Review

Primary and secondary autoimmune neutropenia

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Abstract

Antineutrophil antibodies are well recognized causes of neutropenia, producing both quantitative and qualitative defects in neutrophils and increased risk for infection. In primary autoimmune neutropenia (AIN) of infancy, a moderate to severe neutropenia is the sole abnormality; it is rarely associated with serious infections and exhibits a self-limited course. Chronic idiopathic neutropenia of adults is characterized by occurrence in late childhood or adulthood, greater prevalence among females than among males, and rare spontaneous remission. Secondary AIN is more commonly seen in adults and underlying causes include collagen disorders, drugs, viruses and lymphoproliferative disorders. In most patients with AIN, antibodies recognize antigens located on the IgG Fc receptor type 3b but other target antigens have been recently identified in secondary AIN. Granulocyte colony-stimulating factor is a proven treatment in patients with AIN of all types and is now preferred to other possible therapies.

Introduction

The term 'neutropenia' is used to define a condition in which circulating neutrophils number less than 1500/μl. Neutropenias can be classified according to the mechanism of induction, and so there are forms due to decreased production of neutrophils, to sequestering of neutrophils from endothelial or tissue pools, and to increased peripheral destruction of neutrophils. It is perhaps more useful for purposes of differential diagnosis to distinguish between congenital and acquired forms, the latter being subdivided according to their pathogenesis or aetiological agent (Table 1).

Regardless of the cause, the clinical result of neutropenia is always an increased infective diathesis, with frequency and severity that are directly proportional to the degree of neutropenia. This is considered mild when the neutrophil count is between 1000 and 1500/μl, moderate when it is between 500 and 1000/μl, and severe when it is less than 500/μl. Other factors may influence the severity of the infective diathesis in a neutropenic patient: the speed of onset and the duration of the neutropenia, the bone marrow myeloid reserves, the absolute circulating monocyte count and the functional status of phagocytes.

Immune mediated neutropenias (Table 1) involve a low neutrophil count resulting from increased peripheral destruction due to antibodies directed against the cell membrane antigens. The field of immune mediated neutropenias includes various conditions such as alloimmune neutropenias (caused by maternal–fetal incompatibility or transfusion reactions) and true autoimmune forms. This review focuses on the true autoimmune forms, which may be primary (i.e. not associated with other pathologies) or secondary (usually to autoimmune or haematological diseases).

Autoimmune neutropenias: pathogenesis and diagnostic tests

The first convincing evidence that antineutrophil autoantibodies could cause neutropenia was presented in 1975, when Boxer and coworkers [1] described five cases caused by antineutrophil antibodies that facilitated phagocytosis of opsonized neutrophils by splenic macrophages, and altered some functional features of neutrophils. In the same year, Lalezari and coworkers [2] showed that, to some extent, autoantibodies could cause chronic neutropenia. Earlier experiments conducted by Lawrence and coworkers [3] and Simpson and Ross [4] had already demonstrated the importance of antineutrophil autoantibodies in causing neutropenia; those investigators showed that infusion into guinea pigs of rabbit anti-guinea-pig neutrophil antibodies caused neutropenia, as a result of phagocytosis of opsonized neutrophils by splenic and bone marrow macrophages. In humans autoantibodies also play a major opsonizing role – possibly the main one – in inducing autoimmune neutropenia (AIN) [1,5].

AIN = autoimmune neutropenia; FasL = Fas ligand; FcγR = Fcγ receptor; G-CSF = granulocyte colony-stimulating factor; GIFT = granulocyte immunofluorescence test; HNA = human neutrophil antigen; LGL = large granular lymphocyte; SLE = systemic lupus erythematosus.

Table 1

Classification of neutropenia

Type of neutropenia	Neutropenias
Congenital	Severe infantile agranulocytosis (Kostmann's syndrome)
	Shwachman–Diamond–Oski syndrome
	Myelokathexis/neutropenia with tetraploid nuclei
	Cyclic neutropenia
	Chediak–Higashi syndrome
	Reticular dysgenesis
	Dyskeratosis congenita
Acquired	Postinfectious neutropenia
	Drug-induced neutropenia
	Complement activation (haemodialysis, leukapheresis, ARDS)
	Immune neutropenia
	Isoimmune neonatal neutropenia
	Alloimmune neutropenia (transfusion reaction)
	Autoimmune neutropenia – primary
	Benign of childhood
	Adult chronic form
	Autoimmune neutropenia – secondary
	Autoimmune diseases
	Large granular lymphocyte
	Other (see Table 3)
	Pure white cell aplasia
	Chronic idiopathic neutropenia
	Hypersplenism
	Nutritional deficiency (vitamin B_{12} or folate deficiency)
	Diseases affecting the bone marrow
	Postchemotherapy
	Aplastic anaemia
	Fanconi anaemia
	Myelodysplastic syndrome
	Acute and chronic leukaemia

ARDS, acute respiratory distress syndrome.

