

## Review Article

# Integrative Clinical and Practical Hematology

## A Review on Chronic Neutropenia of the Adult: Emerging Clinical Dilemmas

Fattizzo B\*

Department of Hematology, Fondazione IRCCS Ca' Granda Policlinico Hospital of Milan, Italy

\***Correspondence:** Bruno Fattizzo, Hematology Unit, Fondazione IRCCS Ca' Granda Policlinico Hospital of Milan, Via F. Sforza 35, 20122 Milan, Italy, Tel: +39 025503 3345; E-mail: brunofattizzo@gmail.com

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### Abstract

Chronic neutropenia of the adult is a cause of often unjustified anxiety for both the patients and the medical community. Various studies show that the condition is generally benign with little risk of infection and clonal evolution. Here we provide a review of the available literature, focusing on patient evaluation and clinical management of the adult with chronic idiopathic/autoimmune neutropenia. Data presented advise to evaluate the clinical severity basing on neutrophil counts ( $<$  or  $>$   $0.5 \times 10^9/L$ ) and on the history of infections, to carefully examine personal and family history and to exclude congenital and benign forms of the infancy. Furthermore, nutritional deficit, infections, autoimmune diseases and neoplasms should be looked for and excluded. Hematologic constitutional symptoms, LDH, beta2microglobulin levels and lymphocytosis may hint the diagnosis of an underlying hematologic disease (lymphoproliferative syndrome). Once secondary forms have been excluded, the research for anti-neutrophils autoantibodies and bone marrow evaluation should be performed in case of persistent severe neutropenia, whilst follow up may be enough for mild/moderate cases. The use of G-CSF and prompt broad-spectrum antibiotics, covering for *Pseudomonas aeruginosa*, is suggested in case of febrile neutropenia only. Finally, the introduction of new clinical entities (ICUS, IDUS, CCUS, and CHIP) within the myeloid diseases classification is going to change the diagnostic scenario in the next future.

**Keywords:** Chronic idiopathic neutropenia, Autoimmune neutropenia, Myeloid neoplasms, Lymphoproliferative disorders

### Introduction

Neutropenia is defined by a decrease of the Absolute Neutrophil Counts (ANCs) below the threshold of  $1.8 \times 10^9/L$  in the Caucasians and  $1.5 \times 10^9/L$  in people of African origins. This is valid from 1 year of age until adulthood, as the cut off for normality would be  $1 \times 10^9/L$  in newborns and children  $<1$  year of age [1]. Neutropenia is considered chronic if persists longer than 3 months, and is usually graded into mild (ANCs  $1-1.5 \times 10^9/L$ ), moderate (ANCs  $0.5-1 \times 10^9/L$ ), and severe forms (ANCs  $<0.5 \times 10^9/L$ ) [1]. The condition is further classified into congenital and acquired, and the latter in primary and secondary forms

[2]. Neutropenia cause is often obscure, particularly in adults, where idiopathic neutropenia is one of the most frequent reasons for hematologic referral. Moreover, the general practitioner and the hematologist himself can find it difficult to orientate among emerging clinical dilemmas: how much one should worry about moderate/mild forms? What tests to perform? Which is the priority for visits and workup? Once excluded oncologic and common secondary forms, how will I follow a patient with chronic idiopathic disease? In this review we scanned the most recent literature on acquired neutropenia of the adult, focusing on chronic benign forms and their differential diagnosis. Moreover, we provide some practical advice for

patient' evaluation and follow up in the clinical practice.

## Body

While evaluating an adult patient presenting with chronic neutropenia, it is necessary to go through a hypothetical flow chart to exclude one by one each cause from the commonest to the rarer. Moreover, the presence of concomitant acute infections or active underlying diseases might alter the clinical picture.

## Secondary neutropenia

Considering and excluding all secondary forms of neutropenia is therefore fundamental [1-3], as it allows to potentially eliminate the pathogenic trigger permitting ANC's recovery. Here follows a schematic summary of the commonest secondary causes of isolated neutropenia.

