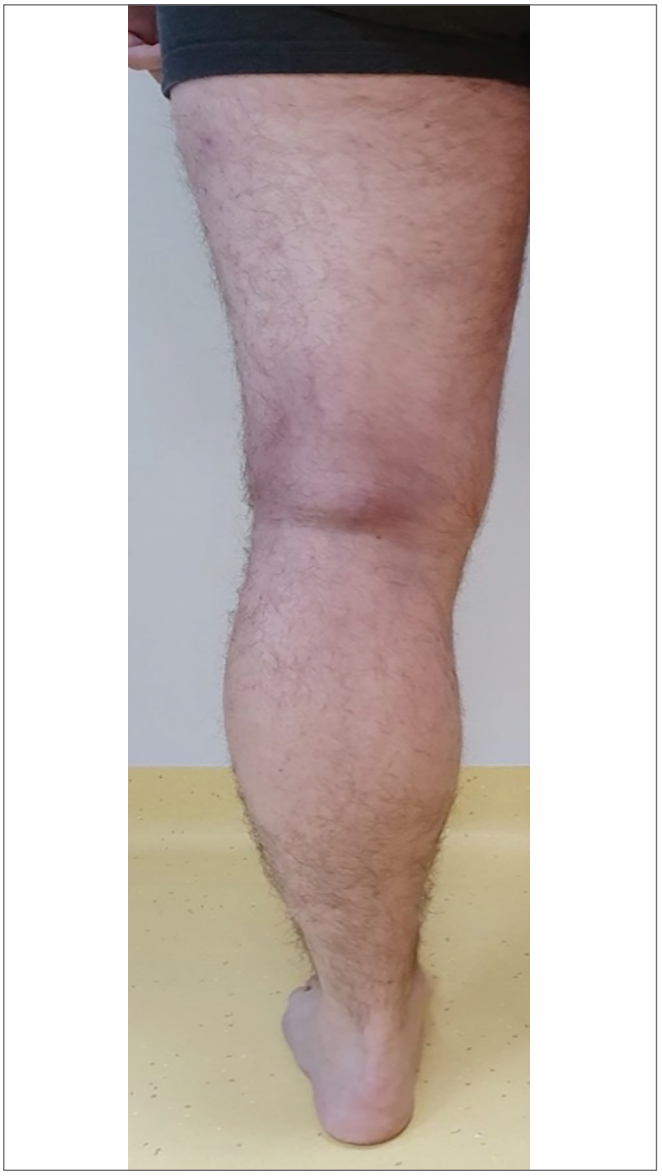

Figure 1: Cellulitis-like oedema in the left popliteal fossa. Source: archive of the Department of Dermatology and Venereal Diseases, University Medical Centre Maribor.

His medical history revealed that he has AATD (PiZZ genotype) with known liver damage (liver steatosis). First, deep vein thrombosis was ruled out with Doppler Ultrasonography. Then, based on the clinical picture and patient's history, AATD-associated panniculitis was suspected.

While waiting for the laboratory and histopathologic results, the patient was started on doxycycline for three weeks. However, the response to the treatment was not satisfactory, as new nodules began to appear alongside the existing ones. These new nodules developed in the

