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Rare Manifestations

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Rare manifestations

Alessandro N. Franciosi[1,2], Tomás P. Carroll [1,3] and Noel G. McElvaney[1,2]

AATD is usually diagnosed following pulmonary or hepatic manifestations; however, rarer presentations may alert clinicians to its presence. Of these, panniculitis and anti-neutrophilic cytoplasmic autoantibody (ANCA)-positive vasculitis are the most commonly reported. Panniculitis is a histopathological finding from skin biopsies attributable to many causes. However, lobular fat necrosis with dense neutrophil infiltration on biopsy may represent AAT-related disease, a subtype associated with significant morbidity and frequent relapses. Treatment with doxycycline, dapsone and AAT replacement therapy have all shown reliable effect, with the latter particularly effective in refractory disease. A significant body of work has been performed examining the role of AATD variants in ANCA vasculitis. The association between antibodies against both myeloperoxidase and proteinase (PR)3 (both neutrophil derived) and AATD has been shown to be significant, with clear evidence of over-representation of the AATD variants in ANCA vasculitis cohorts. While *in vitro* mechanistic evidence exists demonstrating a role for AAT replacement in anti-PR3 positive disease, there is little evidence for its use *in vivo*. In addition to these two conditions, AATD has also been associated with other systemic illness but the associations are as yet not fully proven.

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Rare manifestations of AATD such as panniculitis and ANCA vasculitis can be among the most fulminant presentations of the condition. Awareness of their relationship to AATD will allow clinicians to recognise them and make informed therapeutic choices.
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While lung and liver disease are the most commonly encountered clinical consequences of AATD, this chapter focuses on other, rarer manifestations of AATD such as panniculitis and anti-neutrophilic cytoplasmic autoantibody (ANCA) vasculitis. Though rare, these manifestations can represent the most fulminant complications of AATD and, if untreated, may have lethal outcomes. Fortunately, effective treatments, though not all universally accessible, are available. The role of AAT as a potent immuno-modulator is likely to be central to these issues. This chapter also touches on other less well documented disease associations with AATD.

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AATD and panniculitis

Background

The first two reports of painful subcutaneous nodules and atrophy of the subcutaneous fat with associated inflammation occurred independently in the 1920s, by Frederick Parkes Weber and Henry Asbury Christian. Both described the entity as "panniculitis" though this constellation of findings subsequently garnered the eponym "Weber–Christian disease". Over 50 years later, and a decade after the discovery of AATD [1], the first association between panniculitis and proteases inhibitor deficiency occurred in France in 1972, when WARTER *et al.* [2] reported a case describing a 47-year-old female with relapsing Weber–Christian disease and associated low serum trypsin-inhibitory capacity. Moreover, her three children were also found to have reduced inhibitory capacity of trypsin in serum, and the patient's sister had died aged 54 years, with an apparent history of severe lung disease. The subsequent decades saw increasing numbers of reports of Weber–Christian disease associated with AATD, by then being specifically described by phenotype.

Features

The eponym Weber–Christian disease has gradually fallen out of favour, with descriptors of specific clinical and histopathological features now being preferred. The classic description of AATD-associated panniculitis is that of tender, nodular, often ulcerating skin lesions most commonly described on the trunk, arms and groins. Skin biopsy requires sufficient sub-epidermal fat tissue and classically reveals neutrophil-predominant, lobular fat necrosis and absence of vascular damage, though a mixture of lobular and septal patterns are often seen [3].

The incidence in severe AATD is estimated at 0.1–0.9% [4, 5], and as such it represents a rare manifestation of an already rare condition. In the National Heart Lung and Blood Institute AATD registry only one out of 1129 study subjects reported panniculitis [6].To date, approximately 85 cases of panniculitis associated with AATD have been described (table 1), occasionally manifesting as just one of a number of inflammation dependent phenomena presenting in complicated clinical cases [47, 52]. Recognition of the role of AATD in such cases can be the breakthrough that leads to successful treatment.

Whether the association between heterozygous AATD and panniculitis is incidental or causal has not been fully elucidated. Most reports feature single cases, and only one review of AATD prevalence in biopsy proven panniculitis cohorts has been published to date [19]. This single centre review retrospectively reported 15 cases of AATD diagnosed in 96 biopsy proven cases of panniculitis, demonstrating a clear over-penetrance compared to normal populations. A further retrospective review from the same centre some 30 years later [54] reported 10 cases of AATD-associated panniculitis, with phenotypes being PI*ZZ (n=5), Pi*MZ (n=2), Pi*SZ (n=1) and Pi*MS (n=1) and Pi*M/?Null (n=1). This distribution of phenotypes, with the Pi*ZZ phenotype predominating, has been reported in previous reviews of the topic [5, 40]. Though cases of panniculitis associated with heterozygous forms of AATD have been described [23, 28, 48], they are more frequently associated with clear precipitating triggers than in Pi*ZZ individuals [37, 39].