The lack of close relation between the degree of neutropenia and the levels of circulating autoantibodies [6] has been attributed to various factors. The additional opsonizing activity of complement, activated by antineutrophil autoantibodies, may amplify phagocytosis [7]. Alternatively, the functional status of the phagocytic system may render clearance of the opsonized cells more or less effective [6]. Another important point is that in some cases the capacity of autoantibodies to induce neutropenia is related to their ability to recognize antigenic determinants expressed not only by mature cells but also by bone marrow myeloid precursors [8]. In such cases the severe neutropenia is accompanied by bone marrow hypoplasia, with maturational arrest and a significant infective diathesis.

From the diagnostic point of view, the various methods for detecting antineutrophil autoantibodies suffer from different limitations and so they are not entirely comparable. These limitations help to account for the different percentages of patients positive for antineutrophil autoantibodies reported in case series of AIN. No single method can identify all possible antineutrophil autoantibodies [9,10]. The Second International Granulocyte Serology Workshop [11] suggested that a minimum of two methods be used to detect antineutrophil autoantibodies: the granulocyte agglutination test and the granulocyte immunofluorescence test (GIFT). The granulocyte agglutination test is used to check whether a serum sample sensitizes and therefore agglutinates control neutrophils. The main limitation of this test is that neutrophils tend to agglutinate spontaneously. The direct GIFT detects autoantibodies bound to patient's neutrophils, using fluorescinated human anti-immunoglobulin antibodies. The test suffers from the difficulty of obtaining enough cells from a neutropenic patient; furthermore, considerable observer experience is required to recognize the autofluorescence typical of activated neutrophils, and because of the false-positive results due to immune complexes bound to Fcγ receptor (FcγR)II or FcγRIII and the possible presence of antineutrophil alloantibodies.

For the indirect GIFT the patient's serum is placed in contact with control neutrophils, and autoantibodies are then detected using a fluorescinated human anti-immunoglobulin antiserum. This test also suffers from possible false-positive findings due to immune complexes and antineutrophil alloantibodies. These methodological difficulties can be overcome by using the MAIGA (monoclonal antibody-specific immobilization of granulocyte antigen) assay [12], which uses specific monoclonal antibodies to capture neutrophil membrane antigens that have bound human antibodies, thus circumventing the interference from alloantibodies or immune complexes. The assay, which is not routinely available, has been used to identify antibodies against various human neutrophil antigens (HNAs; see below).

However, whichever method is selected, it is often difficult to detect antineutrophil autoantibodies because they are present at low titres and bind to their targets with low avidity. It is often necessary to repeat tests several times before it may be concluded reliably whether antibodies are present.

Primary autoimmune neutropenia

The AINs are classified as primary (i.e. not associated with other detectable pathology) or secondary, in cases in which there is another pathology, usually rheumatological (particularly Felty's syndrome and systemic lupus erythematosus [SLE]) or haematological (large granular lymphocyte [LGL] syndrome).

Primary autoimmune forms are the most frequent in newborns, with an incidence of 1/100,000 [9,10,13], and are usually diagnosed during the first few months (5–15 months). Although there is significant neutropenia at presentation (500–1000 neutrophils/μl) the clinical course is usually benign, with a moderate infective diathesis and a tendency to

Table 2

Human neutrophil antigen nomenclature

Antigen system	Antigen	Glycoprotein	Acronym	Caucasian phenotype frequency (%)
HNA-1	HNA-1a	FcγRIIIb	NA1	58
	HNA-1b	FcγRIIIb	NA2	88
	HNA-1c	FcγRIIIb	SH	5
HNA-2	HNA-2a	gp50-64	NB1	97
HNA-3	HNA-3a	gp70-95	5b	97
HNA-4	HNA-4a	CD11b	MART	99
HNA-5	HNA-5a	CD11a	OND	96

Based on Bux [14]. FcγR, Fcγ receptor; HNA, human neutrophil antigen.

resolve spontaneously by the age of 2 or 3 years in 95% of cases. Severe infectious complications (pneumonia, sepsis, meningitis) are seen in about 12% of the patients.