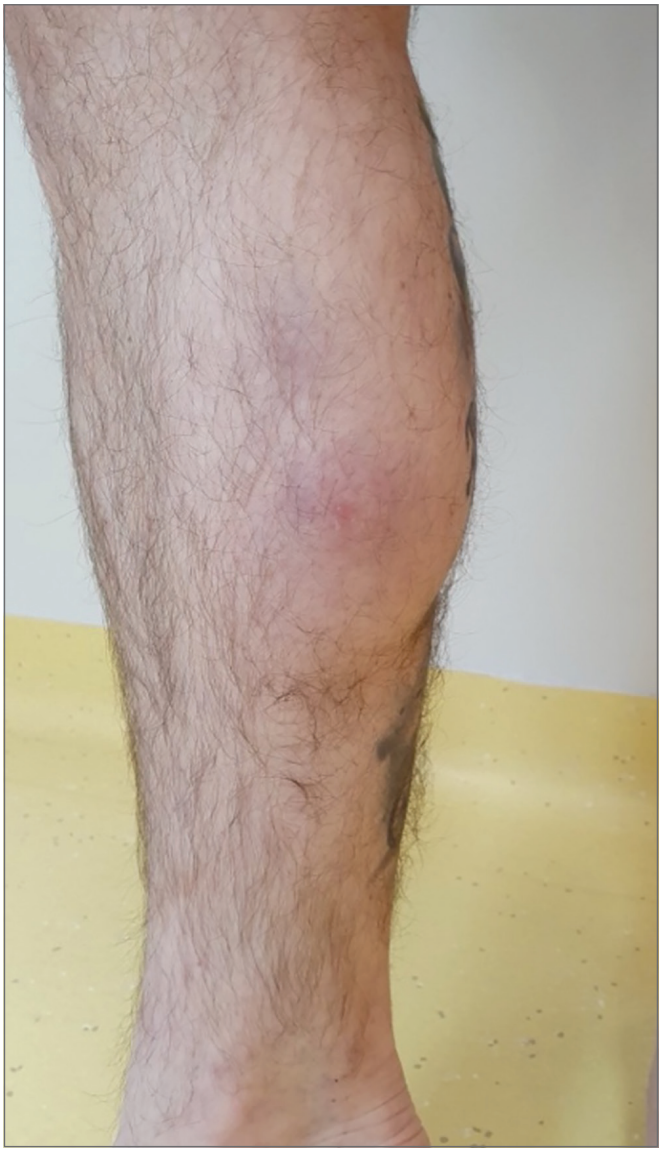

Figure 2: Tender, erythematous nodule on the medial and posterior side of the right calf.
Source: archive of the Department of Dermatology and Venereal Diseases, University Medical Centre Maribor.

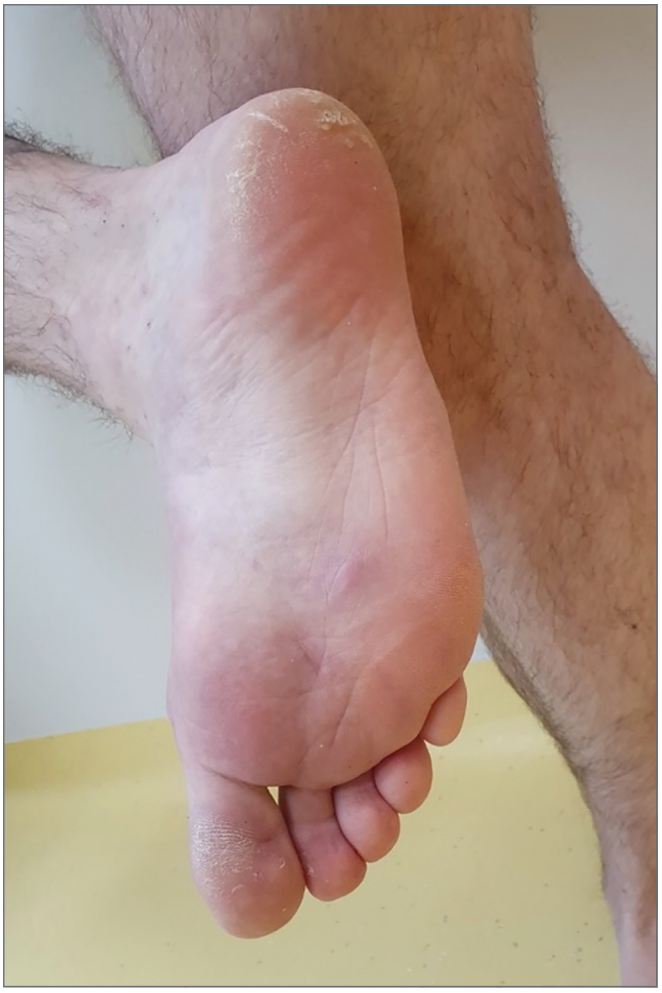

Figure 3: Tender, erythematous nodule on the sole of the right foot.
Source: archive of the Department of Dermatology and Venereal Diseases, University Medical Centre Maribor.

left gluteal region and were so painful that the patient had trouble sitting, significantly affecting his quality of life.