Reviewing the cases published to date it would appear that the very mildest (Pi*MS) forms of AATD are not overrepresented in this cohort. Detecting the MS phenotype of AATD in the

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Table 1. List of reported AATD-associated cases of panniculitis to date

First author [ref.]	Year	n	Genotype/phenotype	Sex	Age years
Warter [2]	1972	1	N/A	F	47
Rubinstein [7]	1977	2	Pi*ZZ, N/A	M=2	36, 32
Guilmot [8]	1980	1	Pi*N/A	N/A	N/A
Olmos [9]	1981	1	Pi*MZ	M	51
Balk [10]	1982	1	Pi*ZZ	M	49
Clark [11]	1982	2	Pi*ZZ, Pi*ZZ	M=2	29, 36
Pottage [12]	1983	1	N/A	N/A	N/A
Bleumink [13]	1984	1	Pi*ZZ	F	35
Lonchampt [14]	1985	1	Pi*ZZ	F	47
Bleumink [15]	1985	1	Pi*ZZ	F	44
Viraben [16]	1986	1	Pi*ZZ	M	36
Smith [17]#	1987	3	Pi*ZZ, Pi*ZZ, Pi*ZZ	F=3	65, 36, 35
Hendrick [18]	1988	3	Pi*ZZ, Pi*ZZ, Pi*ZZ	M=2, F=1	24, 7, 33
Smith [19]	1989	15	N/A	N/A	N/A
Irvine [20]	1990	1	Pi*ZZ	M	30
Humbert [21]	1991	3	Pi*MS, Pi*MS, N/A	F=2, M=1	73, 50, 73
Edmonds [22]	1991	1	Pi*ZZ	F	13
Pinto [23]	1993	1	Pi*SS	M	22
Martinon Sanchez [24]	1993	1	Pi*ZZ	F	11
Traulsen [25]	1994	1	Pi*ZZ	F	56
Furey [26]#	1996	1	Pi*ZZ	F	62
O'Riordan [27]#	1997	1	Pi*ZZ	F	62
Gaillard [28]	1997	1	Pi*MZ	F	31
Linares-Barrios [29]	1998	1	N/A	F	53
Loche [30]	1999	1	Pi*MS	F	16
Werner [31]	1999	1	Pi*ZZ	F	61
Filaci [32]	2000	1	Pi*ZZ	F	33
Albes [33]	2001	3	Pi*MS, Pi*MZ, Pi*ZZ	F=3	16, 40, 56
Chang [34]	2001	1	Pi*SZ	F	16
Voigtlander [35]	2001	1	Pi*ZZ	F	37
Chowdury [36]#	2002	1	Pi*ZZ	F	33
Rajagopal [37]	2002	1	N/A (level 50 mg·dL^{-1})	F	48
Kjus [38]#	2003	1	Pi*ZZ	F	21
Parr [39]	2003	1	Pi*ZZ	F	34
Geraminejad [40]	2004	2	Pi*MS,Pi*MS	M=1, F=1	42, 43
Ortiz [41]	2005	1	Pi*ZZ	F	52
Gross [42]#	2009	1	Pi*ZZ	F	31
Fernandez-Torres [43]	2009	1	Pi*ZZ (acquired by liver transplant)	F	56
Al Niaimi [44]#	2011	1	Pi*ZZ	M	16
Olson [45]#	2012	1	Pi*ZZ	M	36
Laureano [46]	2014	1	Pi*MS	F	55
Elsensohn [47, 48]#	2015	1	Pi*ZZ/, Pi*FZ	F	36, 71
Cathomas [49]	2015	1	Pi*ZZ	M	50
Vigl [50]#	2015	1	Pi*MZ	F	38
Eckhard [51]#	2015	1	Pi*ZZ	M	54
Franciosi [52]#	2015	1	Pi*ZZ	M	23
Storan [53]#	2017	2	Pi*ZZ, Pi*ZZ	F=2	24, 38
Johnson [54]#	2018	10	Pi*ZZ (n=5), Pi*SZ (n=1), Pi*MZ (n=2), Pi*MS (n=1), Pi*M/?(n=1)	F=7, M=3	Mean 35 (18–58)
Jouhadi [55]	2018	1	Q0Cairo/Q0Cairo	F	17
Lopes [56]	2018	1	N/A (level 51.8 mg·dL^{-1})	M	49

#: cases treated with intravenous AAT augmentation as monotherapy or adjuvant therapy. F: female; M: male; N/A: AAT typing results not available at time of review or not performed.

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setting of panniculitis may represent a serendipitous diagnosis, though the similarity in histopathological features between this phenotype and more severe Pi*ZZ AATD skin biopsies give credence to a possible shared mechanism.

