



CORRESPONDENCE

Morphology As a Guide to the Diagnosis of a Rare Cause of Neutropenia

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Dear editor,

Systematic approach to neutropenia is very important to arrive at timely appropriate diagnosis. Myelokathexis is a very rare morphological variant presenting with neutropenia and associated with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis [WHIM syndrome]. We present a case of an adolescent boy who was incidentally detected to have myelokathexis.

A, 15 year-old developmentally normal boy underwent routine investigation due to parental anxiety as his elder sibling succumbed to metastatic neuroblastoma. Investigation revealed severe neutropenia and other two cell lines were normal. Child was asymptomatic with no recent infections, loss of appetite/weight, bleeds, bone pain or fever. He had normal growth and didn't have dysmorphism, lymphadenopathy or organomegaly. Past history suggested drainage and antibiotics for an episode of neck abscess at 8 years of age.

Total WBC count was 1400/ μ L with differential count of Neutrophils-19% [Absolute Neutrophil count-ANC-266/ μ L], Lymphocytes-64%, Eosinophils-4%, Monocytes-12%. Peripheral smear showed leukopenia with no abnormal morphology. Vitamin B12 level was normal; ANA was

negative and all serum immunoglobulins were decreased with low-normal levels [in g/L-IgG-7.15 7–16], IgM-0.427[0.4–2.3], IgA-0.78[0.8–4] and IgE < 18 in IU/mL].

Bone marrow examination showed myeloid hyperplasia with myeloid-erythroid ratio of 4.4:1. Almost all the neutrophils in marrow show hypersegmented nuclei with highly condensed chromatin, nuclear lobes separated by long, thin strands of chromatin, and cytoplasmic vacuolation consistent with the diagnosis of myelokathexis (Fig. 1). Karyotyping was normal. Clinical exome sequencing revealed a heterozygous nonsense variation in exon-1 of the CXCR4 gene [chr2:136872498G > A]. Complete blood counts of parents were normal.

In the index child, trial of G-CSF at 5 μ g/kg showed good neutrophil increment. We have planned to support him during febrile neutropenia with G-CSF injections and appropriate antibiotics. Child has remained asymptomatic during 1 year of follow-up with ANC ranging between 220 and 460/cubic mm. Parents were counselled regarding the neutropenic care and Human Papilloma virus [HPV] vaccine.

The diagnostic approach to neutropenia involves a careful analysis of clinical pattern, peripheral smear, bone marrow aspiration/biopsy, immunodeficiency screening and genetic evaluation.

Myelokathexis, initially described by Zuelzer [1], is a congenital disorder that causes severe chronic leukopenia. Recurrent bacterial infection is due to neutropenia and depressed functional activity of neutrophils.

Despite the peripheral neutropenia, bone marrow aspirates from affected individuals contain abundant mature myeloid cells, a condition termed myelokathexis, which means retention of myeloid cells. Characteristic findings include myeloid hyperplasia and hyper-segmentation of mature neutrophils due to accelerated apoptosis of