The blood analysis showed a decreased concentration of AAT in the serum (0,29 g/L) and a reduced alpha-1 globin band on protein electrophoresis (2,5%), alongside lymphocytopenia (14,7%), an elevated concentration of CRP in the serum (41 mg/L), and a high sedimentation rate (34 mm/h). All other markers in the extensive laboratory panel (complete blood count with differential, biochemical markers of kidney and liver function, electrolytes, lipids, most common tumour markers, specific antibody tests, urinalysis), including the concentration of glucose-6-phosphatase in the serum, were within the normal range. The deep skin biopsy revealed extensive lobular and focally septal panniculitis with the replacement of fat lobules by dense neutrophilic infiltration in the subcutis. Additionally, focal necrosis admixed with lymphocytes, eosinophilic granulocytes, neutrophils, histiocytes, and some lipophages, accompanied by collagenolysis and elastolysis were observed. The lesion was relatively sharply delineated and even juxtaposed with areas of relatively normal fat (Figures 4 and 5). There was also no evidence of leukocytoclastic vasculitis. In the next step, direct immunofluorescence (DIF) was performed. DIF revealed granular deposits of complement component 3 (C3) at the dermo-epidermal junction and in the vessel walls of the subcutaneous layer. Only a few globules of immunoglobulin (Ig) A, IgG, and IgM were identified in the papillary dermis, and dense deposits of fibrin/fibrinogen were found in

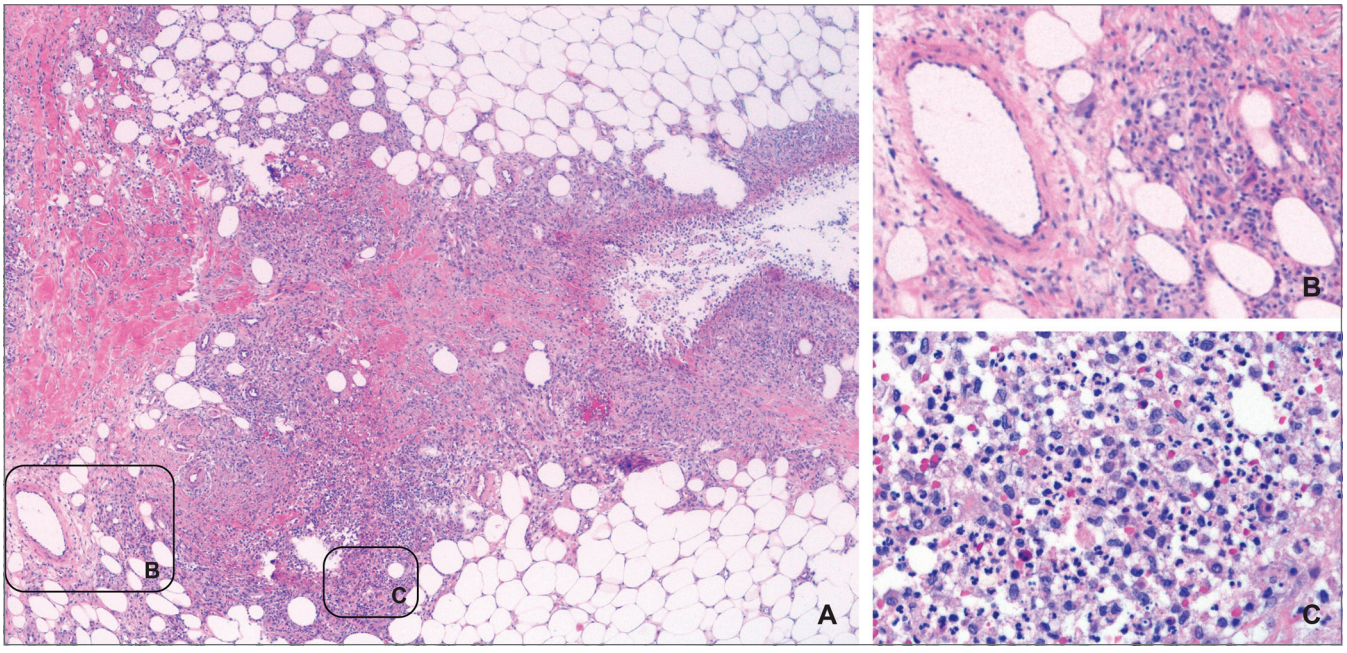

Figure 4: Deep skin biopsy with lobular panniculitis of the subcutis and adipose tissue (A). The affected fat lobules are necrotic, replaced with an intense neutrophilic infiltrate admixed with lymphocytes, eosinophilic granulocytes, neutrophils, histiocytes, and some lipophages (B - the composition of the infiltrate in higher magnification). Typical histopathological features of vasculitis are absent (C - the vessel wall without neutrophils and inflammation) (hematoxylin-eosin, original magnification x4).
Source: archive of the Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

the vessel walls of the superficial layer of the dermis. The histopathologic findings suggested neutrophilic panniculitis, while erythema nodosum, pancreatic, and possibly infective panniculitis were considered in the differential diagnosis. DIF excluded potential vasculitis or autoimmune disease. Based on the clinical picture, patient history, and low serum AAT levels, the diagnosis of AATD-associated panniculitis was established.