## Nutritional deficiencies

Nutritional deficiencies may generally cause mild to moderate neutropenia in patients with nervous anorexia or with deficit of B group vitamins, including B12 and folic acid, or copper. This may be due to abnormalities in gastro-intestinal absorption, reduced intake, or increased requirement of the nutrient (i.e., celiac disease, gastro-intestinal resections, vegans or vegetarians patients, pregnancy, adolescence and growing age). In these patients, other cytopenias may also be present, including macrocytic anemia and thrombocytopenia; an attentive clinical history, including recent symptoms of glossitis and peripheral neuropathy, together with the blood smear showing hyper-segmentation of the neutrophils may lead to the diagnosis of B12 deficiency, and vitamins serum levels are diagnostic [4].

## Chemicals and radiation

While it is expected to observe neutropenia in patients treated with chemotherapy or radiotherapy, usually in the context of a pancytopenia, it is much rarer to consider the condition after other drugs of common use. Drug-induced neutropenia may often be severe and, if isolated, is defined drug-induced agranulocytosis [5]. The latter, although often sporadic and transient, exposes the patient to a considerable infectious risk. Among the responsible drugs there are anti-thyroid agents (thiouracil, propyl-thiouracil, methimazole, Carbimazole), antibiotics (cephalosporins, penicillin, sulfonamide, chloramphenicol), anti-epileptics (carbamazepine and valproic acid), neuroleptics (chlor-promazine, clozapine), and immune suppressors (rituximab, cyclophosphamide,

azathioprine, and methotrexate). The pathogenic mechanism can be that of a direct toxicity due to the drug effect on highly duplicating cells, as also observed for many chemotherapeutics. Agranulocytosis can also be idiosyncratic (Idiosyncratic Drug Reaction IDR) and the targets may be both mature neutrophils and bone marrow precursors [5]. This B-cell mediated hypersensitivity reaction is specific for each individual; many IDRs are associated to the development of anti-drug antibodies or autoantibodies, as observed for reactions to beta-lactams and aminopyrine. Tests evaluating patient's lymphocyte activation after exposure to the drug in vitro, favor the immune pathogenesis of the phenomenon. The latter can occur through a hapten-carrier mechanism (the drug forms a complex or modifies self-peptides, rendering them reckonable as non-self by the immune system) or through the so called "danger" hypothesis, where an infectious or mechanical trigger [6] provides the second signal to evoke the immune reaction. Another case is that of rituximab, a monoclonal antibody targeting B-cells, widely used for both onco-hematologic and autoimmune diseases. It can induce prolonged neutropenia associated to hypogammaglobulinemia and lymphopenia, by linking to Fc-gamma receptor on marrow granulocyte precursors [7]. Finally, some drugs like etoposide, diclofenac, and sodium-thiomalate, may induce neutropenia by altering bone marrow microenvironment. The incidence of IDRs varies from 1/100 to 1/100.000 individuals per year and can be observed as far as 6 months after drug discontinuation; re-exposure does usually re-induce IDR, except for mild reactions where immune-tolerance may occur [4]. Severity is highly variable, reaching a mortality of 5%, depending on the degree and duration of the neutropenia, patients' age and comorbidities, particularly sepsis [8]. Considering recovery, it can take also several weeks, whilst the persistency of agranulocytosis usually has a bad prognosis. The best clinical approach consists on the close monitoring of the patient with agranulocytosis, on the prompt withdrawal of the toxic agent in case of neutropenia, and on the use of G-CSF in severe and long-lasting forms. The diagnosis is usually clinical, and may benefit of the use of low available tests: the research of drug induced autoantibodies by flow-cytometry, ELISA, and immunoblotting, and the granulocyte agglutination test [9].

## Infections

Infectious episodes may lead to a decrease proliferation of myeloid precursors, due to microenvironment alterations. Among viral agents, Parvovirus B19 can give a transient neutropenia in the acute phase, rarely

chronicizing in case of persistence of the infection within marrow precursors and consequent lymphocyte activation and destruction of the infected cells. Other viruses are HIV (particularly in the advanced phase of the disease), because of both direct myeloid toxicity of the virus and because of anti-retrovirus therapy [10], EBV, CMV, and HBV and HCV [11]. Considering bacteria, a high prevalence of *Helicobacter pylori* infection has been found among patients with chronic neutropenia and a normalization has been described after eradication [12,13]. Finally, neutropenia can be observed also during chronic granulomatous infections, such as tuberculosis, brucellosis, typhus, and leishmaniasis.

