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Review

Management of neutropenia in patients with rheumatoid arthritis

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ABSTRACT

Neutropenia is defined as a neutrophil count lower than 1.5 g/L, with categorization as mild, moderate, or severe when the count is 1.5–1 g/L, 1–0.5 g/L, or < 0.5 g/L, respectively. The main complication is infection, whose risk increases with the depth and duration of the neutropenia. Comprehensive etiological investigations are mandatory to determine the best treatment strategy. Constitutional neutropenia is rarely seen in everyday rheumatology practice. It predominantly affects patients of African descent and is usually moderate and well tolerated. Congenital neutropenia due to genetic abnormalities is severe and chiefly seen in the pediatric population. Most cases of neutropenia in patients with rheumatoid arthritis (RA) are acquired. Medications are the most common causes, making detailed history-taking crucial. Many medications used to treat RA can induce neutropenia. Folic acid deficiency should be sought routinely in patients taking methotrexate. A less common cause of neutropenia is an RA-related autoimmune reaction. Splenomegaly suggests Felty's syndrome, which is accompanied with large granular lymphocytic (LGL) leukemia in 40% of cases. The treatment depends on the depth of the neutropenia and findings from the etiological workup. A neutrophil count below 0.5 g/L, a fever, and the presence of clinical signs indicate a life-threatening condition requiring emergent treatment. In other patients, the first step is immediate discontinuation of any possibly involved drugs, simultaneously with the etiological workup.

1. Background: red flags

Neutrophils are granulocytes that differentiate from the myeloid lineage. The normal peripheral neutrophil count in adults is 1.5 to 7 g/L [1]. A number of factors, including glucocorticoids, lead the neutrophils to detach from the vessel walls, a phenomenon known as demargination that increases the neutrophil counts in the bloodstream. Neutropenia is defined as a neutrophil count lower than 1.5 g/L, regardless of the normal ranges for the laboratory. Four grades are distinguished: 1.9–1.5 g/L (grade I), minimal; 1.5–1 g/L (grade II), mild; 1–0.5 g/L (grade III), moderate; and < 0.5 g/L (grade IV) or agranulocytosis, severe. Acute agranulocytosis is a life-threatening emergency [2]. The risk of infection depends on the neutropenia grade, the pace of the neutrophil drop, and the duration of neutropenia when longer than 10 days. Other factors that influence the severity of neutropenia include the presence of other cytopenias (anemia, thrombocytopenia) or of lymphocytosis. The risk of infection is increased in patients with chronic foci of infection, particularly in the upper or lower airways or ears; and in those with comorbidities such as kidney, respiratory, or heart failure. The main incident infections are due to bacteria (*Staphylococcus aureus* and Gram-negative bacilli) and fungi; there is no excess risk of viral or parasitic infections [3]. The risk of infection increases with the duration of the neutropenia. Acute agranulocytosis is the main reason for emergent hospital admission.

2. Pathophysiology

Most neutrophils reside in the bone marrow. Fewer than 10% are located in the vascular compartment, including 45% circulating in the bloodstream and 55% adhering to the vessel walls (marginated pool).

In patients with neutropenia, three mechanisms should be considered (Fig. 1) [4]:

- peripheral destruction by an autoimmune reaction or toxic agent;
- sequestration in the splenic or endothelial tissues (excessive margination);
- and inadequate neutrophil production due to a congenital abnormality, bone marrow invasion, vitamin deficiency, or toxic agent.

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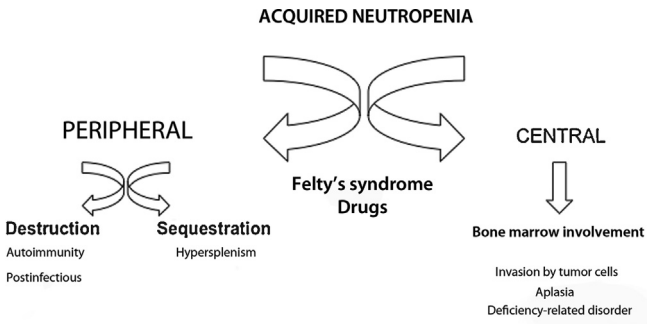

Fig. 1. The main causes of neutropenia.

3. Causes of neutropenia

Although congenital neutropenia should be considered as a matter of principle in children and young adults, neutropenia in patients with rheumatoid arthritis (RA) is usually acquired.

