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CASE REPORT

Uncommon cause of recurrent infections

Uday R. Deotare,
Pranav D. Patel[1],
Rohan P. Parikh[2],
Eva A. Bhagat

Department of Hematology, Sterling Hospital, Memnagar, Ahmedabad, [1]Research Volunteer, St Luke's Roosevelt Hospital, New York, [2]Resident, General Medicine, B. J. Medical College, Ahmedabad, Gujarat, India

Address for correspondence:
Dr. Pranav Dineshkumar Patel,
Plot No-1235/2, Sector-7 D,
Opp. Chaudhary School,
Gandhinagar - 382 007,
Gujarat, India.
E-mail: pranav1151@gmail.com

ABSTRACT

We descibe the case of a girl of Indian origin who presented with recurrent infections. The only abnormality detected in the armoury of the immune system was consistent neutropenia. Mutation analysis revealed ELA2 (neutrophil elastase) gene mutation that has been associated with severe congenital neutropenia phenotype. Patient was treated with the granulocyte-colony stimulating factor (G-CSF) as prevention of infectious manifestations along with appropriate measure to curb secondary complications. She showed poor response to the G-CSF during stringent surveillance. After being on treatment for 1 year, she developed acute myelogenous leukemia as inherit complication of this disease.

Key words: *Acute myelogenous leukemia, ELANE (elastase, neutrophil expressed) gene – related neutropenia, granulocyte-colony stimulating factor, hematopoietic stem-cell transplant, kostmann syndrome, severe congenital neutropenia*

INTRODUCTION

A common reason for bringing an infant or child for medical visit is recurrent infections. This may refer to infections that are too great in number, too severe, or too long lasting; that are associated with unusual complications; or that fail to resolve with standard therapy.

Only 10% of such cases are due to deficiency in immunity either adaptive or innate.[1] Congenital neutropenia has an estimated frequency of two to three per million in the general population.[2]

ELANE (elastase, neutrophil expressed) gene – related neutropenia includes congenital neutropenia and cyclic neutropenia, both of which are primary hematologic disorders characterized by recurrent fever, skin, and oropharyngeal inflammation (ie, mouth ulcers, gingivitis, sinusitis, and pharyngitis), and cervical adenopathy. The diagnosis of ELANE-related neutropenia relies primarily on serial measurements of the absolute neutrophil count (ANC) and clinical findings. Molecular genetic testing of the ELANE gene, the only gene known to be associated with ELANE-related neutropenia, is available on a clinical basis.

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CASE REPORT

A 3-year-old girl was presented to the clinic with the complaint of recurrent fever in mid-September of the year 2009. There was no significant birth history. During infancy, she had normal growth and no complaints suggestive of exocrine pancreatic insufficiency. On examination her stature was normal, there were no abnormality in skin pigmentation. On per abdominal examination no organomegaly was evident. Investigations revealed ANC of 639 cells/mm^3, that is, moderate neutropenia but other parameters were in normal range. Symptomatic treatment along with proper antibiotics were given. She was advised biweekly follow-up for repeat cell count and monitoring for objective evidence of illness due to lack of authoritative past history, ie, history of recurrent fever prior to presentation in the clinic.

She had to present everytime prior to the date of follow-up due to fever with either boils on skin or upper respiratory tract infection symptoms. Everytime the only culprit on investigation sheet was ANC. It was in the range of moderate neutropenia. It was then decided to put her on antibiotic prophylaxis and self-care advise including dental hygiene were explained to parents. Henceforth, incidences and severity of infection dropped significantly.

Follow-up visit throughout the period of 3 months showed consistent neutropenia with no cyclical variation in the count. She neither had any evidence of infection or disease that could result in neutropenia nor was on any drug that could result in the same. So the probability of the Kostmann syndrome was rated high. Parents of the patient were explained about the possibility of various differential diagnosis that were probable. Sample was taken for mutation analysis. The report showed heterozygous mutation in Exon2 at nucleotide position T201>A causing a codon change C55>S on polymerase chain reaction amplification followed by direct sequencing of all five exons and the promoter region of the neutrophil elastase (ELA2) gene. Hence, the diagnosis of ELANE-related congenital neutropenia was made.