### **Hematologic and oncologic diseases**

During hematologic diseases [14], a neutropenia can be observed, due to either the substitution of the hemopoietic bone marrow as observed during chronic and acute leukemia and lymphoproliferative diseases, or to the bone marrow insufficiency. The latter can be congenital, as observed in Fanconi Anemia, or acquired, partly due to immune-mediated inhibition of bone marrow precursors, as occurs in myelodysplastic syndromes and aplastic anemia. Among lymphoproliferative disorders, hairy cell leukemia induces neutropenia through marrow infiltration, cytokine inhibition of myeloid precursors by neoplastic cells, and increase splenic sequestration [15]; treatment of the underlying disease usually leads to neutropenia recovery and to the resolution of the, often severe, infectious complications. Finally, neutropenia can be associated to the chronic expansion of the Large Granular Lymphocyte pool (LGL-expansion) [15,16], as observed in secondary forms like Felty syndrome (neutropenia, rheumatoid arthritis, splenomegaly, and HLA-DR4), or in primitive conditions (i.e. LGL leukemia). The diagnosis is usually suspected in case of clonal absolute lymphocytosis with phenotypic characteristics suggestive for LGL by morphology and flow-cytometry. Immunosuppression with cyclophosphamide or methotrexate can lead to good responses, as well as the stimulation with G-CSF in case of severe neutropenia and infections [15].

### **Endocrinopathies and sequestration**

Hypothyroidism, hyposurrealism, and panhypopituitarism may be associated with chronic neutropenia, clinically following the course of the main disease; finally, all conditions characterized by hypersplenism can also display neutropenia.

### **Allo-immune neutropenia**

Allo-immune neutropenia is mainly observed in the newborn due to a reaction of maternal iso-immunization to neutrophils antigens inherited by the father; it usually spontaneously resolves within the first 11 weeks and rarely requires therapy. In the adult, an alloimmune reaction can occur as part of a transfusion reaction [1].

### **Secondary autoimmune forms**

Secondary autoimmune forms are usually associated to systemic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, where anti-neutrophils autoantibodies can be found [1]. Increased splenic sequestration, cytokine mediated bone marrow inhibition, and increased apoptosis of circulating granulocytes, all participate to neutropenia in these forms. Hemolytic anemia and thrombocytopenia may also associate and usually recover after therapy of the underlying disease. The above mentioned Felty syndrome can be particularly severe with increased infectious risk and high mortality, and usually requires G-CSF and immunosuppression [1].

### **Primary neutropenia**

Primary forms encompass congenital and acquired conditions [17,18].

### **Congenital forms**

These conditions are usually diagnosed during infancy and are characterized by a strong increase in bacterial and viral infections with high risk of death. The diagnosis is suggested by the early onset of severe neutropenia, possibly associated to clinical signs and symptoms from other organs (neurologic, cardiac, and cutaneous alterations) indicating the presence of defined clinical syndromes. The type of hereditary transmission (autosomal or X-linked, dominant or recessive) is also of aid to the diagnosis [19-21]. Molecular studies aimed to individuate the pathogenic mutation in genes involved in neutrophils maturation and functioning (most commonly ELANE, HAX1, GFI1, G6PC3, and WAS) are usually diagnostic [21,22]. These conditions may rarely remain under the diagnostic threshold during infancy and adolescence and become evident during adulthood. In these cases, a careful personal and family history, as well as the evaluation of past blood counts, will be of aid to address the diagnosis [23].