3.1. Acquired neutropenia

Drugs are the main cause of neutropenia in RA. The culprits include synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate; and immunosuppressants such as cyclophosphamide and azathioprine, which are used only in systemic forms of RA. Many other drugs prescribed by rheumatologists can induce neutropenia, including nonsteroidal anti-inflammatory drugs, antimalarials, and sulfasalazine. More recently, neutropenia has been reported in patients taking biological agents such as rituximab, tocilizumab, and TNFα antagonists, although these drugs theoretically have little myelosuppressive potential. In rituximab-treated patients, the incidence of neutropenia has ranged across studies from 3% to 27%. The neutropenia is delayed (median time to development, 6 months) and correlates both with the depth of B-cell depletion and with an increased risk of infection [5–7]. With tocilizumab, neutropenia has been estimated to occur in 1/100 to 1/10 patients and develops within a few days after the infusion [8]. A correlation between the depth of neutropenia and the efficacy of tocilizumab was suggested but not confirmed by a recent cohort study [9,10]. TNFα antagonists has been reported to induce neutropenia with an incidence that varied but was lower than 1/10 patients overall. The pathophysiological mechanisms involved in biotherapy-induced neutropenia remain unclear. Recent work by Wright et al. established that tocilizumab has no pro-apoptotic effects on neutrophils [11]. The concomitant use of DMARDs in most patients complicates the assessment of a causal link between biotherapies and neutropenia and probably increases the risk of neutropenia. Therefore, a routine detailed inventory of all drug exposures must be established in all patients with neutropenia in order to detect a possible iatrogenic cause, before conducting investigations for other etiologies. Folic acid deficiency should be considered, most notably in patients taking methotrexate. Neutropenia may also be related to deficiencies in other substances, such as vitamin B12 or copper.

Autoimmunity with the production of antibodies against granulocytes can cause neutropenia [12]. In patients with RA, the autoimmune process is usually related either to the RA itself or to concomitant Sjögren's syndrome [12,13]. In this situation, autoantibodies against granulocytes exhibit pan-RFγIIIb (pan-CD16b) activity. Primary autoimmune neutropenia is rare in adults. Women are affected in 70% of cases, and the course is usually chronic. Although spontaneous resolution does not occur, the disease is generally mild. Anti-granulocyte antibodies are detected in only 35% of cases and the diagnosis is therefore one of elimination [14]. In pediatric patients, primary autoimmune neutropenia is the leading cause of neutropenia, with an estimated incidence of about $1/10^5$ between 5 and 15 months of age [15]. The neutropenia is usually moderate to profound, and concomitant monocytosis is present in 30% of cases. The autoantibodies are chiefly directed against the RFcγIIIb receptor group (HNA-1), principally the HNA-1a antigen. These autoantibodies cause excessive destruction of peripheral neutrophils. The bone marrow is usually normal. Associated infections are non-serious in most cases.

Autoimmune neutropenia has also been reported in patients exposed to drugs. The autoimmune nature of the neutropenia is difficult to establish, as the diagnostic tests are extraordinarily difficult to interpret.

A few cases of autoimmune neutropenia occur in patients with primary immune deficiencies such as common variable immune deficiency, Good syndrome, and IPEX syndrome.

When there is no evidence that a drug, autoimmune process, or deficiency is responsible for the neutropenia, Felty's syndrome or large granular lymphocytic (LGL) leukemia should be considered [16,17]. Felty's syndrome is defined as the combination of neutropenia, RA, and splenomegaly. The neutropenia may be induced by antibodies directed against elongation factor A1, which is found in the nucleus but may be expressed on the cell membrane during apoptosis [18]. Neutrophil apoptosis may be induced by an interaction between the soluble pro-apoptotic cytokine FasL and the Fas receptor expressed on neutrophils. Among cases of Felty's syndrome, 40% are related to LGL leukemia, which is characterized by proliferation of a T-cell or NK-cell clone. LGL leukemia should be considered in patients with moderate-to-severe neutropenia and lymphocytosis [17] (Fig. 2). The diagnosis rests on immunophenotyping of the blood lymphocytes: the results show expansion of CD3+, CD8+, CD57+, CD56− T cells or of CD3−, CD16+, CD56+ NK cells. The clonal nature of the proliferation should then be established, by TCR rearrangement or Vβ repertoire tests for T cells and by KIR receptor or CD94 expression tests for NK cells. Neutropenia in patients with LGL leukemia is multifactorial: anti-granulocyte antibodies are produced, and neutrophil apoptosis is excessive. The prognosis depends chiefly on the risk of infection, with a 20% mortality rate after 4 years and a median survival longer than 10 years [19].

Finally, bone marrow invasion should be suspected, particularly when the neutropenia is accompanied with other cytopenias and/or the serum protein electrophoresis shows monoclonal gammopathy.

3.2. Congenital neutropenia

Congenital forms of neutropenia are seen mainly in pediatric patients [20]. The three classical forms are severe congenital neutropenia, cyclic neutropenia, and WHIM syndrome.

Severe congenital neutropenia or Kostmann syndrome is characterized by increased myeloid cell apoptosis [21]. A mutation in the *ELA2* gene is identified in 50% of cases. Profound neutropenia is the rule, and there may be other biological abnormalities such as thrombocytosis or hypergammaglobulinemia. Patients are at risk for severe infections and secondary acute leukemia. Osteoporosis is often present in children and should be sought routinely.

In contrast to severe congenital neutropenia, cyclic neutropenia and WHIM syndrome may produce only minimal symptoms, so that the diagnosis is not made until adulthood. Cyclic neutropenia is inherited on an autosomal dominant basis [22]. Episodes of neutropenia occur in 3-week-long cycles. Mutations in the *ELA2* gene have been found. WHIM is the acronym for "warts, hypogammaglobulinemia, infections, myelokathexis". WHIM syndrome is a rare autosomal dominant disease due to an activating mutation in the gene that encodes the chemokine receptor CXCR4 [7]. The depth of the neutropenia is variable.