Then, considering the unsatisfactory response to doxycycline, the patient was administered a gradually increasing dose of dapsone. Total remission was achieved with a maximum daily dose of 100 mg after two months of treatment. Following careful monitoring of the clinical picture, potential side effects, and laboratory marker values, dapsone was gradually decreased and discontinued six months after initiation. No regression was observed throughout this period, and the treatment was well-tolerated by the patient.

3 Discussion

AATD is a genetic disorder of autosomal codominant inheritance, primarily manifesting as a disease of the lungs, liver, and, rarely, the skin or blood vessels. It is characterized by decreased levels of AAT protein in the serum. AAT is an enzyme, a serine protease inhibitor, with a crucial role in protecting tissues from proteolytic damage (2-4). It is primarily synthesized in the liver and, to a lesser extent, in the lungs, colon, pancreas (3,5), and cornea (5). After being secreted into the serum, the enzyme is distributed throughout the body. AAT is most recognized for neutralizing neutrophil elastase in the lungs, although it also inhibits several other proteases, such as trypsin, proteinase-3, pancreatic elastase, thrombin, plasmin, etc. (2,3). Additionally, it has been identified as relevant in modulating the

Table 1: *Most common clinical manifestations of alpha-1 antitrypsin deficiency (2-4,10).

Affected organ	Clinical manifestation
Lungs	COPD, emphysema, bronchiectasis
Liver	Cirrhosis, cholestasis, hepatocarcinoma
Skin	Panniculitis
Blood vessels	Systemic vasculitis, aneurysms

Legend: * It must be taken into account that the most prevalent manifestations are pulmonary, followed by liver disease.

