Alpha-1-Antitrypsin Deficiency Panniculitis

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KEYWORDS

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Alpha-1-antitrypsin (A1AT) deficiency panniculitis is an unusual diagnosis not only because of it being an infrequent cause of panniculitis but also because of its misdiagnosis. A1AT panniculitis is a well-established entity that usually presents clinically and histopathologically as an ulcerated panniculitis (mainly lobular panniculitis but with septal involvement) with remarkable tissue destruction. This autosomal recessive inborn error of metabolism was first described by Eriksson and colleagues in the 1960s. In 1972, Warter and colleagues[1] linked A1AT deficiency with some familial cases of Weber-Christian syndrome panniculitis. Finally, Rubinstein and colleagues[2] described the first two cases of A1AT deficiency–related panniculitis. A1AT panniculitis prevalence is equal in both sexes, and no racial predominance has been described. Its age of onset ranges from infancy to old age (7–73 years; mean age, 7.39 years).[3]

PATHOGENESIS

A1AT is the most important serine proteinase (responsible for 90% of total activity), and it consists of 394 amino acids organized into three beta-sheets and nine alpha-helices. The active site of the protein (reactive center loop) consists of 20 amino acids that induce conformational changes that lead to inactivation of serine proteases when they contact with A1AT.[4] A1AT inhibits several sera proteases, such as trypsin, chemotrypsin, neutrophilic neutral protease, neutrophilic elastase, pancreatic elastase, collagenase, factor VIII, plasmin, thrombin, kallikrein, urokinase, and cathepsin G. It also works to inhibit complement activation.

Approximately 90 allelic variants for the gene that encodes this protein (located in 14q32.1) have been described to date.[4] The most frequent allele, PiM, which is defined by its protein isoelectrophoretic mobility (M means medium mobility). The homozygous PiMM phenotype is associated with normal serum levels of A1AT (0.78–2 g/L).[5] Two alleles, PiS (slow mobility) and PiZ (very slow mobility), originated from a single nucleic acid substitution (in Z variant 342 position substitutes glutamic acid for lysine)[6] and are considered to be involved in pathologic manifestations. The homozygous phenotype for Z allele (PiZZ) is associated with very low serum levels of A1AT (0.187–0.385 g/L). The heterozygous phenotype for PiMZ or PiMS presents a discrete reduction of A1AT serum levels. A null allele variant (without any apparent gene alteration but with no detectable mRNA produced) has been described. In the homozygous Pi phenotype, null/null condition serum A1AT is not detectable at all.[7]

A heterozygous condition for A1AT (PiMS, PiMZ, PiSZ) is estimated to affect 10% of general population.[8] The Z heterozygous condition affects approximately 1 in 50 persons in the general population.[9] The homozygous PiZZ phenotype is

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present in approximately 1 in 3500 persons in the Northern Europe population.[6] In individuals who carry the S or Z allele, A1AT production and function are apparently normal, but only a small amount of A1AT enters the circulation from its production site on the liver. The mutation induces a high tendency to polymerize in Z variant and—to a lesser degree—in S variant (not only in homozygous but also in heterozygous phenotypes), and polymerized A1AT protein cannot be released from the liver. The slow electrophoretic mobility is also explained by the level of polymerization.

Under triggering situations such as smoking (emphysema), trauma (panniculitis),[3] and release of hepatotoxins (cirrhosis), the absence of this proteinase results in uncontrolled activation of lymphocytes and macrophages, lack of restraint for complement cascade (including C3a-C5a neutrophilic chemotactic factors), and accumulation of neutrophils that release proteolytic enzymes with uncontrolled secondary tissue damage.[10] Special vulnerability of the subcutis to proteolytic degradation in the absence of A1AT has been described based on the high density of fatty acids (typical of this tissue), which change elastin conformation and render it more sensitive to degradation.[11]

A1AT deficiency panniculitis can be found not only in homozygous PiZZ conditions but also in heterozygous ones (PiMS,[4,11] PiMZ,[12] PiSZ,[13] or even in PiSS[14]) and PiM_1M_1[15] homozygous variants, which suggests that other triggering agents must be present in addition to the A1AT phenotype. Some authors consider that patients with an abnormal phenotype (abnormal isoelectrophoretic mobility study) and normal A1AT level may develop panniculitis (mutant variants affect the reactive center loop without inducing polymerization but being nonfunctional or normal values secondary to the body's up-regulation caused by stress),[4,13] which emphasizes the importance of other factors yet to be identified.

CLINICAL MANIFESTATIONS

A1AT deficiency panniculitis presents as erythematous nodules and plaques located on wide areas of the lower extremities, arms, trunk, or face,[16] and it sometimes mimics cellulitis.[9] The lesions occur predominantly on the trunk and proximal extremities[11] and frequently develop ulcers that drain an oily material (**Fig. 1**).[16] Necrosis and hemorrhage also can be seen. Lesion healing is accompanied by atrophic scars. Chronicity and recurrence are common. Occasionally (one third of cases),[11] an antecedent of trauma at lesion locations is referred,

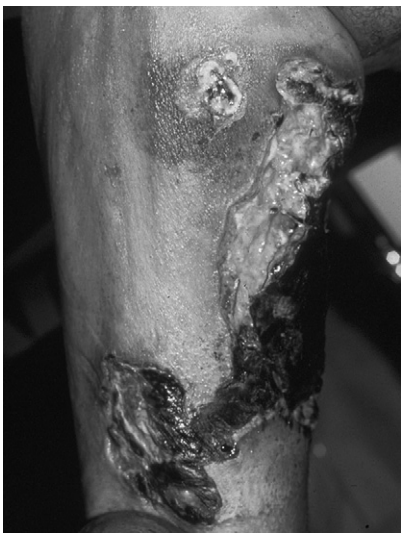

Fig. 1. Clinical appearance of panniculitic lesions on a patient with A1AT deficiency showing ulcers draining an oily material on the right thigh.

and surgical debridement[16] or even cryosurgery[17] can exacerbate tissue damage, although sometimes debridement may be necessary if severe infection is associated.[6] Other cutaneous manifestations associated to A1AT deficiency include vasculitis, acquired angioedema, psoriasis, atopic dermatitis, prurigo nodularis, and Marshall's syndrome (Sweet syndrome and cutis laxa).[5,18,19]

Visceral extension has been reported in two patients, one with involvement of perinephric fat and the other with hepatic and splenic sterile abscesses.[14] Systemic manifestations of A1AT deficiency include emphysema (panacinar), neonatal hepatitis, cirrhosis, pancreatitis, and membranoproliferative glomerulonephritis.[20] Fifty percent of patients who have the ZZ phenotype die from emphysema-related complications, and 10% develop liver disease. The PiMZ phenotype is associated with slightly increased risk of lung and liver disease; no increased likelihood of either lung or liver disease in patients who have PiMS has been found.[4] The null/null phenotype is accompanied by emphysema, but cirrhosis or liver cancer is not associated because there is no A1AT synthesis and no possible chronic damage because of its hepatic accumulation.[7]

HISTOPATHOLOGY

In the early stages, neutrophils extend into the reticular dermis and produce an infiltrate between the collagen bundles (splaying of neutrophils) (**Fig. 2**).[21] Secondarily there is dissolution of