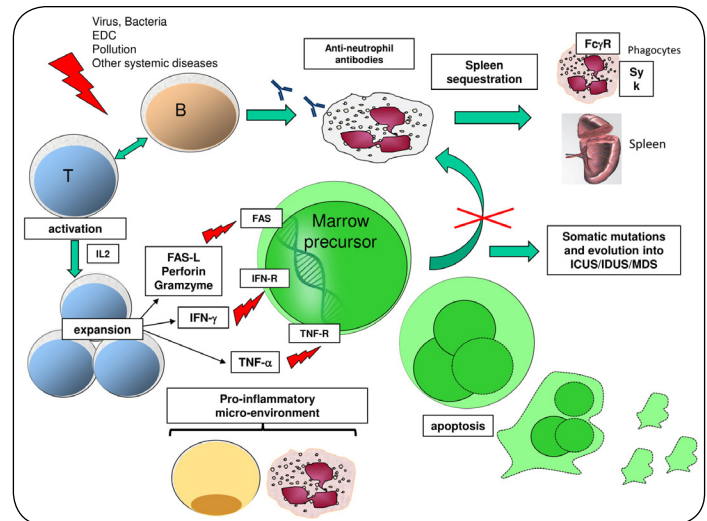
## Primary acquired neutropenia

Primary acquired neutropenia is a diagnosis of exclusion, characterized by neutropenia in the absence of an underlying cause. Two conditions belong to this group: chronic benign neutropenia (CBN) of the adult and autoimmune neutropenia of the infancy and childhood [18]. Chronic benign neutropenia of the adult is characterized by a decrease of ANCs lasting at least 3 months. It is a rare hematologic condition, with an estimated prevalence of 1% in Caucasians and 5% in people of African ancestry [18,22-24]. We classically distinguish two forms of CBN: primary immune neutropenia (PIN, also called autoimmune neutropenia AIN), if the anti-neutrophil autoantibodies are present, and chronic idiopathic neutropenia (CIN), if they are absent [25-27]. PIN is usually more prevalent among females in their 20s-30s and displays a lower tendency to spontaneous remission. It has been recently been speculated that the two conditions belong to a common spectrum of immune activation, ranging from cellular mediated, typical of CIN, towards autoantibody mediated in PIN. Moreover, the low sensitivity of the available tests do not allow a clear-cut differentiation of the two forms that will be therefore discussed together.

## Pathogenesis of CBN

CBN pathogenesis (Figure 1) encompass the Antibody-Dependent Cellular Cytotoxicity (ADCC) in autoantibodies positive forms, but also a cytokine dysregulation typical of a sort of low-grade chronic inflammatory process, involving activated macrophages. In this context, Papadaki et al showed significantly increased levels of Interleukin 1 $\beta$  (IL-1 $\beta$ ), Interleukin 6 (IL-6), Transforming Growth Factor- $\beta$ 1, (TGF- $\beta$ 1), Interleukin 8 (IL-8), RANTES (CCL5), Tumor Necrosis Factor- $\alpha$ , (TNF- $\alpha$ ), and of its soluble receptor (sTNF-RI) in 132 patients with CIN compared to controls [28]. Cytokine levels correlated with the severity of neutropenia. The involvement of bone marrow precursors and microenvironment has been suggested by the demonstration of an infiltrate of activated T cells and of an increased concentration of interferon- $\gamma$  (IFN- $\gamma$ ) and TGF- $\beta$ 1 in bone marrow trephines from CBN cases [29]. Increased levels of Fas Ligand (FasL) expressing cells have also been described in CIN, also demonstrating increased apoptotic phenomenon in precursors [30]. An increased expression of toll like receptor 4 on the surface of marrow monocytes has also been reported in these patients [31]. Finally, a recent study described the presence of small PNH clones in 91 CIN cases [32], further suggesting that CIN may belong to the immune-mediated

bone marrow failure syndromes. In this context, the evolving scenario of WHO classification, has recently included some forms of cytopenia and dysplasia, with features borderline with the diagnosis of myelodysplastic syndromes (i.e. idiopathic cytopenia/dysplasia of unknown significance ICUS/IDUS, clonal cytopenia of unknown significance CCUS, and clonal hematopoiesis of indeterminate potential CHIP). These conditions may also appear as isolated neutropenia and would probably include a proportion of patients previously diagnosed as CBN [33].



**Figure 1:** Pathogenesis of chronic benign neutropenia.

The abnormal activation of the immune system through B- and T-cell cross-talking results in both the production of anti-neutrophil autoantibodies as well as the attack towards bone marrow precursors leading the apoptosis of granulocyte progenitors. EDC Endocrine Disrupting Compounds; TNF Tumor Necrosis Factor; FAS-L Fas Ligand; IL2 Interleukin 2, IFN Interferon, ICUS/IDUS Idiopathic Cytopenia/Dysplasia of Uncertain Significance; MDS Myelodysplastic Syndromes; Fc gamma R Fc gamma receptor; Syk spleen tyrosine kinase.