In these forms of AIN the bone marrow is typically normocellular or hypercellular, with a normal or low number of mature neutrophils. The response of bone marrow to infection is usually preserved, explaining the moderate infective diathesis. There is often peripheral monocytosis. In the few cases with a more severe clinical course there may be maturation arrest in the myelocyte/metamyelocyte stage or bone marrow hypocellularity, probably because the autoantibodies recognize antigens expressed not only by mature neutrophils but also by their bone marrow precursors.

The autoantibodies responsible for primary AIN act against HNAs, which are defined and classified in Table 2, in accordance with the findings of the International Granulocyte Antigen Working Party [14]. In most cases these antigens are glycosylated isoforms of FcγRIIIb (or CD16b), which are linked to the plasma membrane via a glycosylphosphatidylinositol anchor and are selectively expressed by neutrophils [15].

Bux and coworkers [13] reported that 35% of their patients with primary AIN had anti-HNA-1a and anti-HNA-1b autoantibodies. Bruin and coworkers [16] found that about 80% of their neutropenic patients were positive for these autoantibodies. Less frequently the antineutrophil autoantibodies recognize adhesion glycoproteins of the CD11/CD18 (HNA-4a, HNA-4b) complex [17], the CD35 molecule (CR1) and FcγRIIb (for review, see Maheshwari and coworkers [9]).

We do not know the origin of these autoantibodies. However, like other autoimmune responses, it might involve molecular mimicry of microbial antigens, modification of endogenous antigens as a result of drug exposure, increased or otherwise abnormal expression of HLA antigens, or loss of suppressor activity against self-reactive lymphocyte clones.

In the presence of antineutrophil autoantibodies, the infective diathesis is not solely due to the severity of the neutropenias; these antibodies can influence various phagocyte functions, sometimes without causing substantial neutropenia [10,18]. Defects of adhesion, aggregation, chemotaxis, phagocytosis and metabolic activation have been reported in patients with AIN, and antineutrophil autoantibodies induced similar defects in control neutrophils. The clinical significance of these functional alterations is not clear but they may explain the infective diathesis seen in some patients with antineutrophil autoantibodies but no significant neutropenia.

Chronic idiopathic neutropenia in the adult differs from the neonatal autoimmune form in that, by definition, it appears much later in life; the incidence is higher among females (70% of cases); it exhibits little tendency toward spontaneous remission (although it remains clinically benign); it may be associated with anaemia and thrombocytopenia (40%); and only 35% of cases are positive for antineutrophil autoantibodies [10,19].

The primary AINs are usually benign or at any rate self-limiting. Most cases therefore require no specific therapy. Antibiotics are normally sufficient to deal with infections. The utility of medium-term to long-term antibiotic prophylaxis, usually with cotrimoxazole [10,13], must be assessed on a case by case basis.

In patients with severe infections or in those who require surgical intervention, remission can be achieved by treatment with corticosteroids, intravenous IgG and growth factors, particularly granulocyte colony-stimulating factor (G-CSF) [9,10,13]. Steroids, used in small case series in the past, appear to have limited effect on immune-mediated neutropenias, although there are reports of activity in primary and secondary autoimmune forms [13]. They seem to work by blocking the reticuloendothelial system and by reducing the formation of autoantibodies. However, their multiple side

effects, particularly the increased incidence of infection, have limited their use in this pathology.

Treatment with intravenous IgG is potentially useful in AIN because it transiently inhibits the reticuloendothelial system. However, such treatments are not always active (50% of cases) and, importantly, the effect is short lasting (1–2 weeks) [13].

For primary forms of AIN, G-CSF is currently the first-line therapy to achieve remission of the neutropenia (for review, see Smith and Smith [20]). The goal is to keep the neutrophil count above 1000/μl, which can usually be done by giving G-CSF intravenously or subcutaneously at a dose of 5–10 μg/kg per day for 3 days, after which further doses can be given, depending on the response. The biological effect of G-CSF is not merely to stimulate proliferation and maturation of neutrophil progenitors or to release mature cells into the bloodstream. This factor also stimulates phagocyte function; reduces neutrophil apoptosis; reduces neutrophil membrane antigen expression, thus making the autoantibodies less active; and raises levels of soluble FcγRIIIb, sequestering autoantibodies [20]. The long-term adverse effects of G-CSF (reduction in myeloid precursors, formation of anti-G-CSF antibodies, osteopenia; for review, see Maheshwari and coworkers [9]) do not normally affect patients with primary AIN, which is usually benign and self-limited, but they must be borne in mind in more severe forms of immune-mediated neutropenia, which require lengthy treatment. The use of G-CSF in AIN is justified in cases of severe infection or in those who are scheduled for surgery.