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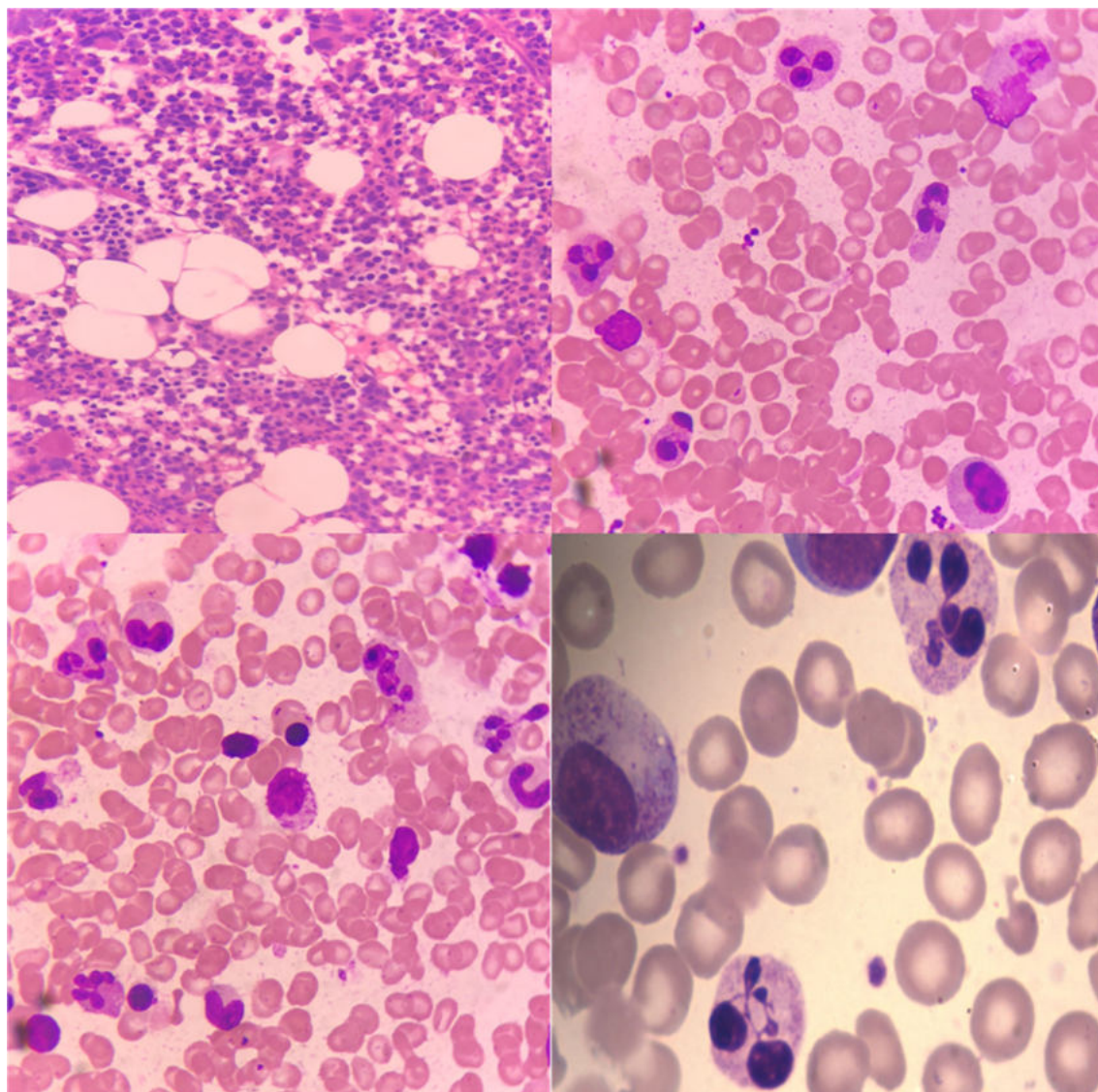


Fig. 1 Mature neutrophils with thin chromatin bridges connecting the multiple lobes and myeloid hyperplasia found in the bone marrow aspirate of index child (low and high power fields shown)-stain used is MGG stain (May Grunwald Giemsa stain)

neutrophil precursors and prolonged retention of neutrophils in bone marrow compartment. Pathogenesis is mediated by CXCR4 hyperfunction, leading to increased responsiveness to its unique ligand CXCL12, which causes impairment of cellular homeostasis and trafficking in the bone marrow [2].

WHIM syndrome, caused by heterozygous mutations in the CXCR4 gene, is inherited in an autosomal dominant pattern and is characterized by neutropenia and hypogammaglobulinemia. Rarely, patients with WHIM syndrome have been reported with congenital cyanotic heart diseases, most commonly, tetralogy of Fallot. Reduction in the number of naïve T-cells and circulating memory B cells explains the immunodeficiency state associated with this condition. There is very high predisposition to HPV

infection leading to warts in 70% population and related malignancies [3].

The onset of symptoms usually happens in first decade; however, late presentations in second or third decade of life have been reported. Hence, long term follow-up plan must be clearly explained to the family regarding infection prevention, HPV vaccination and need to screen for malignancies at periodic intervals. Administration of G-CSF/GM-CSF in these patients helps in release of neutrophils and symptomatic improvement, especially during episodes of infection [4]. Pleraxifor has also been shown to be useful in release of mature neutrophils from bone marrow [5].

Meticulous observation of morphological features can aid in diagnosis of this rare condition, avoid unnecessary investigations and guide in appropriate management.

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