Pathogenesis

AATD-associated panniculitis has usually been reported to occur spontaneously (or following minor skin trauma) in the setting of severe deficiency, or in combination with an identifiable precipitant in moderate deficiency states.

Over time, the increasing association between cases of neutrophilic necrotising panniculitis and protease deficiency, along with the early recognition of the anti-protease capacity of AAT, led to the hypothesis that an imbalance in protease/anti-protease activity was centrally implicated in the occurrence of this rare skin manifestation. Certainly, the fact that many patients with refractory necrotising disease were found to respond clinically to intravenous AAT augmentation therapy reaffirmed this belief. Furthermore, cases have been reported of patients developing panniculitis following receipt of a Pi*ZZ transplanted liver [43], and of patients having pre-existing panniculitis resolve following receipt of a normal Pi*MM liver transplant [27]. Notwithstanding all this, growing knowledge about the immunomodulatory properties of AAT give us further clues as to other potential mechanisms, which may precipitate or facilitate the development of a proteolytic milieu in the skin.

Whilst it has been known for many years that carriage of the Pi*S or Pi*Z alleles of AAT result in reduced circulating levels of AAT [57, 58], reduced anti-NE capacity and reduced association rates with NE [59, 60], Z AAT and Z-polymers have also been shown *in vitro* to act as both a direct and indirect neutrophil chemoattractant (figure 1) [61, 62]. In 2009, Gross *et al.* [42] reported their finding of Z AAT polymers in skin biopsy tissue, alongside immunoglobulin (Ig)M and complement C3.

Part of the mechanism for increased neutrophil chemotaxis is explained by disruption in the ability of AAT to bind interleukin (IL)-8, preventing the latter from interacting with CXCR1 on neutrophil membranes (figure 2). Neutrophils isolated from AAT deficient individuals demonstrate increased chemotactic response to IL-8, and this finding is normalised by treatment of the deficient individuals with intravenous AAT augmentation. Previous studies have demonstrated that neutrophil influx into the lungs in increased in AAT deficient individuals [61, 63], and this may be reflective of mechanisms in the skin as well.

Further promotion of neutrophil chemotaxis may be driven by the impact of AAT deficiency on regulation of TACE. Neutrophil engagement with soluble immune complexes leads to increased TACE activity. The subsequent release of the glycosylphosphatidylinositol-anchored Fc receptor (FcγRIIIB), has been shown to play a role in neutrophil chemotaxis. *In vitro*, the addition of AAT was shown to modulate TACE activity, thus preventing the release of membrane FcγRIIIB [62] (figure 3).

Compounding the cyclical process of AATD-mediated inflammation, leukotriene (LT)B_4 has been shown to affect neutrophil adhesion, chemotaxis and ultimately degranulation [64–66]. The released NE has been shown to signal back to the neutrophil, increasing

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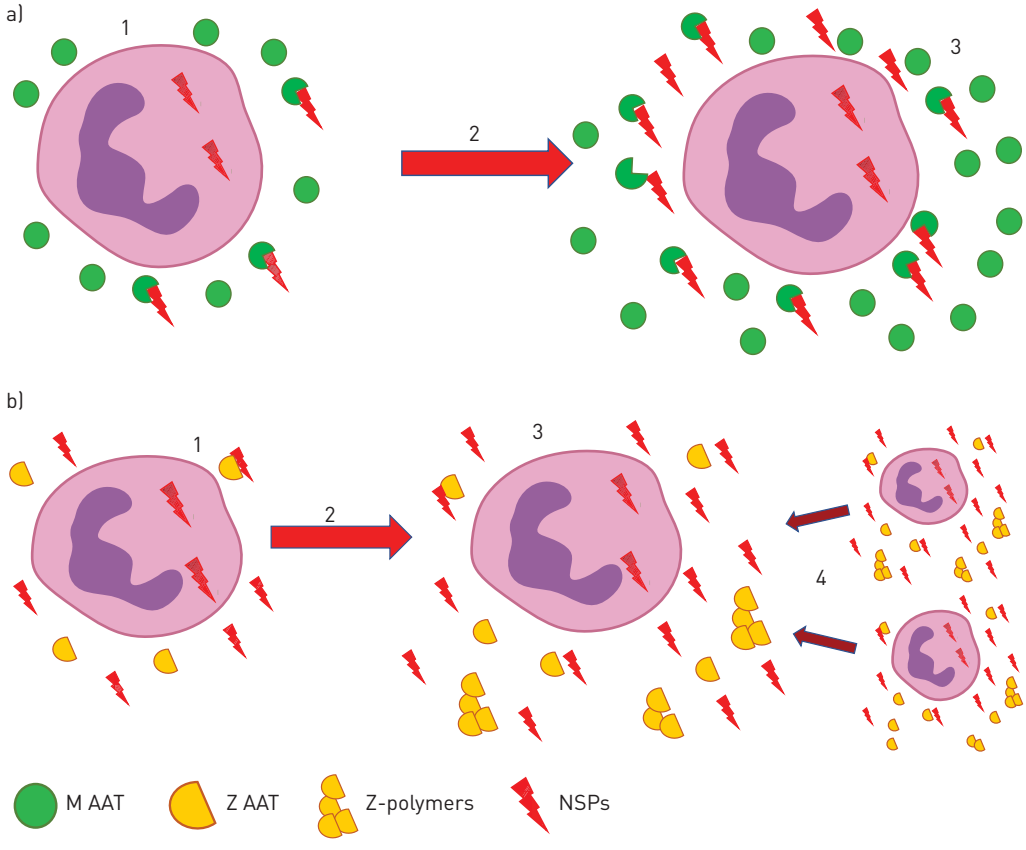

