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Cyclic Neutropenia – Case Report

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Abstract: ***Cyclic neutropenia is a rare disorder characterized by a cyclic reduction in the granulocyte proliferative pool in the bone marrow followed by the onset of neutropenia. We report a male patient 79 years of age, with 33-year history of disease. Antineutrophil antibody investigations revealed that the indirect granulocyte immunofluorescence test was positive (IgM), suggesting the presence of granulocyte-specific IgM antibodies in the serum of the patient. The impression gained was of highly stimulated reactive immune system. Treatment started with G-CSF (and occasionally antibiotics) only in the periods when WBC count was less than 1,5x10^9/L for several years, but lately the patient has been on weekly and the last year on twice weekly therapy with G-CSF, with normal WBC count and ANC varying from 110-3960, without any significant infection. The novel treatment like the CXCR4 antagonist plerixafor (Mozobil, Genzyme), shows promise in the way it raises blood counts, including both neutrophils and lymphocytes.***

Keywords: cyclic neutropenia, granulocyte colonies stimulating factor (G-CSF)

1. Introduction

Cyclic neutropenia is a rare disorder characterized by episodes of neutropenia occurring at more or less regular intervals. The most commonly reported period of oscillation is 20-21 days, but intervals as short as 14 and as long as 35 days are recorded. There is a cyclic reduction in the granulocyte proliferative pool in the bone marrow followed by the onset of neutropenia.This is to say, they change during the cycle and although numbers are recurrently low, their function is normal.[1]In addition to consistent neutropenia, this condition is associated with lymphocytosis, variable eosinophilia, monocytosis, and decreased normal leukocyte count. [2]This disorder also has the capacity to affect other blood counts. When patients reach adolescence, they experiment symptom decrease and cycles become less noticeable. [3]The clinical picture might include the following manifestations: susceptibility to infections, fever, fatigue, impetigo, increase in the size of lymph nodes, periodontitis, cheilitis,stomatitis.

Diagnosis can be emitted when the following can be established: cyclic episodes of 200 total neutrophils per mm^3, every three weeks for a period of 3 to 6 days. To achieve confirmation, blood count must be performed 2 to 3 times a week, during 8 weeks.

Cyclic neutropenia was first described by Leale in 1910as a distinct entity in a 19-month-old boy who presented with periodic regular recurrence of neutropenia, mouth ulcers, and fever. He depicted it as a condition with autosomal dominant character, a result of the mutation of EIA2 gene, position 13.3 of the short arm of chromosome 19 which codifies neutrophil elastase. Its time span is occurrence within a rank of 14 to 36 days, normally around day 21, with duration of 3 to 6 days. It is more common for infections to appear during the period when there are few circulating neutrophils. [4]

Berardinis and Reiman in 1949 suggested the cause for this disease to be an autosomal dominant inheritance, which was later confirmed by Morley *et al*. in 1967. On the other hand, congenital neutropenia is a heterogeneous disorder of less well-defined entity. [4]Described by Kostmann in 1956, it is also known as Kostmann syndrome.[5]

This is a rare condition with prevalence of one in a million. Congenital neutropenia has estimated frequency of 2:1,000,000–3:1,000,000 in the general population, however, the cyclic variant has a frequency of 1:1,000,000 in general population including those cases of familial and simplex type.[6]With respect to incidence it can be said that frequency is 2 cases per million subjects. [7]

Cyclic neutropenia occurs in people of all racial and ethnic groups around the world. It affects males and females in equal numbers. Most cases of cyclic neutropenia are thought to be present at birth (congenital); however, in some cases, the symptoms may not become obvious until childhood, adolescence, or early adulthood.[8]

Cyclic neutropenia is a subdivision of severe chronic neutropenia. Severe chronic neutropenia is estimated to affect approximately 0.5 to 1 per million population in the United States. (For more information on severe chronic neutropenia, see the Related Disorders section of this report.)Chronic idiopathic neutropenia in adults is also acquired. It occurs predominantly in adolescent girls and women, beginning at approximately age 15 and usually lasting, in terms of its initial onset, until the mid-30s. The pattern is similar to that of lupus and some other autoimmune diseases, but it is not a predecessor of those diseases. [8]

The cause of cyclic neutropenia is almost always a mutation in *ELANE*, the gene that encodes neutrophil elastase. This gene is for an enzyme that is produced and packaged in the primary granules of neutrophils. The mutation causes the production of an abnormal protein that damages the cells as they develop, leading to a failure of cell production. Among the many different mutations that can occur, some are associated with cycling of blood counts. This manifestation is probably a milder abnormality than that associated with severe congenital neutropenia, in which mutations are so severe that patients have very low blood counts all the time.Chronic neutropenia—neutropenia that lasts for weeks, months, or years—has a number of other causes. In some patients, it is due to a congenital disorder; we know of

several mutated genes that can be detected. In other patients, it is an acquired disorder that is not yet well understood. The acquired conditions are much more common. The most common is chronic benign neutropenia of childhood, which may be an autoimmune disease. [8]

Although an autosomal dominant pattern of inheritance has been described in few cases, most were isolated.[9]. We do not know the cause of the genetic mutations that result in cyclic neutropenia.

