A case of cyclic neutropenia in adults

Muhammad Sohail Mansoor,[1] Muhammad Bilal Salman Khan[2]
Medical Ward-D, Khyber Teaching Hospital, Peshawar,[1] Department of Medicine, Agha Khan University Karachi.[2]

Abstract

A 22 years old patient presented with recurrent episodes of diarrhoea, pharyngitis, apthous ulcers and fever for the past 6 months. The episodes lasted a week each time. The patient was admitted and blood studies revealed neutropenia with increased number of Large Granular Lymphocytes. Later on it was found out that his neutrophil count dropped to less than 0.2 x 10^9/L after every 3 weeks. Bone marrow study revealed decreases neutrophil precursors during these episodes. He was diagnosed with adult onset cyclic neutropenia and his episodes were treated with G-CSF and Ceftriaxone.

Keywords: Diarrhoea, Pharyngitis, Apthous ulcers, Neutropenia, Granular lymphocytes.

Introduction

ELANE-related neutropenia includes congenital neutropenia and cyclic neutropenia, both of which are primary haematologic disorders. Cyclic neutropenia is a rare neutrophil disorder in which the neutrophil count drops to a very low level at intervals of about 3-4 weeks. This is due to oscillation in the production of neutrophils by bone marrow.[1] The symptoms include fever, aphthous stomatitis, lymphadenopathy, malaise and sometimes severe infections. It can be present in several members of the same family. The disease can arise spontaneously or it can be autosomal dominant in which case it is inherited by mutations in ELANE previously known as ELA-2, which is the gene encoding neutrophil elastase. In between neutropenic periods, affected individuals are generally healthy.

Case Report

A 22 years old male patient, presented with diarrhoea, sore throat and fever for the past 3 days. The diarrhoea was non-bloody with abdominal pain. The sore throat was associated with dysphagia and ulcers in the mouth. He was having these symptoms every month for the past 6 months and these symptoms resolved within a week. He had no family history of such symptoms and rest of the history was unremarkable. On examination he had weight loss, cervical lymphadenopathy and fever of 104°F. Examination of the throat revealed pharyngitis and aphthous ulcers while abdominal examination showed generalized abdominal tenderness with no other abnormality. Rest of the physical examination was unremarkable. Various laboratory tests were performed including full blood count, bone marrow studies and various cultures which showed neutropenia, streptococcal pharyngitis and Campylobacter jejuni in stools. Further studies revealed decreased neutrophil precursors in bone marrow. The patient's condition improved after treatment with G-CSF and Ceftriaxone. Three weeks later he came with the same complaints as before. This time his neutrophil count was monitored on alternate days for 2 months and it showed a mean of 0.128 x 10^9/L neutrophils during the spells of fever with normal counts in-between. Thus a diagnosis of cyclic neutropenia was made. The patient was provided symptomatic treatment, G-CSF and Ceftriaxone during the subsequent neutropenic spells. This reduced the duration and frequency of neutropenic spells and the severity of infection.

Discussion

Cyclic neutropenia is a rare benign haematological disorder and has an estimated frequency of 1:1,000,000 in the general population.[2] It is one of the two types of ELANE related neutropenias with cyclic neutropenia being rarer than the other. Pathogenesis of cyclic neutropenia became clear with cellular studies demonstrating that accelerated apoptosis of neutrophil precursors is the proximate cause of the reduced neutrophil production.[3]

Cyclic neutropenia is usually diagnosed within the first year of life while in this case the disease was diagnosed in adulthood. Difference in onset of disease suggests heterogeneity in its pathophysiology. Patients with adult onset cyclic neutropenia have increased numbers of circulating large granular lymphocytes (LGL) while children with cyclic neutropenia have a normal number of LGL as was evident in this case showing increased number of LGL.[4] The symptoms of cyclic neutropenia tend to be more severe in children than in adults. More than 60% of individuals with cyclic neutropenia experience oral ulcerations, gingivitis, lymphadenopathy, fever, pharyngitis/tonsillitis, fatigue, and skin infections five or more times a year. More than 30% of adults report five or more episodes per year of sinusitis and/or otitis media, and over 20% of children report at least five episodes per year

of bone pain or tooth abscesses. More than 10% of individuals report pneumonia, bronchitis, diarrhoea, or anal ulcers.[5]

The diagnosis of ELANE-related neutropenia relies primarily on serial measurements of the absolute neutrophil count (ANC) and clinical findings; in this case which were pharyngitis, aphthous ulcers and a mean ANC count of 0.128 x 10^9/L during the neutropenic episodes. Molecular genetic testing of ELANE, the only gene in which mutation is known to cause ELANE-related neutropenia, is available. Unlike this case which had no family history, individuals with known affected family members, the mutation detection rate is as high as 100%.[6] Mutations in more than one gene associated with neutropenia have been identified in some individuals.