Figure 1. a) In Pi*MM plasma (1), baseline neutrophil serine protease (NSP) activity is easily balanced out by abundant AAT. Following neutrophil activation (2), release of NSPs increases the proteolytic potential of the peri-cellular space, with an eventual rise in AAT synthesis restoring the antiprotease balance (3). b) In Pi*ZZ plasma (1), the baseline plasma antiprotease potential is reduced. Activation of neutrophils (2) results in exaggerated NSP release, greater proteolytic radius and reduced rate of NSP abrogation (3). The presence of Z-polymers further exacerbates the protease burden by attracting more neutrophils (4). Figure partially created with BioRender.com.

production of LTB_4, upregulation of its receptor BLT1 on the neutrophil membrane, and in turn, propagating the cycle of inflammation and neutrophil recruitment. The inflammatory effects of LTB_4 have been shown to be strongly inhibited by AAT *in vitro* (figure 4). This inhibition occurs by binding of LTB_4 to a central hydrophobic pocket on the AAT protein surface, thereby preventing engagement of BLT1 on the neutrophil plasma membrane.

Further evidence of the ability of AAT to modulate degranulation was shown in a study examining the expression of TNF-α in AATD individuals, and the subsequent impact of the addition of exogenous AAT *in vitro* [67]. TNF-α expression in circulating neutrophils of AAT deficient individuals was shown to be elevated to levels comparable to rheumatoid arthritis patients. Subsequent *in vitro* studies demonstrated the effectiveness of AAT in reducing secondary and tertiary neutrophil granule release, thereby blocking TNF-α interaction with TNF receptors, reducing the downstream signalling required for degranulation.

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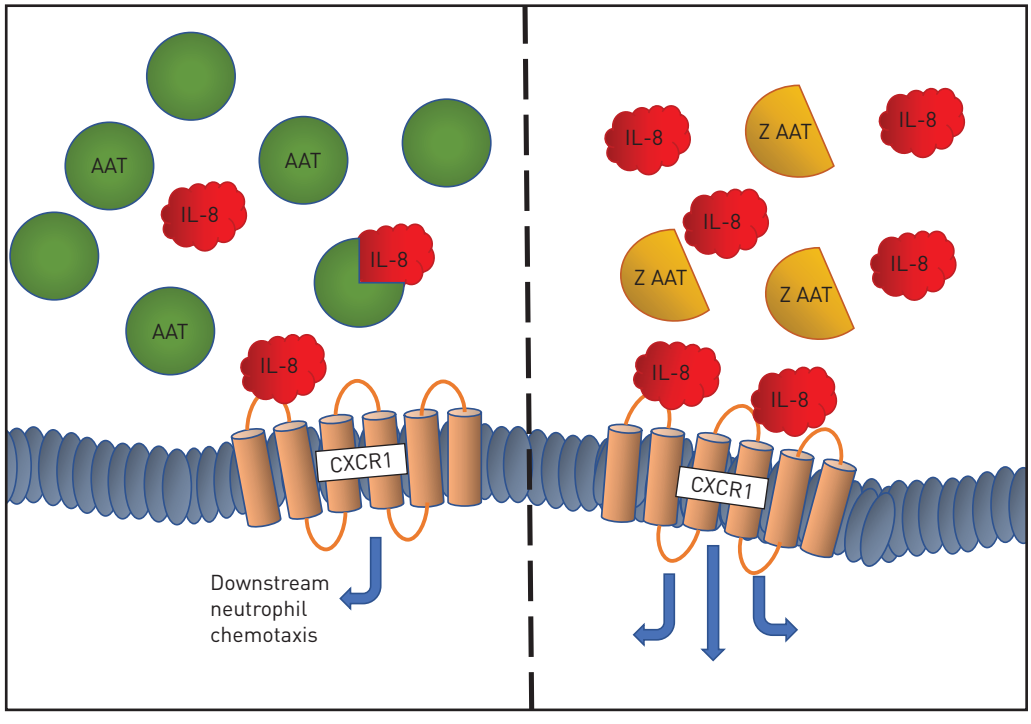

Figure 2. Normal binding of interleukin (IL)-8 is disrupted in Z AAT, allowing greater interaction of IL-8 with CXCR1.