The best evidence suggests that the mutations occur spontaneously. It is also unknown why chronic neutropenia occurs. The acquired diseases that hematologists see are unpredictable in their onset. We have not identified, for example, an immunotype, human leukocyte antigen type, or blood type that predisposes to these illnesses. Chronic neutropenia can also be a feature of other diseases and infections; in the 1990s, HIV infection was a common predisposing cause. It is not understood, however, how a viral infection could trigger chronic neutropenia. In some patients, an autoimmune disease can trigger a T-cell response. Neutropenia can develop in patients with large granular lymphocyte syndromes, and this condition might be a predisposing factor.

Pharmacological treatment of granulocyte colonies stimulating factor (G-CSF) promotes maturation of neutrophil-precursor cells.Under normal circumstances, G-CSF is mainly produced in the bone marrow. When there is bacterial infection, G-CSF production increases due to the stimuli produced by certain components of the infectious agent on immune system cells. Final result is increase of neutrophil maturation in the bone marrow, greater release of said neutrophils into the bloodstream as well as activation of said cells functions, that is to say, their ability to destroy pathogen agents.Treatment is IV administration of «granulocyte colonies stimulation factor» (G-CSF), whose function, as indicated by its name, is to stimulate neutrophil production and shorten neutropenia duration, which brings along symptom's decrease. In cases when the patient does not react favorably, bone marrow transplant or corticosteroids can be used.

2. Results

We report a male patient 79 years of age, with 33-year history of disease, with recurrent fevers lasting 5 days with gaps in between, every 4-5 weeks, showing tendency these gaps to be reduced in the course of years up to 10 days in the last months. Fevers have been accompanied by aphthous ulcers, and rarely by more severe infections as well as weight loss. The initial WBC count was $2{,}3x10^9$/L without neutrophils recorded on blood film. Immunophenotyping revealed that majority of these were T-lymphocytes CD 3+, with both kappa and lambda light chains present. The immunoglobulin investigations confirmed high polyclonal levels of immunoglobulin IgG 28,5g/L, IgA 10,8g/L and IgM 4,7g/L. In February 2001 these investigations were repeated and confirmed by Prof.E.C.Gordon-Smith in St.George's Hospital in London, UK. Antineutrophil antibody investigations were carried out by the International Blood Group Reference Laboratory in Bristol, UK. The indirect granulocyte immunofluorescence test was positive (IgM), suggesting the presence of granulocyte-specific IgM antibodies in the serum of the patient. The impression gained was of highly stimulated reactive immune system. In 1999 the treatment was started with G-CSF (and occasionally antibiotics) in the periods only when WBC count was less than $1{,}5x10^9$/L in the next 9 years. In 2005-2006 a trial was made with Rituximab 375mg/m^2-12 doses, without spectacular improvement. From 2008 till 2015 he has been on weekly therapy with G-CSF, and from 2016 till now on twice weekly therapy with G-CSF, with normal WBC count and ANC varying from 110-3960, without any significant infection. It has to be noticed that from 2012 the patient has had thrombocytopenia varying from 60 - 110x109/L, without haemorrhage.

3. Discussion

The novel treatments go hand in hand with understanding the disease mechanisms and finding ways to target them. Dale et al. published a study in *Blood* examining the use of a targeted therapy, the CXCR4 antagonist plerixafor (Mozobil, Genzyme), for a rare cause of chronic neutropenia known as myelokathexis or WHIM syndrome (for warts, hypogammaglobulinemia, infections, and myelokathexis). This drug shows promise in the way it raises blood counts, including both neutrophils and lymphocytes. [10]They are planning clinical trials to test long-term effectiveness.Studies are under way to explore the hypothesis that blocking the effect of the mutated gene might impair its ability to damage cells and cell production. In other diseases, research of this approach is in various stages of development. The next few years will be exciting as we attempt to develop specific, targeted therapies for patients with these conditions.[8]

One of the biggest questions is why some people with chronic neutropenia have disorders that predispose to leukemia. The underlying mechanisms for leukemic evolution are not known, but patients with severe congenital neutropenia caused by mutations in neutrophil elastase or genes such as *HAX1* develop leukemia at a high rate. We estimate that the lifetime risk is approximately 20–30%.

There are also opportunities for research on the basic causes of neutropenia. We know now that several genes can be mutated to cause neutropenia, but we do not know all of the mechanisms or all of the genes, and much research is focused on these areas. G-CSF has been a very effective therapy, but we would like to find other widely applicable ways to treat neutropenia.[8]

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