Studies show that G-CSF and antibiotics are the first line treatments: Our patient was given these and he showed remarkable improvement within a month. In cyclic neutropenia, G-CSF shortens the periods of neutropenia as well as the length of the neutropenic cycle. This treatment is known to be effective at least as early as the age of six months to one year. For affected individuals with a well-matched donor, haematopoietic stem cell transplantation (HSCT) may be the preferred treatment option.[7]

Untreated individuals have recurrent oropharyngeal inflammation; they are particularly prone to developing oral ulcers during neutropenic periods at three-week intervals. Cellulitis, especially perianal cellulitis, is common during these periods. Bacteraemia is rare and the greatest risk of mortality appears to be from necrotizing enterocolitis, peritonitis, and Clostridium and/or E. coli sepsis.[8]

New therapeutic interventions like cord blood transplantation for these patients is being investigated but the results depend upon the compatibility of the donor.[9] Cyclic neutropenia is not associated with risk of malignancy or conversion to leukaemia.[3] but recent studies show that some ELANE mutations may possibly be associated with severe congenital neutropenia and increased risk of acute mycboid leukaemia.[10]

Conclusion

Cyclic neutropenia is a rare blood disorder that may occur spontaneously or it may be autosomal dominant. Periodicity of cyclic neutropenia has a cyclic pattern reoccurring usually at 21 or 28 days interval. This diagnosis can be easily over looked due to its rarity and non specific symptoms. Despite the intermittent and chronic nature of the disease, patients with cyclic neutropenia grow and develop normally and under the proper care of a physician, they can lead a normal life.

References

1. James William D; Berger Timothy G. Andrews' Diseases of the Skin: Clinical Dermatology. USA: Saunders Elsevier 2006; ISBN 0-7216-2921-0.
2. Dale DC. "ELANE- Related Neutropenia," 2000. Bookshelf ID: NBK1533 PMID, 2002; 20301705.
3. Aprikyan AA, Liles WC, Rodger E, Jonas M, Chi EY, Dale DC. Impaired survival of bone marrow hematopoietic progenitor cells in cyclic neutropenia. Blood 2001; 97: 147-53.
4. Loughran TP Jr, Clark EA, Price TH, Hammond WP. Adult onset cyclic neutropenia is associated with increased large granular lymphocytes. Blood 1986; 68: 1082-7.
5. Palmer SE, Stephens K, Dale DC. Genetics, phenotype, and natural history of autosomal dominant cyclic hematopoiesis. Am J Med Genet 1996; 66: 413-22.
6. Dale DC. Neutropenia and neutrophilia. In: Williams WJ, et al, eds. Hematology, 6th ed. New York: McGraw-Hill, 2001; pp 823-34.
7. Choi SW, Levine J. Indications for hematopoietic cell transplantation for children with severe congenital neutropenia. Pediatr Transplant 2010; 14: 937-9.
8. Barnes C, Gerstle JT, Freedman MH, Carcao MD. Clostridium septicum myonecrosis in congenital neutropenia. Pediatrics 2004; 114: e757-60.
9. Mino E, Kobayashi R, Yoshida M, Suzuki Y, Yamada M, Kobayashi K. Umbilical cord blood stem cell transplantation from unrelated HLA-matched donor in an infant with severe congenital neutropenia. Bone Marrow Transplant 2004; 33: 969-71.
10. Bellanne-Chantelot C, Clauin S, Leblanc T, Cassinat B, Rodrigues-Lima F, Beaufils S, et al. Mutations in the ELA2 gene correlate with more severe expression of neutropenia: a study of 81 patients from the French Neutropenia Register. Blood 2004; 103: 4119-25.