Diagnosis

The likelihood of a diagnosis of AATD-related panniculitis is clinician dependent. Whilst AATD testing is specifically recommended in the workup of panniculitis [68–70], these guidelines are not published by dermatology societies. As the clinical specialty most likely to encounter severe cases of panniculitis, it is essential that dermatologists be aware of the technical modalities available for AATD testing. Testing for AATD remains low even among lung physicians [71]. Specific guidelines published by dermatology societies may improve uptake of testing for AATD in panniculitis and help clarify the true prevalence of deficiency in this cohort.

Full thickness incisional skin biopsies should be performed in the first instance to definitively establish the presence of panniculitis. Where possible, these should be performed in the setting of active inflammation, and should be of sufficient depth to adequately inspect the subdermal fat layer [3]. One series comparing histological findings in four confirmed cases of AATD-related panniculitis reported the shared features to be large areas of normal panniculus adjacent to severe necrotic panniculitis, with replacement of fat lobules by extensive neutrophil infiltration causing necrosis [72]. Furthermore, haemorrhage at the periphery of acute panniculitis was seen, alongside proliferation of histiocytic cells and lipophages. Whilst some evidence of secondary leukocytoclastic vasculitis may be seen in areas of necrosis and inflammation, no evidence of primary vasculitis should be present in classic AATD panniculitis. Direct immunofluorescence of tissue has also demonstrated C3 deposition in the blood vessels of the panniculus and/or the dermis, and IgM present in blood vessels (figure 5).

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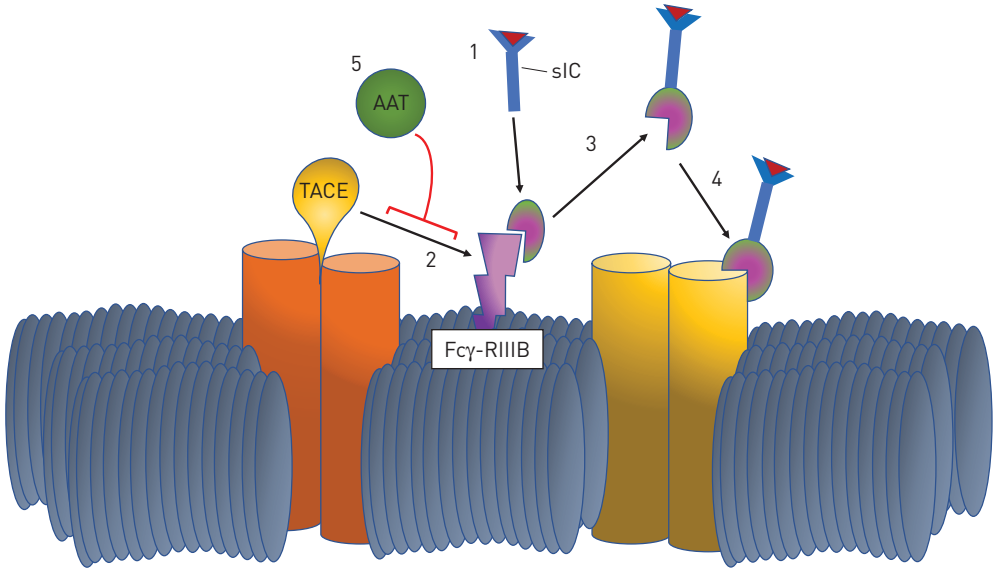

Figure 3. Neutrophil interaction with soluble immune complexes (sIC) (1) increases TACE activity (2) leading to the release of $F_{c\gamma}$-RIIIB (3) and the activation of a number of pathways which play a role in neutrophil chemotaxis (4). AAT (5) has been shown to modulate TACE activity.