## Diagnosis of CBN

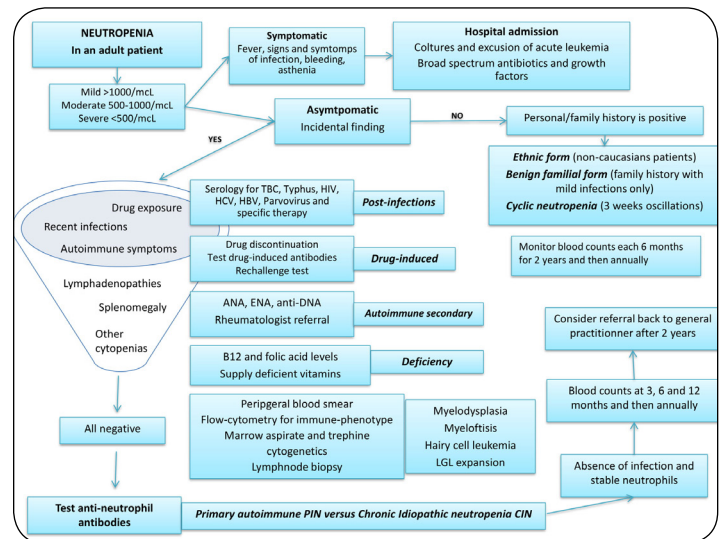
The diagnostic flow chart of CBN (Figure 2), encompass the exclusion of all other secondary forms, as well as of the primary congenital neutropenia [1,18,27]. A careful evaluation of the personal and family history is necessary, and subsequently, physical examination and routine laboratory tests should aim to unravel any possible secondary form. The diagnosis is based on the demonstration of the pathogenic autoantibodies, which is complicated by the low surviving of the granulocytes ex vivo [34]. Among available tests [35-40] there are the

Granulocyte Agglutination Test (GAT), where patient serum is incubated with normal neutrophils and the Granulocyte Immuno-Fluorescence Test (GIFT), where neutrophils are fixed with glutaraldehyde, and the presence of surface IgG is detected with anti-human IgG anti-serum through fluorescence test. The GIFT test is preferred compared to the indirect test (GIIFT) that demonstrates the presence of the anti-neutrophils autoantibodies in the serum. Although GIFT displays low specificity, because of the low number of neutrophils isolated and the unspecific binding of the anti-serum to the Fc gamma receptor of the IgG, the negative predictive value is high, and a negative GIFT is useful to exclude AIN. On the contrary, the indirect test is characterized by low sensitivity due to the small amount of circulating autoantibodies and to the low coverage of the HNA patterns within the neutrophil test suspension (that should include at least one test cell homozygous for HNA-1a/1a and one HNA1b/1b). Finally, HNA also display highly variable expression. The Guidelines from the International Granulocyte Immunology workshop suggest the combined use of GAT and GIFT to obtain the highest sensitivity and specificity [35]. The use of a fluorescein marked autoantibody allows the use of flow-cytometry for autoantibodies detection [39]. Other available methods are ELISA and MAIGA (Monoclonal Antibody Immobilization of Granulocyte Antigens), based on the use of monoclonal antibodies directed against granulocyte surface proteins [40]. The Guidelines of the pediatric association AIEOP suggest to perform GIIFT at least 3 to 4 times in 4-6 months to diagnose PIN. If the test is negative and the bone marrow normal, the diagnosis of chronic idiopathic neutropenia is made [19]. Despite the availability of these test, the detection of anti-neutrophils autoantibodies is not routinely performed in most hematologic centers and carries as low as 62,5 % sensitivity, and less than 85% specificity. A bone marrow evaluation (aspirate and trephine) should be considered in all patients with an idiopathic neutropenia to exclude signs of dysplasia, cytogenetic abnormalities and onco-hematologic diseases. However, in those patients with a long history of isolated, mild neutropenia, bone marrow evaluation is often inconclusive, or leads to the diagnosis of ICUS/IDUS. Moreover, it is often not necessary for the diagnosis of lymphoproliferative disorders, including LGL expansion, that can be identified by flow cytometry on the peripheral blood in many cases [41,42].

