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Quarterly Medical Review

Autoimmune neutropenia

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Summary

Autoimmune neutropenia (AIN) is a rare entity caused by antibodies directed against neutrophil-specific antigens. It includes primary and secondary autoimmune neutropenia. Acute autoimmune neutropenia can be related to drug-induced mechanism or viral infections. Chronic autoimmune neutropenias occur in the context of autoimmune diseases, hematological malignancies, such as large granular lymphocyte leukemia, primary immune deficiency syndromes or solid tumors. The therapeutic management depends on the etiology. Granulocyte growth factor is the main therapeutic option, raising the question of their long-term utilization safety. Corticosteroids or immunosuppressive therapy are indicated in infection-related AIN or in case of symptomatic autoimmune disease or LGL leukemia.

Autoimmune neutropenia (AIN) is a rare and heterogeneous group of diseases with variable clinical manifestations coming from asymptomatic to severe forms associated with infectious complications [1]. AIN is characterized by the presence of autoantibodies directed against neutrophils and leading to their destruction. However, anti-neutrophils antibodies are not easily detected due to the weak sensitivity of available tests. This review will focus on the description of neutrophils cells (regulation, function and consequence of neutropenia), the methods of anti-neutrophils antibodies detection and the physiopathology of autoimmune neutropenias. We will discuss the clinical spectrum of AIN and finally propose how to manage patient with AIN.

Polymorphonuclear neutrophils (PMN)

How PMN homeostasis is regulated?

In physiological situation, bone marrow produces about 10^9 PMN per kilo of body weight per day [2,3]. Progenitors, precursors and marrow mature neutrophils represent 95% of PNN reserves [4]. Myeloid stem cells and progenitors will divide four or five times before beginning the maturation

phase. During this maturation stage, the nucleus segments and the primary and secondary cytoplasmic granules appear. Primary granules contain bactericidal proteins (MPO, proteinase 3, elastase or cathepsin G) whereas secondary granules' proteins are involved in the neutrophil migration and in the maintaining of the inflammatory response (lysozyme, cathelicidin, leukolysin, collagenase and lactoferrin). Each maturation stage, mitotic and post-mitotic, lasts for seven days. The mature neutrophil is a 12 to 14 µm cell with a lobulated nucleus. It exits from the bone marrow through a barrier formed by the basal membrane, endothelial cells and post-capillary venule adventitial cells [5,6]. Five percent of PNN are in the circulation or in the post-capillary venule endothelium. Once neutrophils have moved into tissues, their lifetime is short, between 6 and 8 hours [7].

Neutrophils traffic is regulated by various mechanisms. SDF-1, also called CXCL-12, is produced by osteoblasts [8] and binds to CXCR4, which is found on the neutrophils' surface. This interaction keeps neutrophils inside the bone marrow compartment. G-CSF acts on this SDF-1/CXCR4 axis in two ways:

- it reduces CXCR4 expression on neutrophils surface [9];
- it reduces SDF-1 level by limiting osteoblasts proliferation.

Therefore, it promotes neutrophils release in the peripheral circulation. Finally, G-CSF production is reduced when a large amount of neutrophils cells are present in tissues [10,11]. This latter cytokine is the main regulator of granulopoiesis. G-CSF-R (G-CSF-receptor) also activates granulopoiesis specific transcription factors: C/EPB (CCAAT/enhancer binding protein), PU-1, GFI-1 or CBF and c-Myb. The combination of these transcription factors is characteristic of granulopoiesis.

The normal PMN count and the consequences of neutropenia

Normal neutrophils level ranges between 1500 and 7000/mm^3 during adulthood [3]. A neutrophil count below 1500/mm^3 defines the term neutropenia. This neutropenia is severe when neutrophils are below 500/mm^3, moderate between 1000 and 500/mm^3 and mild between 1000 and 1500/mm^3.

Neutrophil count depends on age, sex and ethnic origin. At birth, the normal value of PMN is between 12,000 and 15,000/mm^3 and reaches adult's standard after one year old. The American Registry NHANES (National Health and Nutrition Examination Survey) studied leukocytes and neutrophils levels in a cohort of 25,222 subjects. This study confirms that sex, smoking status, age and ethnicity impact on neutrophil values [12]. Smokers and females present a higher neutrophil mean than non-smokers or males. There is a higher prevalence of neutropenia (below 1500/mm^3) among African-American subjects (4.5%) than Hispanic or Caucasian Americans (respectively 0.38 and 0.49%). Eighty percent of those subjects present a mild neutropenia. Moderate or severe neutropenia remain rare with a prevalence of less than 1% (0.57% to 0.08% depending on the ethnic groups). This lower quantity of neutrophils among the African-American population may correspond to the ethnic or benign neutropenia. This entity is poorly understood; the genetic transmission type is still unknown but seems to be multifactorial. At the individual level, this entity remains unclear, but it is defined by four simple criteria: mild or moderate neutropenia, absence of infection due to neutropenia, any identified etiology and a compatible ethnicity. Explorations have been reported in a very limited number of subjects and are strictly normal, especially the bone marrow, which showed no quantitative or qualitative abnormalities.

Neutrophil functions and clinical manifestations of chronic neutropenia

Infection risk is well described when neutropenia is chemotherapy-induced or in case of severe congenital neutropenia. Neutropenia severity, installation velocity and duration modulate the infectious risk. When neutropenia is severe and lasts for at least two weeks, 80% of the patients are infected and nearly 100% after three weeks, mainly due to mycotic infections, such as aspergillosis or candidemia [13].

In the case of chronic AIN, the infectious risk has been poorly investigated. This risk appears to be correlated to the number of neutrophils when it is lower than 500/mm^3 [14]. In case of AIN, the infectious risk is lower than observed during drug-induced neutropenia. This observation could be based on the fact that neutropenia is isolated in the chronic immune case whereas it is associated to monocytopenia in the drug-induced case. Those monocytes may counterbalance the neutropenia defect in the innate immune system. In the case of chronic AIN, infections are mainly caused by bacteria: *Staphylococcus aureus* and Gram-negative *Bacilli* are the most frequent germs. The nearly absence of symptom is explained by the absence of pus formation. The evolution is usually necrotic. Patients frequently present gingivitis, aphtoses, stomatitis, periodontitis and cutaneous infections, like perirectal abscess and cellulitis [15]. Severe and profound infections, such as pneumonia or digestive tract infections are rarely described. Those data have been described from series with mild or moderate chronic neutropenic patients. They might underestimate the severity and the frequency of infection in severe chronic AIN. The neutrophil count itself is not sufficient to define patient risk groups and to propose a prophylactic strategy. The soluble fraction of FcRIIIb or CD16 (receptor to immunoglobin Fc fragment) amount was measured in neutropenic patients by Koene et al. and they showed a correlation between a lower rate of FcRIIIb soluble and the occurrence of infections [16].

Physiopathology of autoimmune neutropenias

The acquired autoimmune neutropenia are characterized by the presence of an antibody, usually of immunoglobulin G (IgG)