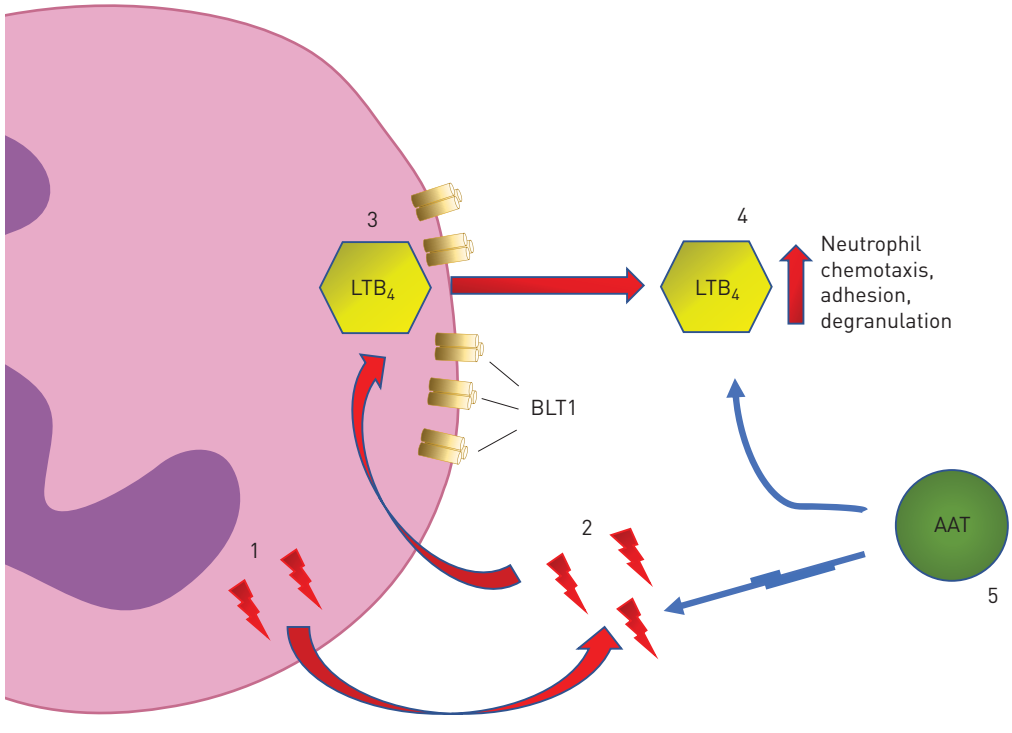

Figure 4. NE is released from the neutrophil (1). NE signals back to the cell (2) resulting in increased leukotriene (LT)B_4 production and BLT1 upregulation (3), with downstream effects on neutrophil function (4). The addition of exogenous AAT inhibits LTB_4-mediated cell signalling (5). Partially created with BioRender.com.

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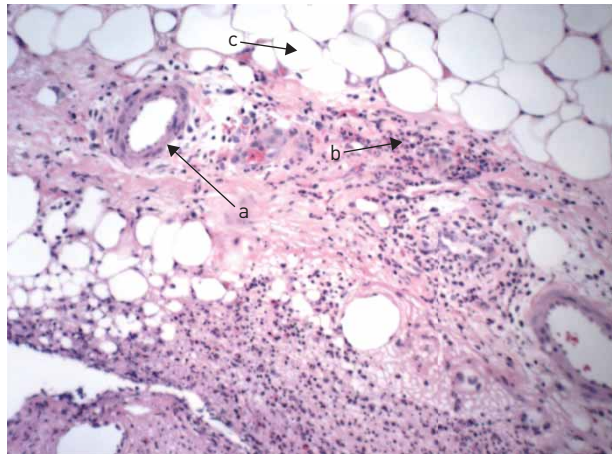

Figure 5. Skin biopsy from a 23-year-old Pi*ZZ AATD male. Haematoxylin and eosin showing a blood vessel (a) surrounded by dense neutrophil infiltrate (b) and fat necrosis (c).

Once AATD is suspected, testing for AATD should be performed according to local algorithms, but should include diagnostic methodologies such as phenotyping or genotyping [73]. Given the likely coexistence of systemic inflammation and panniculitis at the time of investigation, screening for AATD by measurement of serum levels should be avoided, given the risk of transiently elevated AAT in the acute phase response, leading to a falsely reassuring test [74].

Management

The relapsing nature of AATD-related panniculitis is such that expectant management is rarely satisfactory. Many cases, presenting in an advanced stage, feature ulceration and serous discharge, causing pain and risk of further irritation and infection. Rarely, the nature of the presentation is complicated by other clinical features, equally if not more critical than the panniculitis itself [47]. In one review of 42 reported cases of panniculitis [40], three patients, all <50 years of age (mean age 29 years), died within 2 years of diagnosis, with treatment-refractory disease being a feature common to all cases. These deaths all occurred in the 1970s and early 1980s, at a time when the mechanisms of not just panniculitis, but AATD in general were still being elucidated.

Classical therapy

Initial treatments focused on glucocorticoid treatment and antibiotics, and favourable results have been achieved with doxycycline, possibly owing to its putative anti-collegenolytic properties [75]. As such, it is worth considering doxycycline, and other tetracyclines as a credible alternative monotherapy or adjuvant therapy to current first-line options. Use of minocycline [40], colchicine [46, 53], prednisolone and a host of antimicrobials have all been described, with varying degrees of effectiveness.