## Clinical features and management of CBN

Clinically, CBN has a benign course in the majority of patients, with a small proportion of infectious complications (23%) that usually do not require

hospitalization, nor specific therapy with growth factors. During work up (Figure 1), hospitalization is needed in case of new onset of severe neutropenia ( $<0.5 \times 10^9/L$ ), particularly if the patient is febrile or presents other cytopenias requiring the prompt exclusion of leukemic forms. In case of febrile neutropenia, after blood cultures collection, a prompt, broad spectrum antibiotic therapy should be initiated, including agents active on *Pseudomonas Aeruginosa* and gram negative bacteria. The use of G-CSF is limited to cases with severe recurrent infections, and cutaneous or mucosal erosions. In these cases non-pegylated products are usually preferred to avoid bone pain, and should be continued to maintain the patient asymptomatic and with ANC's around  $0.25-0.3 \times 10^9/L$ . CBN patients may also display splenomegaly in 10-20% of cases and mild to moderate associated cytopenias typical of chronic inflammation, such as anemia (15%) and thrombocytopenia (10%).



**Figure 2:** The clinical and laboratory flow-chart of neutropenia management in adults.

As regards other drugs used in autoimmune bone marrow failures, thrombopoietin agonists are approved for ITP and aplastic anemia and data on their use in MDS have also been provided. The trilineage effect is due to TPOa action on the common stem cell, but only a case report on autoimmune neutropenia of the adult in a patient who also had ITP has been reported, with very limited evidence [43].

Osteopenia and osteomalacia have also been described in these patients (44% and 15% respectively), probably due to bone reabsorption mediated by cytokines like TNF- $\alpha$  and IL-1 $\beta$  [41,44]. Our group recently described vitamin D deficiency, associated with increased

autoimmune activation, in a large cohort of autoimmune cytopenias including CBN, autoimmune hemolytic anemia and primary immune thrombocytopenia [45]. Therefore, we evaluate vitamin D levels and advice bone densitometry evaluation in the elderly and in cases potentially benefiting from vitamin D supplementation.

## Large retrospective studies

In another recent study of 76 adult cases with CBN [42], we focused on the clinical course of the condition, and showed that ANCs display a huge range of inter-individual oscillation (range  $0.1-2.5 \times 10^9/L$ , median  $1.143 \times 10^9/L$ ), whilst single cases showed low intra-individual variations. One third of cases had a positive GIFT test, similar to what reported in a large French study. In the French cohort, interestingly, 47% of cases displayed autoantibodies other than anti-neutrophils (ANA, anti-DNA, ANCA, and rheumatoid factor) [22]. Considering organ specific autoantibodies, Kyritsi et al reported thyroid autoimmune disease in 44% of 218 neutropenia patients in a prospective follow up [46]. In our study [42], 21% of cases had polyclonal hypergammaglobulinemia, and 10.7% a monoclonal gammopathy of unknown significance. These findings highlight the presence of a lymphoproliferative activity in this condition, underlying the autoimmune epiphenomenon. ANCs were lower in males, in patients with positive anti-neutrophil antibodies, and in those with splenomegaly and monoclonal gammopathy. Bone marrow evaluation had been performed in about half of cases at onset, without leading to a definite hematologic diagnosis. However, during a 5 year follow up, a quarter of cases displayed a variation of blood counts, including anemia, thrombocytopenia, lymphocytosis, monocytosis, or worsening of the neutropenia, that triggered a bone marrow re-evaluation or peripheral blood immune-phenotyping. This led to the diagnosis of three cases of myelodysplastic syndrome (one chronic myelomonocytic leukemia, one MDS with unilineage dysplasia, and one MDS with multi-lineage dysplasia), four hairy cell leukemias, and 5 cases of chronic LGL expansion. The latter showed a mild peripheral lymphocytosis that was already present at onset, and 3 of them had increased LGLs at flow-cytometry, although below the diagnostic range. Finally, revision of these patients' trephine by an expert hemopathologist, with use of specific staining, showed the presence of an LGL infiltrate that was already present at diagnosis. We therefore advise, in case of bone marrow evaluation of a patient with neutropenia and lymphocytosis, to perform a panel including CD3, CD4, CD5, CD7, CD8, CD57, TIA1 and granzyme-B. Once the diagnosis of CBN, either CIN or

PIN, has been established, available studies suggest to perform periodic hematologic visits, using second and third level diagnostic tools (bone marrow aspirate and trephine, and peripheral blood immune-phenotype) in case of worsening of the neutropenia or appearance of lymphocytosis or associated cytopenias.