Patient was started with Filgrastim, recombinant methionyl human granulocyte-colony stimulating factor (G-CSF) (r-metHuG-CSF) on the weight-adjusted dosage schedule in February, 2010. Other ancillary measures were continued to prevent secondary complications. Routine follow-up visits showed no improvement in ANC. But in December, 2010 total count rose to 50 × 10^3 cells/L. Ultrasound of the abdomen showed few mesentric lymph nodes. Bone marrow biopsy was performed. Histopathological examination of bone marrow specimen showed malignant transformation into acute myelogenous leukemia (AML).

DISCUSSION

Most congenital neutropenia is diagnosed because of fever and severe infection in infants and young children. In 1956, Kostmann described congenital neutropenia (agranulocytosis) as an autosomal recessive disease occurring in an extended family in northern Sweden. Phenotypically similar sporadic cases and families with autosomal dominant congenital neutropenia have been reported.[3] ELANE (previously known as ELA2) is the only gene known to be associated with ELANE-related neutropenia. Neutrophil elastase is a serine protease of neutrophil and monocyte granules.[4] Its key physiologic role is in innate host defense, but it can also participate in tissue remodeling and possesses secretagogue actions important to local inflammatory responses.[5]

Individuals have fever and recurrent skin and oropharyngeal inflammation, that is, mouth ulcers, gingivitis, sinusitis, pharyngitis, and cervical adenopathy. Diarrhea, pneumonia, and deep abscesses in the liver, lung, and subcutaneous tissues are common. Omphalitis immediately after birth may be the first sign.[6] Bacteremia occurs infrequently but has severe consequences in affected individuals.

ELANE-related neutropenia includes congenital neutropenia and cyclic neutropenia. Congenital neutropenia and cyclic neutropenia were initially thought to be distinct disorders; however, following the discovery of the molecular basis of ELANE-related neutropenia, individuals with findings intermediate between these two phenotypes are also recognized. Nonetheless, identification of the two phenotypes is helpful for diagnosis, prognosis, and management.

Diagnosis requires at least three ANCs lower than 500 cells/mm^3 obtained at least 3 months after the birth. Bone marrow aspirate typically shows "maturation arrest" at the promyelocyte or myelocyte stage of neutrophil formation. Increased bone marrow monocytes and eosinophils may be present. Cytogenetic analysis of bone marrow is normal. The finding of an ELANE mutation in an individual with neutropenia establishes the diagnosis of ELANE-related neutropenia.[2]

Treatment with G-CSF is effective in elevating blood neutrophil counts. Common side effects of G-CSF include bone pain and headache, splenomegaly, and osteoporosis. Vasculitis, rashes, arthralgias, and glomerulonephritis have been infrequently reported.[7] Individuals with congenital neutropenia (with or without an ELANE mutation) who are treated with G-CSF have approximately the same risk of the myelodysplasia syndrome/AML. The respective cumulative incidences 15 years after starting treatment with G-CSF were 36% and 25% (P=0.96).[8,9] The development of AML in our patient was within 10 months after starting G-CSF. This is in contrast to the long 6-year observation period with 9% risk of transformation.[10] Hence, it is prudent to consider the AML as the predisposed malignancy associated with the natural history of these diseases.

Hematopoietic stem-cell transplant is the only alternative therapy for individuals with congenital neutropenia who are refractory to high-dose G-CSF or who undergo malignant transformation. In our country, where infections are very common and the cost of G-CSF treatment is high and self-financed, and also when a number of upcoming transplant centers are emerging, it is worthwhile to consider allogenic sibling stem-cell transplant, as one of the treatment modality, especially when there is an human leukocyte antigen (HLA)-matched sibling donor available. The cost-benefit ratio is much higher with the absence of long-term infectious complications and lesser infrequent hospital admissions. In our centre, we would start on prophylaxis with G-CSF and then search for the HLA-matched donor (especially sibling) for an allogenic transplant.

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