To date, the most efficacious oral treatment for remission of disease and ongoing maintenance is dapsone, usually prescribed at a dose of 50–100 mg per day. The beneficial effects of dapsone in AATD are attributed to possible modulation of reactive oxygen

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species generation, neutrophil adhesion, TNF-α levels and IL-8 mediated neutrophil chemotaxis [76]. Unfortunately, patient tolerance can be an issue, side-effects of dapsone are common, and glucose-6-phosphate-dehydrogenase deficiency should be ruled out prior to initiation of therapy.

Intravenous augmentation therapy

In 1987, intravenous purified pooled human AAT (Prolastin®) was approved for the treatment of AATD-associated emphysema [77]. That same year saw the first successful treatment of two cases of AATD-associated panniculitis, with both patients achieving remission [17]. Over the intervening decades, *i.v.* AAT augmentation has been used at least 15 times for the treatment of AAT-associated panniculitis, repeatedly demonstrating efficacy (table 1), though the sporadic and rare nature of the disease has not allowed for formal clinical trials.

Summary of therapy

Whilst numerous therapies have been tried in AATD-associated panniculitis, only plasma exchange, liver transplantation, dapsone and *i.v.* AAT augmentation have demonstrated effectiveness >50% of the time, with only the latter two in sufficient numbers of cases to consider them reliable in this condition.

Of these, dapsone is clearly the most cost-effective and practical, especially when compared with *i.v.* AAT augmentation [5, 42], prompting many clinicians to consider it as first-line treatment, though the evidence for the latter is highly compelling given its frequent successful use as a second-line agent following non-response to oral agents including dapsone in many reported cases [17, 38, 44, 45]. Furthermore, AAT augmentation provides the dual benefit of control of skin disease, along with long-term benefits to lung health in patients with severe AATD [78].

Consequently, given the variability in availability, cost and patient tolerance for each of the treatments, the single best therapeutic option varies in each case.

Long-term outcomes in panniculitis are not well documented, with clear follow-up times only presented in some case reports but generally remission is achieved, with episodic relapses commonly described, especially in those patients not receiving *i.v.* augmentation therapy.

ANCA vasculitis

ANCA vasculitis is a severe autoimmune disease comprising of three distinct sub-entities: granulomatosis with polyangitis (GPA), microscopic polyangiitis and, less frequently, eosinophilic granulomatosis with polyangiitis (EGPA). ANCA-associated vasculitides are often life-threatening emergencies, frequently resulting in significant morbidity with pulmonary haemorrhage and renal failure being the disease defining findings. These entities are associated with high mortality, onerous treatment regimens and significant relapse rates.

The detection of antibodies against proteinase 3 (PR3) or myeloperoxidase (MPO) is highly suggestive of ANCA vasculitis, especially in conjunction with evidence of end organ

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damage. GPA is classically associated with airway granulomatous disease and with PR3 ANCA vasculitis in most cases, but can present with MPO antibodies in a subset of patients. Conversely, microscopic polyangiitis lacks granulomatous features and is associated with MPO antibodies in most cases, but less frequently PR3 antibodies [79]. The rarer entity of EGPA is frequently antibody-negative, associated with eosinophilia in tissues and blood, and characterised by asthma, rhino sinusitis, skin disease, neuritis, cardiac and renal disease. The presentation of EGPA is often surreptitious, with the emergence of the respiratory components often preceding the other end organ diseases by many years [80].

ANCAs and AATD

The association between AATD and ANCA vasculitis has been suggested for some time, not only due to the association of antibodies against PR3 (a neutrophil-derived serine protease targeted by AAT) [81] and MPO (derived from the neutrophil primary granule), with ANCA vasculitis, but also due to evidence of over-representation of AATD phenotypes in PR3-ANCA-positive vasculitis cohorts [82–85]. Prevalence estimates for the Pi*Z allele in PR3-ANCA-positive vasculitis individuals varies between 5.6% and 17.6%, far exceeding the frequency in non-AATD population (3–9-fold) [86]. Furthermore, there is evidence to suggest that AAT deficient phenotypes within ANCA vasculitis cohorts display different phenotypic features of disease, with pulmonary haemorrhage more being common in AATD individuals [83, 87, 88].

In a 2012 landmark genome-based study [89] it was shown that SERPINA1 single nucleotide polymorphisms had a significant association with PR3 ANCA GPA and PR3 ANCA microscopic polyangitiis, but not MPO-positive ANCA subtypes. Further genetic associations have subsequently been demonstrated between SERPINA1 and PR3 ANCA [90]. It has also been suggested that the excess of unbound and uninhibited free PR3 occurring due to increased neutrophil burden in AATD may represent a persistent stimulus which in fact drives autoantibody production against PR3 [84].

Moreover, there is evidence to suggest a possible role for AAT in attenuating PR3 ANCA mediated neutrophil burst [91]. The addition of exogenous AAT to TNF-α primed neutrophils prior to the addition of a monoclonal PR3 antibody prevents binding of the antibody to PR3 on the neutrophils and results in a subsequent 47% reduction in anti-PR3 induced activation.