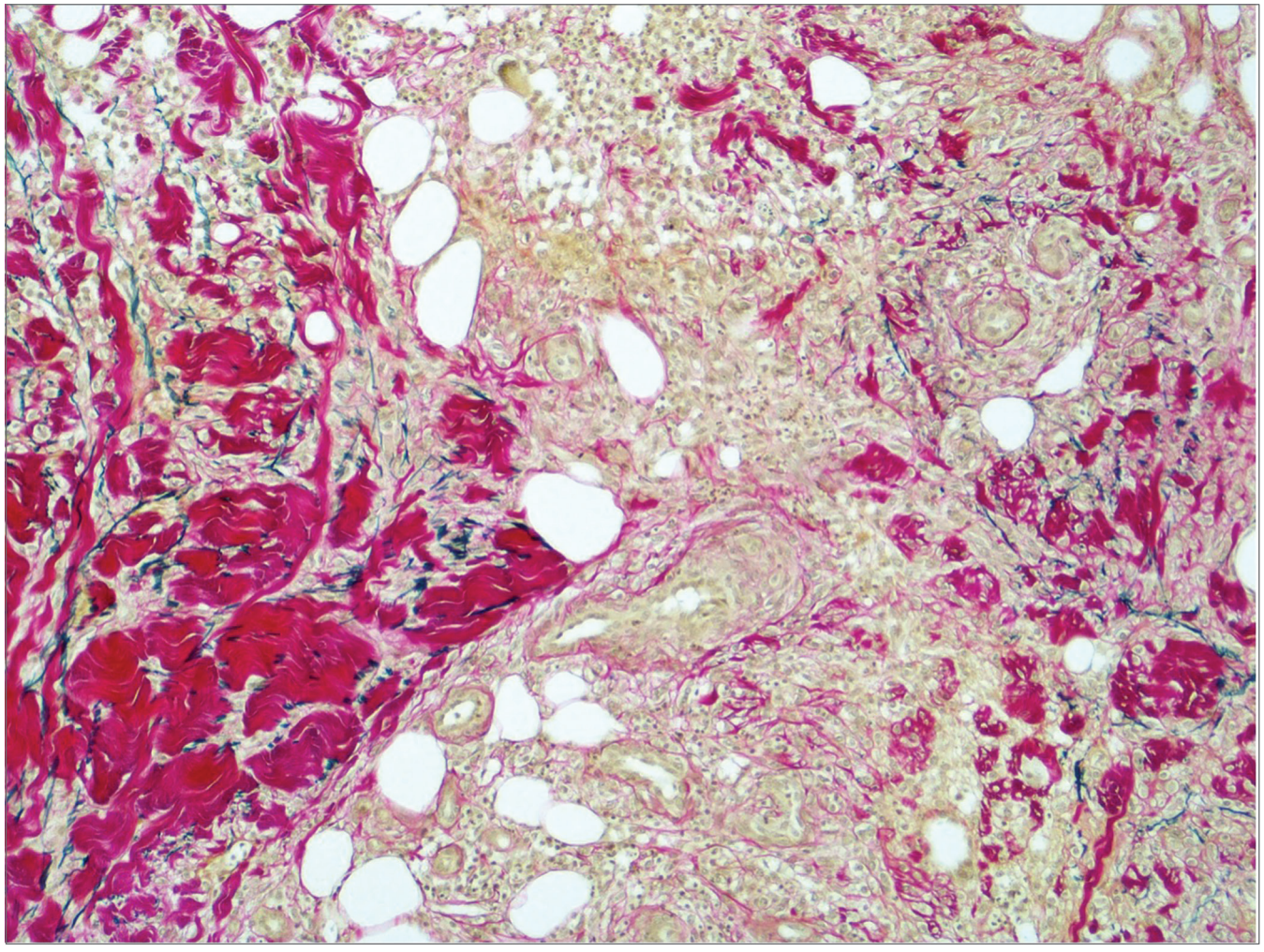

Figure 5: Weigert-Van Gieson staining, based on the affinity towards elastic fibers, better visualized the presence of collagenolysis and elastolysis, with "floating fat" separated from the reticular dermis (Weigert-Van Gieson, original magnification x10).
Source: archive of the Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

activity of certain immune cells (2) and pro-inflammatory cytokines, such as interleukin-8, tumour necrosis factor-α, and leukotriene B4 (4).

AATD is caused by mutations in the SERPINA1 gene, which codes for the AAT protein. These mutations result in the production of dysfunctional AAT, predisposing individuals to the development of several diseases (Table 1). Most commonly, antiprotease insufficiency manifests as a lung disease. The unopposed action of neutrophil elastase, an enzyme that degrades elastin and other components of connective tissue, can result in emphysema, early-onset chronic obstructive pulmonary disease, and even bronchiectasis. The accumulation of the defective enzyme in the liver may lead to neonatal cholestasis, cirrhosis in children or adults, and even hepatocarcinoma in adults (2-4). Due to its potential role in accelerating the degradation of the aortic wall, AATD has also been linked to systemic c-ANCA (anti-neutrophil cytoplasmic antibody) vasculitis and aneurysmal disease (10). The disorder has also been associated with panniculitis, although the exact pathophysiology remains unclear. Presumably, the lack of the enzyme's protective functions promotes an exaggerated neutrophilic response and increased proteolytic damage to the subcutis (2,4). One of the hypothesized mechanisms includes the role of the complement system, as some evidence suggests that the degradation product of C3 is increased in AAT-deficient individuals (4). AAT deficiency may also be associated with other cutaneous disorders, including psoriasis, chronic urticaria, acquired angioedema (3,7), prurigo nodularis, atopic dermatitis, and Marshall's syndrome (7). However, the underlying mechanisms are not proven (3,7).

The clinical manifestation of AATD depends on the individual's genotype and the concentration of the affected enzyme in the serum. Panniculitis is particularly common in individuals with the most severely deficient genotype PiZZ, characterized by markedly decreased levels of AAT (1,4). In such individuals, the serum concentration of AAT is usually below 0.5 g/L, whereas it normally ranges from 1 to 2.0 g/L (2-4,6). Panniculitis can be the sole manifestation of AATD, or it develops alongside other associated pulmonary or hepatic conditions. Most frequently, it occurs in individuals without a previous diagnosis of AATD, whereas prior pulmonary or liver dysfunction has been documented in almost a third or 10% of cases respectively (4). However, the patient's age at presentation and smoking status must also be considered. In addition, Elsensohn et al. reported panniculitis as part of a systemic illness, along with anasarca, pulmonary embolus, and hypogammaglobulinemia (11).