Other therapeutic approaches for patients with severe neutropenia that is not responding to conventional therapies have been reported in very small series or even single patients; they include plasmapheresis, splenectomy and cytotoxic drugs [10]. Sustained remission of severe resistant AIN has been achieved with Campath-1H, a humanized monoclonal antibody that recognizes the nonmodulating panlymphocyte antigen CD52 and induces cellular lysis in the presence of complement [21,22].

Secondary autoimmune neutropenia

Although AIN is most likely to be secondary to systemic autoimmune diseases [23-27], it is also seen in other clinical situations. Examples are infectious diseases [28-30], solid or haematological neoplasms [31,32], neurological diseases [33], bone marrow or stem cell transplants [34,35], kidney transplants [36,37], and use of certain drugs [38-40] (Table 3).

Secondary forms of AIN have some distinguishing features. First, in secondary AIN antineutrophil antibodies are usually only one of the causes of the neutropenia, which may be associated (depending on the case) with peripheral sequestration, bone marrow inhibition, or apoptosis (see below). Second, in most cases of secondary AIN the target of the autoantibodies is unknown. Third, these cases quite commonly also present with thrombocytopenia and/or haemolytic anaemia, and they may also have functional defects of phagocytes in the absence of neutropenia [41-43]. Finally, in most of these situations therapy for the cytopenia is the same as – or at least includes – treatment for the underlying disease.

Table 3

Secondary autoimmune neutropenias

Type of disorder	Disease	Ref.
Systemic autoimmune diseases	PBC	[23]
	Sjögren's syndrome	[24]
	SS	[25]
	SLE	[26]
	RA	[27]
Infectious diseases	*Helicobacter pylori*	[28]
	HIV	[29]
	Parvovirus B19	[30]
Tumor	Wilms tumor	[31]
	Hodgkin's disease	[32]
Neurological diseases	MS	[33]
Transplantation	Stem cell	[34]
	BMT	[35]
	Kidney	[36,37]
Drugs	Fludarabine	[38]
	Propylthiouracil	[39]
	Rituximab	[40]

BMT, bone marrow transplantation; MS, multiple sclerosis; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic sclerosis.

The systemic autoimmune diseases most often seen together with AIN include rheumatoid arthritis (i.e. Felty's syndrome) and SLE. There is also a complex haematological condition known as 'large granular lymphocyte' (LGL) syndrome, which closely resembles Felty's syndrome clinically. The fact that AIN is frequently seen with these pathologies has led to a better pathogenic definition of the cytopenia.

Felty's syndrome is a rare but severe form of seropositive rheumatoid arthritis, which is usually long-lasting and associated with neutropenia and, although not necessarily, splenomegaly. The neutropenia in these patients has a complex, multifactorial pathogenesis. There is destruction and peripheral margination by the antineutrophil autoantibodies and by immune complexes adhering to these cells [27], but the severe neutropenia is also partly due to inhibition of bone marrow granulopoiesis by proinflammatory cytokines (interleukin-1, tumour necrosis factor-α, interferon-γ) [44]. The resulting neutropenia is frequently severe ($<0.2 \times 10^9$/l) and, together with functional alterations to circulating cells, leads to an equally severe infective diathesis, often with poor prognosis.

In Felty's syndrome recent studies have started to clarify the antigenic specificity of the antineutrophil autoantibodies. In most of these patients, in fact, the target antigens of autoantibodies were the eukaryotic elongation factor 1A-1 antigens. This molecule, which is needed for peptide synthesis, can – *in vitro* at least – be translocated from the nucleus to the membrane during apoptosis, suggesting how the autoantibodies could bind to the cell surface of neutrophils [45].

As we mentioned above, therapy for neutropenia in Felty's syndrome is often the same as the patient needs for the underlying pathology, usually methotrexate [46], cyclosporine A [47], leflunomide [48] and parenteral gold [49]. Corticosteroids have shown some transient activity in neutropenia but their side effects are a contraindication in these patients, except for special cases. Splenectomy for patients not responsive to other therapies has shown some utility but there is a higher incidence of postoperative sepsis [50,51].

As things stand at present, the therapeutic approach to infectious complications in Felty's syndrome involves continuing the basic therapy and adding a growth factor, specifically G-CSF, to achieve prompt recovery of the circulating neutrophil count and better control of infection [52]. Nevertheless, the larger supply of circulating activated leukocytes raises the risk of arthritic flare-ups and/or leukocytoclastic vasculitis in these patients [53]. These complications can at least partially be prevented by using low doses of G-CSF (3 μg/kg per day) [52] with medium or low doses of corticosteroids (0.3–0.5 mg/kg per day prednisone equivalent).

