LETTER TO EDITOR (VIEWERS CHOICE)

FEBRILE NEUTROPENIA - CAN IT BE CYCLIC NEUTROPENIA?

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A 5 month old infant girl presented to her paediatrician with fever of 39oC, cough and runny nose of 1 day duration. Apart from reduced feeding and mild irritability, there were no other localising symptoms. Physical examination revealed a well-appearing infant who was febrile but not toxic. There were a few ulcers over the hard palate and a mildly injected pharynx. The rest of the physical examination was normal. The primary paediatrician ordered a complete blood count (CBC) and C-reactive protein (CRP), in view of the infant's young age and high grade fever. Hemoglobin was 11.9 gm/dL, white blood cells (WBC) were 8330 cells/cumm (84.9% lymphocytes, 11.4% monocytes, 2.5% neutrophils) with absolute neutrophil count (ANC) of 90 cells/cumm and platelet count was 319,000 cells/cumm. CRP was 78 mg/L. She was admitted to our unit and blood and urine cultures were obtained before starting empiric broad spectrum IV antibiotic (cefepime). Blood culture grew acinetobacter baumannii, which usually causes nosocomial infections but can be a pathogen in patients with organ transplants and febrile neutropenia. The absolute neutrophil count (ANC) dropped further to 50 cells/cumm in 2 days, but the rest of the cell lines remained normal. Her fever resolved by the 4th day of antibiotics and repeat blood cultures were also sterile. She received intravenous cefepime for 7 days and antibiotic was then switched to oral trimethoprim-sulfamethoxazole prophylaxis. Her ANC had shown recovery to 1750 cells/cumm by the time of discharge from the hospital. The patient was given weekly follow up appointments for evaluation of neutropenia. Serial blood counts were performed twice a week after her discharge. Serial ANCs are depicted in Table 1. About 10 days following her discharge, the ANC dropped again, by the end of 2 weeks from the last nadir. This was accompanied by low grade fever and mild coryzal symptoms. Blood culture this time was negative. This periodicity of the neutropenia which continued in cycles of 2-3 weeks is highly suggestive of cyclic neutropenia. The genetic testing was offered but not accepted by parents. The patient was on antibiotic prophylaxis with trimethoprim-sulfamethoxazole which was discontinued after week 3 as ANC improved with higher nadirs. G-CSF was not given as the patient remained very well and the periodic ANC nadirs were higher. Bone marrow examination was considered initially but was not pursued as the ANC showed significant improvement to the normal levels after the initial months. At 8 weeks, after her initial presentation, the ANC improved to 2400 cells/cumm and it remained over 2000 cells/cumm most of the time except during the nadir period and other cell lines were perfectly normal.

Cyclic neutropenia is an autosomal dominant hematological disorder affecting 0.5-1 per million persons. (1) It is characterised by regular oscillations of the peripheral blood neutrophil counts with periods of severe neutropenia occurring roughly every 2 to 3 weeks and lasting 3 to 6 days. (1) Cyclic fever in an otherwise well child or a family history of neutropenia or recurrent infections may alert the clinician to this condition. Obtaining blood counts 2 to 3 times a week for 4 to 6 weeks in an effort to observe this periodicity would usually clinch the diagnosis. Mutations of the ELANE gene are considered largely responsible for most cases of cyclic neutropenia and molecular genetic testing is positive in 90-100% of the patients. (2) Cyclic neutropenia is not associated with risk of malignancy or conversion to leukemia. (3) A steadily declining ANC would suggest alternative diagnoses such as an infectious, autoimmune or neoplastic cause and would require further investigation. During periods of profound neutropenia, the patients are predisposed to fever, mouth ulcers, gingivitis, lymphadenopathy and bacterial skin infections. (2) The young infant is particularly at risk of developing bacteremia and septic shock, especially with prolonged durations of severe neutropenia as was seen in our patient. Treatment with granulocyte-colony stimulating factor (G-CSF) will shorten the periods of neutropenia as well as the length of the neutropenic cycle. (3) Daily or alternate-day injections of G-CSF, in a dose of approximately 2 µg/kg/day may be given if neutropenia is profound and there are frequent bacterial infections. (1,3)

Table 1: Serial neutrophil counts of the patient

Week 1			**Week 2**		**Week 3**		**Week 4**		**Week 5**		**Week 6**		
Day	1	3	7	3	7	3	7	3	7	3	7	3	7
ANC (cells/cumm)	90	50	1750	1030	960	830	120	860	950	1200	760	330	760

Note: ANC – absolute neutrophil count

Hematopoietic stem cell transplantation (HSCT) is a treatment option for patients who are refractory to high-dose G-CSF treatment. (3) Prophylactic antibiotics are used as additional protection when ANC is very low. All immunizations should be done according to the routine vaccination schedule, as long as the neutropenia is not associated with an immunodeficiency syndrome. (1) Prenatal testing is possible for pregnancies at increased risk if there is family history; however, requests for prenatal testing is not common as this is a benign condition. (3) The disease has a benign course as symptoms improve in adulthood. (3)

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References :

1. Segel GB, Halterman JS. Neutropenia in Pediatric Practice. Pediatr Rev. 2008;29(1):12-23; quiz 24
2. Dale DC, Bolyard AA, Aprikyan A. Cyclic Neutropenia. Semin Hematol. 2002 Apr; 39(2):89-94.
3. Dale DC. ELANE-Related Neutropenia. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al (eds). GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. 2002 Jun 17

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