Clinical suspicion of AATD-associated panniculitis is supported by deep-skin biopsy and complemented by the serum concentration of AAT or protein electrophoresis (12). The histopathological features of panniculitis in AATD include predominantly lobular inflammation of the subcutaneous fat, accompanied by fat necrosis and dense neutrophilic infiltration, which is typical of neutrophilic panniculitis (1,4,8). Neutrophilic panniculitis is a heterogeneous group of inflammatory and infectious skin disorders. The differential diagnosis is wide and includes pancreatic panniculitis, infective panniculitis, subcutaneous Sweet syndrome, panniculitis associated with rheumatoid arthritis, erythema induratum, and erythema nodosum. The characteristic histologic findings of AATD-associated panniculitis are collagenolysis and elastolysis, which lead to the development of "floating fat" that is detached from the adjacent reticular dermis and septa. One of the diagnostic hints of early-stage disease is also the identification of neutrophils dispersed among collagen bundles of the deep reticular dermis (2,4,8). Furthermore, while primary vasculitis is not observed in AATD-associated panniculitis (2), secondary leukocytoclastic vasculitis has been reported, although it is not a typical feature of the disease. In such cases, DIF showed vascular deposits of C3 and IgM in the dermal layer (2,4,7). Nevertheless, the findings of deep-skin biopsy are not diagnostic and can be quite variable. The correct diagnosis should be established based on clinical and laboratory data, most commonly the serum concentration of AAT (6,7). Still, AAT is an acute-phase reactant, much like C-reactive protein (CRP), and hence, its levels could be augmented during acute inflammation (2,3). The likelihood of a falsely negative result, meaning a normal AAT value in the serum, could be overcome by simultaneous quantification of CRP and AAT. In addition, the reduction or absence of the AAT (alpha-1 globulin) band in electrophoresis may be helpful (7), although it is no longer commonly used (12). Ultimately, phenotype or genotype characterization is preferred (4,12).

Once the diagnosis of AATD-associated panniculitis is established, the entity must be managed appropriately, as the outcome can be potentially lethal (9). Over the years, various types of drugs and their combinations have been tested in pursuit of the best management strategy. Currently, most clinicians administer dapsone as a first-line treatment (4,5). It is usually administered orally in daily doses of 50-100 mg and remains the most proven, readily available, and affordable treatment. According to a systematic review, dapsone achieves clinical remission in 62% of cases. However, patients may not tolerate it well due to its side effects (5). Before administering dapsone, it is imperative to exclude glucose-6-phosphate dehydrogenase deficiency to avoid haemolytic anaemia (4). Furthermore, tetracyclines, typically doxycycline, could also be effective as monotherapy, with tetracyclines reportedly achieving clinical remission in 33% of cases (5). Hence, they might be a reasonable option offered as an adjuvant to the first-line or as a second-line treatment (4,5). Finally, the most effective treatment for AATD-associated panniculitis proves to be augmentation therapy. The intravenous administration of human-purified AAT was reported to reach total remission in 100% of cases (5). IV-AAT is safe and well-tolerated (2), although it is rather costly, as repeated intermittent or maintenance administration may be required (5). In practice, augmentation therapy is usually used when dapsone, with or without doxycycline, fails to achieve satisfactory remission (2,4,5). Additionally, panniculitis remains an off-label indication for IV-AAT (4). Alternative treatment options include liver transplantation and plasma exchange (5,7). Furthermore, there has been some contradictory evidence regarding the effectiveness of colchicine (13), whereas most antibiotics, immunosuppressants, non-steroidal anti-inflammatory drugs, and conservative therapy all failed to elicit a satisfactory response. All in all, further scientific evidence and detailed research into disease pathophysiology are needed to establish better cost-effective treatments (2,4,5).

In conclusion, a major limitation of our report is that it presents a single case, making generalization to a broader population difficult, if not impossible. Nevertheless, we believe it highlights a potential diagnostic

and management approach for such patients, though the strategy should be tailored to each patient individually. Furthermore, patients diagnosed with AATD should be closely monitored for associated conditions, particularly pulmonary and liver manifestations. More detailed recommendations on diagnostic algorithms and treatment can be found in the literature (14).

4 Conclusion

AATD-associated panniculitis is rare and often misdiagnosed, although proper management remains crucial, even lifesaving. The diagnosis should be established considering the clinical picture, the biopsy findings, and analytical data. It could be demanding to suspect the disease even in patients with previously recognized AATD. However, it should be kept in mind that panniculitis can also be the first clinical manifestation of the disorder. Had this been the case with our patient, the appropriate diagnosis would have most likely been established comparatively later, unfortunately at the cost of the patient's physical and mental well-being. Everything considered, we hope that this case report raises awareness and aids clinicians in reaching a timely diagnosis should they ever encounter panniculitis in AATD.

Ethics approval and consent to participate

The authors complied with the ethical requirements of their institutions.

Consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient.

Conflict of interest

None declared.

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