## Autoimmune neutropenia of the infancy

Briefly, as regards autoimmune neutropenia of the infancy, it is frequent among the newborns, with an incidence of 1/100.000 and a median age at diagnosis of 7-9 months. The disease is due to the presence of autoantibodies directed against granulocytes membrane antigens, like those for the type 3b Fc fragment of the immunoglobulin G (human neutrophil antigen-1, HNA-1). The disease is usually moderate and the clinical course benign, with spontaneous recovery in 2-3 years in up to 95% of cases [47]. Infectious complications can occur in only 12-20% of cases and at bone marrow evaluation, myeloid precursors are usually normal in number, although some late maturation arrest may occur. No specific therapy is required, except for prompt antibiotics in case of fever or infection and killed agent vaccines wherever a concomitant immunodeficiency is suspected. In case of surgery or severe infections, the use of G-CSF at the dose of 1-2 mcg/Kg/day for 5-7 days targeting  $1 \times 10^9/L$  ANCs, is advisable. The diagnosis is based on the demonstration of the pathogenic autoantibodies, with the technical problems that will be described for the adult. The differential diagnosis should encompass all the above mentioned congenital and secondary causes, and the forms associated to pregnancy and partum (67% of patients with perinatal hypoxia; 50% gravidic hypertension; 50% fetal erythroblastosis and in the donor twin of the "twin to twin transfusion") as well as the chronic neutropenia of the newborn from a mother with primary autoimmune neutropenia.

## Conclusions and Key Issues

Chronic neutropenia of the adult is a cause of often unjustified anxiety for both the patients and the medical community. Various studies show that the condition is generally benign with little risk of infection and clonal evolution. The increased frequency of routinely performed blood counts in Western Countries is going to lower the diagnostic threshold for these otherwise benign and unacknowledged forms. Moreover, the classification is object of continuous study.

In case of chronic neutropenia one should evaluate the

clinical severity basing on ANCs (< or > 0.5x10<sup>9</sup>/L) and on the history of infections.

A careful personal and family history evaluating the frequency and severity of the infections starting from childhood is crucial to exclude congenital and benign forms of the infancy. If history is positive, the patient should be referred to a tertiary center for molecular tests.

Dosing B12 and folic acid, as well as TSH, serology for HBV, HCV, and HIV, and small autoimmunity panel with ANA, ENA, rheumatoid factor and anti-DNA will allow the exclusion of most common secondary forms.

LDH and beta2microglobulin levels together with the presence of systemic symptoms (night sweats, fever, loose of weight), or the evidence of lymph nodes and spleen enlargement, or lymphocytosis may hint the diagnosis of an underlying hematologic disease (lymphoproliferative syndrome).

The persistency of isolated neutropenia for more than 3 months, after the exclusion of secondary causes, may trigger the research for anti-neutrophils autoantibodies in tertiary centers.

Once the diagnosis of CBN in an adult patient is established, a clinical-laboratory follow up (complete blood count and physical examination) at 3, 6, and 12 months from diagnosis, and yearly thereafter, is advisable. If counts are stable, consider referring the patient back to the general practitioner for annual follow up.

The use of G-CSF and prompt broad-spectrum antibiotics, covering for *Pseudomonas aeruginosa*, is suggested in case of febrile neutropenia only.

Bone marrow evaluation is indicated whenever an underlying hematologic condition (lymphoproliferative disorder, myeloid leukemia, myelodysplastic syndrome) is suspected or in case of persistent/worsening severe neutropenia. Finally, the introduction of new clinical entities (ICUS, IDUS, CCUS, and CHIP) within the myeloid diseases is going to change the diagnostic scenario in the next future.

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