The link between MPO ANCA vasculitis and AATD is less well defined. Cases of MPO ANCA vasculitis and occasional rarer forms of vasculitis have been described in AATD [92, 93]. One large meta-analysis demonstrated an association with both the Pi*S and Pi*Z allele with ANCA vasculitis, as well as an association with MPO and PR3 ANCA [90], other studies have only demonstrated an association with the Pi*Z allele and PR3 ANCA vasculitis [89].

Despite the demonstrated links between AATD, PR3 expression, anti-PR3 antibodies and the emergence of PR3 ANCA vasculitis, to date no clinical trial has examined the use of *i.v.* AAT augmentation in ANCA vasculitis. A single case report describes treatment of PR3 ANCA microscopic polyangiitis with *i.v.* AAT and oral glucocorticoids in an 84-year-old woman presenting with pulmonary infiltrates, renal failure and skin lesions on a background of known Pi*ZZ AATD. In light of the patient's renal impairment, initial treatment was limited to 3 days of methylprednisolone, resulting in improvement of pulmonary infiltrates, renal

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function and a normalisation of PR3 titres. Due to concerns regarding the patients' medical comorbidities, monotherapy with oral prednisolone was continued and tapered over a month during which improvements in renal indices plateaued. Subsequently, *i.v.* AAT was added to glucocorticoids in an attempt to avoid cyclophosphamide. Further improvement in renal indices and a resolution of skin lesions was associated with initiation of AAT augmentation and no relapse of vasculitis during follow-up [94].

As discussed previously, ANCA vasculitis is associated with poor outcomes and end organ disease, with 5 year mortality >25% [95]. Treatment options include glucocorticoids in combination with cyclophosphamide or rituximab for induction of remission in life-or-organ threatening disease or, less commonly, glucocorticoids with methotrexate in non-threatening disease. Nonetheless, relapse rates are high [96, 97]. Increasing evidence of the role for *i.v.* AAT as a potent immune-modulator *in vivo* in other refractory autoimmune conditions [88, 98] raises the possibility that it may yet have a role in ANCA vasculitis.

Other less common associations with AATD

A number of studies have linked AATD and rheumatoid arthritis. Some have shown an increased frequency of AATD phenotypes in patients with rheumatoid arthritis compared to population frequencies [99, 100], while others have shown a more severe phenotypic and immunologic expression of rheumatoid arthritis in AATD individuals, specifically Pi*MZ [101]. In the setting of AATD-related chronic liver disease, renal impairment has been observed in children and young adults. In these studies, a relatively high prevalence of mesangio-capillary glomerulonephritis was noted in children with AATD and chronic liver disease [102, 103]. In addition to these conditions, AATD has also been reported in association with a large number of other conditions but in small numbers and with little clear evidence of causality and effect. These associations include gastrointestinal disorders such as pancreatitis [104, 105], inflammatory bowel disease, coeliac disease and peptic ulcer disease [106–110], in addition to diabetes [111], aneurysms [112] and conflicting data concerning coronary atherosclerosis risk [113–115]. Linkages have been sought with fibromyalgia [116–118], though the evidence is mixed, with some studies failing to show strong links with AATD [119] and a small negative trial of the use of augmentation therapy in fibromyalgia [120]. As such, it should be borne in mind that many of these associations are tenuous and require further investigation.

Our understanding of AATD has changed over the past number of years, mainly due to an increased realisation of the role of AAT as an anti-inflammatory. AATD is significantly involved in panniculitis and vasculitis and may be involved in other inflammatory conditions but the evidence for these involvements is less clear and requires further evaluation.

Conclusion

As discussed previously, panniculitis and vasculitis associated with AATD, whilst rare, can in fact be the most fulminant and clinically severe consequences of the condition. Given the acute inflammatory response likely to be present in such cases, serum AAT levels may be significantly elevated and therefore an unreliable screening or diagnostic test in such settings. In such instances, genotyping and/or phenotyping should be requested for

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accurate diagnosis. Clinicians should be aware of the possibility of AATD in the setting of panniculitis, and more specific dermatology guidelines for AATD testing in this setting would be welcome.

Finally, the growing evidence surrounding the immunomodulatory effects of AAT may lead to greater evidence of associations between AATD and other diseases, whilst also offering potential new therapeutic roles for AAT augmentation.

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Disclosures: N.G. McElvaney reports that he has been on advisory boards for CSL Behring, Grifols and Shire on intravenous augmentation therapy for pulmonary manifestations of AATD, and with Arrowhead and Alnylam for liver manifestations of AATD, but that he has had no involvement with any company with regard to treatment of vasculitis and panniculitis associated with AATD.

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