Severe congenital neutropenia

Durgesh Kannam[1], Harish G V[2], Swapnik K[3]

[1,2]Assistant Professor, [3]Postgraduate Student, Department of Paediatrics, Prathima Institute of Medical Sciences, Karimnagar, Telanagana, India.

Address for Correspondence: Dr. Durgesh Kannam, Assistant Professor, Department of Paediatrics, Prathima Institute of Medical Sciences, Karimnagar, Telanagana, India.

Email: durgeshkannam1978@gmail.com

ABSTRACT

Severe congenital neutropenia is an uncommon disorder.The incidence of severe congenital neutropenia is estimated to be 1 in 200,000 individuals. One subtype of congenital neutropenia, Kostmann syndrome, was originally described as an autosomal-recessive disorder. Autosomal-dominant and sporadic cases have also been reported. We report the case of 2.5-year-old male child who developed recurrent respiratory tract infections and skin infections, with all the other parameters being normal except persistent severe neutropenia.

Keywords: Congenital neutropenia, recurrent respiratory tract infections, Kostmann syndrome

INTRODUCTION

It has been just over 50 years since Rolf Kostmann, a student at the Karolinska Institute in Stockholm, Sweden, described "infantile genetic agranulocytosis" in his doctoral thesis[1], the first description of severe congenital neutropenia (SCN), also termed Kostmann Syndrome. Neutropenia in children is mostly due to infection especially viral infection and this is not severe (>0.2×10^9 cells per liter). This usually recovers within few days. Chronic neutropenia is one which persists for greater than 3 months. This is relatively rare entity. It is characterized by peripheral blood absolute neutrophil count of less than 500, maturation arrest of myeloid precursors at promyelocyte or myelocyte stage within bone marrow and recurrent bacterial infections[2]. Incidence is 1 to 2 cases per million[3].

CASE REPORT

A 2.5-year-old male child presented with fever, cold and cough for 2 days with a significant past history of recurrent skin infections, recurrent respiratory tract infections and ear discharge, with other histories being unremarkable. On examination child was febrile (102°f), skin showing healed scars, purulent discharge from ears, cervical lymphadenopathy and hepatosplenomegaly. Also the anthropometric measurements were less than 3rd percentile i.e. failure to thrive. Complete blood picture (CBP) was done and values shown in Table 1. Differential leukocyte count shows neutrophils 36%, lymphocytes 54%, eosinophils 4%, monocytes 6%, basophils 0% and absolute neutrophil count (ANC) of 260, Absolute eosinophil count (AEC) of 104, Absolute lymphocyte count (ALC) of 3484.

Table 1: Showing CBP values

Hemoglobin	6.3 g/dl
WBC	6000 cells/cu.mm
MCV	57.7 fl
MCH	17.5 pg
MCHC	30.3 g/dl
Platelet count	6.7 lakh
ESR	45 mm
Absolute neutrophil count	260 cells/cu.mm

Peripheral smear showing microcytic hypochromic picture with few pencil forms and tear drop cells. WBC showing moderate neutropenia, reactive lymphocytosis and monocytosis. Platelets showing reactive thrombocytosis. Bone marrow aspiration showing normal cellularity, myeloid to erythroid ratio of 1:1.5. Erythroid prominence with both normoblastic and micro normoblastic maturation.

Liver function tests (LFT) and Renal function tests (RFT) were within normal limits. FNAC from cervical lymph node showed features of reactive lymphadenopathy.

Child was kept on first line antibiotics. Based on culture reports, antibiotics were changed accordingly. Child responded well clinically and the repeated CBC showed persistent neutropenia of less than 500 cells per cu.mm for the following 6 weeks.

DISCUSSION

Congenital neutropenia is defined as peripheral absolute neutrophil count (ANC) of less than 1500 cells per cu.mm. Further categories include mild neutropenia of absolute neutrophil count between 1000 and 1500 cells per cu.mm, moderate neutropenia of ANC between 500 and 1000

cells per cu.mm, severe neutropenia of ANC between 200 to 500 cells per cu.mm and very severe neutropenia of ANC less than 200 cells per cu.mm[4]. Patients with congenital neutropenia are prone to severe recurrent bacterial infections such as otitis media, bronchitis, pneumonia and osteomyelitis[5].

In contrast to congenital neutropenia, cyclic neutropenia is characterized by oscillating neutrophil count usually following a 21-day period. In addition to quantitative abnormalities, many patients with congenital neutropenia show qualitative neutrophil aberrations. A prominent finding in congenital neutropenia is maturation arrest in neutrophil differentiation. Bone marrow smear typically reveal an absence of mature neutrophil granulocytes while promyelocytes are present[6].

From a clinical perspective, congenital neutropenia may be an isolated hematologic finding or may be a feature associated with involvement of other organs such as skin, brain, heart, pancreas, urogenital tract[7]. The original pedigree described by Kostmann displayed autosomal recessive inheritance of SCN, and these patients did not have mutations in the Ela2 gene. Genome-wide linkage studies reported by Klein et al have confirmed that the gene for autosomal recessive SCN is HAX1[8]. HAX1 is a ubiquitously expressed mitochondrial protein with weak homology to bcl-2 that represses apoptosis. It is hypothesized to have a role in maintaining the mitochondrial membrane potential, loss of which leads to the release of cytochrome C and other proapoptotic proteins into the cytoplasm. Rare cases of SCN have been attributed to mutations in other neutrophil-specific genes. X-linked SCN has been reported in a few patients with novel mutations in the Wiskott-Aldrich syndrome protein (WASp)[9].

CONCLUSION

Apart from the usual causes of neutropenia in children, malignancies and congenital neutropenia should also be considered in differential diagnosis. This would help in the early diagnosis and properly directed treatment to the condition diagnosed.

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