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A case of cyclic neutropenia

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ABSTRACT

A 14-year-old girl presented with recurrent episodes of pharyngitis, aphthous ulcers, diarrhea and fever for the past four years. The episodes lasted a week each time. The patient was admitted and blood studies revealed neutropenia. On further investigations, it was found that her neutrophil count dropped to less than $0.5 \times 10^9/L$ after every three weeks. Bone marrow study was normal. She was diagnosed as cyclic neutropenia.

INTRODUCTIONS

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 located at 19p13.3. This enzyme is synthesized in neutrophil precursors early in the process of primary granule formation. In between neutropenic periods, affected individuals are generally healthy. Cyclic neutropenia is effectively treated with granulocyte colony-stimulating factor (G-CSF).

CASE REPORT

A 14-year-old female patient, presented with fever, repeated vomiting and loose stool for one day. The diarrhoea was non-bloody with abdominal pain. She was having these symptoms and sometimes sore throat and aphthous ulcers every month for the past four years and these symptoms resolved within a week. She had no family history of such symptoms and rest of the history was unremarkable. On examination, she had fever of 101°F with generalized abdominal tenderness. Rest of the physical examination was unremarkable. Various laboratory tests were performed including full blood count, routine urine and blood cultures which showed neutropenia, with normal urine and negative blood culture.

Patient's condition improved after treatment with ceftriaxone. On reviewing her past records, it was found that she had multiple hospital admissions with neutropenia. She also had normal neutrophil count in between. Bone marrow aspiration and biopsy done during her previous hospital admission was normal. Possibility of connective tissue disorder was ruled out with negative antinuclear antibody (ANA). This time her neutrophil count was monitored on alternate days for six weeks and it showed a mean of neutrophils during illness with normal counts in-between. Thus, a diagnosis of cyclic neutropenia was made. The patient was provided symptomatic treatment and ceftriaxone during the subsequent neutropenic spells. Availability of G-CSF and its role in reducing the duration and frequency of neutropenic spells and severity of infections was counselled to parents.

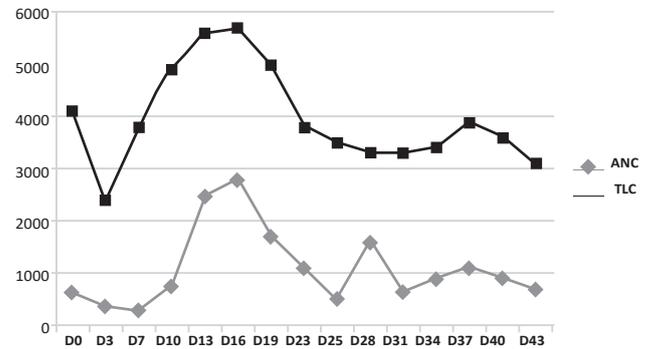


Figure 1. Absolute Neutrophil Count (ANC) and total leucocyte count (TLC) cycle Day 0-Day 43

DISCUSSIONS

Cyclic neutropenia is a rare benign haematological disorder and has an estimated frequency of 1:1,000,000 in the general population.² As blood monocytes, reticulocytes, platelets, and lymphocytes oscillate with the same periodicity as blood neutrophils, the disease is sometimes called periodic or cyclic hematopoiesis. The first case of cyclic neutropenia was reported in 1910 in a 3-month-old boy with recurrent fever, furunculosis, and severe neutropenia.³ In 1930, the blood cell oscillations and continuing cyclic pattern of recurrent illness in this patient was reported again.⁴ Important milestones in the understanding of this disorder was recognition of the autosomal dominant pattern of transmission in 1949.⁵

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.⁶

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. 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, diarrhea, or anal ulcers.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. The diagnosis of ELANE-related neutropenia relies primarily on serial measurements of the absolute neutrophil count (ANC) and clinical findings; in our case which were pharyngitis, aphthous ulcers, diarrhea and a mean ANC during the neutropenic episodes.

Studies show that G-CSF and antibiotics are the first line treatments: our patient was given ceftriaxone and she showed remarkable improvement. In cyclic neutropenia, G-CSF shortens the periods of neutropenia as well as the length of the neutropenic cycle. For affected individuals with a well matched donor, haematopoietic stem cell transplantation (HSCT) may be the preferred treatment option.⁸

Cyclic neutropenia is not associated with risk of malignancy or conversion to leukaemia.⁶ but recent studies show that some ELANE mutations may possibly be associated with severe congenital neutropenia and increased risk of acute myeloid leukaemia.⁹

CONCLUSIONS

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 re-occurring usually at 21 or 28 days interval. This diagnosis can be easily overlooked 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.

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