Another potential problem is that there are no reliable indications regarding the duration of G-CSF treatment in Felty's syndrome. Often, once the infection has been resolved, good control of the basic disease with the usual drugs is sufficient to keep neutropenia within safe limits. If severe neutropenia persists ($<0.2 \times 10^9$/l) then G-CSF could be continued at the lowest effective dose (to maintain circulating neutrophils >1000/μl).

Some patients with Felty's syndrome have not only neutropenia but also an elevated number of circulating and bone marrow LGLs – a heterogeneous population of cells that includes natural killer cells and activated cytotoxic T cells [54]. The expansion of these LGLs may be reactive, but more often it is clonal, giving rise to LGL leukaemia [55].

Independently of whether the patient also has joint symptoms, LGL leukaemia is almost inevitably associated with neutropenia of multifactorial origin [56]: inhibition of myelopoiesis by cytokines produced locally by the LGL cells, and antineutrophil autoantibodies. There seems, however, to be a third pathogenic mechanism as well. The cells of patients with LGL leukaemia, unlike LGL cells in healthy individuals, constitutively express Fas ligand (FasL) in the membrane [57] and their serum contains high levels of soluble FasL [58], probably resulting from 'shedding' of the molecule by metalloproteinases.

In patients with Felty's syndrome and LGL expansion, the neutropenia might be due to apoptosis resulting from the binding of soluble FasL to Fas bearing neutrophils [59]. This is borne out by the observation that when neutropenia improves with methotrexate treatment, FasL always drops or even disappears from serum [59]. Methotrexate and cyclosporine A inhibit FasL secretion by LGLs, reducing the amount of apoptosis, and both drugs have proved effective for controlling LGL leukaemia and its associated neutropenia [60,61].

Although neutropenia is fairly common in SLE patients (47% in the case list reported by Nossent and Swaak [62]), the autoimmune forms are extremely rare, certainly less common than other autoimmune cytopenias (haemolytic anaemia and thrombocytopenia). SLE patients frequently have antineutrophil autoantibodies in their serum or adhering to circulating neutrophils (50–70%) [6,63], but they do not always have neutropenia. One possible reason might lie in the functional defect in the phagocytic system in SLE, which allows opsonized cells to remain longer in circulation [6,41].

The antineutrophil autoantibodies in SLE usually exhibit anti-FcγRIIIb specificity [16], although there are now reports of a correlation between neutropenia and anti-Ro/SSA autoantibodies. These appear to recognize a 64 kDa neutrophil membrane molecule that is antigenically similar to Ro/SSA; in this way, anti-Ro/SSA autoantibodies could opsonize neutrophils and fix complement [64]. Another autoimmune component in the pathogenesis of neutropenia – actually of cytopenia – in SLE might be antibodies against $CD34^+$ haematopoietic progenitors, which significantly inhibit haematopoiesis *in toto* [65].

Finally, the reportedly high number of apoptotic circulating neutrophils in SLE patients might be another cause of neutropenia and a possible indicator of active disease [66].

Therapy for AIN in SLE also starts with good control of the underlying disease. G-CSF was used in nine patients with severe refractory neutropenia and infectious complications [67]. There was prompt recovery of the circulating neutrophils and the infection responded well, but in one-third of these patients the disease flared up and there was one case of leukocytoclastic vasculitis.

Like in Felty's syndrome, in patients with SLE and neutropenia G-CSF should preferably only be used in selected cases, at the lowest dose that achieves a circulating neutrophil count of at least 1000/μl [52].

Conclusion

AINs are rare disorders in which autoantibodies directed against membrane antigens of neutrophils causes their

peripheral destruction. In primary forms of AIN autoantibody specificity has been defined, and usually autoantibodies recognize antigens located on the FcγRIIIb. In secondary forms of AIN autoantibody specificity is often unknown, although possible target antigens of neutrophils were recently identified in patients with Felty's syndrome or with SLE. The diagnosis of AIN is based on evidence of antineutrophil antibodies. Because of the difficulties associated with detection of neutrophil autoantibodies, a combination of immunofluorescence and agglutination tests has proven to be the best antibody screening procedure. G-CSF is at present the first-line therapy for primary AIN to achieve remission of neutropenia. Severe or unresponsive secondary AIN may be treated with G-CSF to increase neutrophil counts and reduce the risk for infection. However, in patients with Felty's syndrome or SLE, the potential for flare-up of rheumatic disease means that judicious use of the growth factor is required.

Competing interests

The author(s) declare that they have no competing interests.

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