CASE REPORT

Malignant Myeloid Transformation in a Child with Severe Congenital Neutropenia (Kostmann's Syndrome)

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Summary

We report a case of a child with severe congenital neutropenia (Kostmann's syndrome) who was treated with daily prophylactic subcutaneous granulocyte colony-stimulating factor (G-CSF) from the age of eight to sixteen years before being discontinued for poor haematological and clinical response. She did not have a HLA-matched sibling to enable bone marrow transplantation. She subsequently developed acute megakaryoblastic leukemia at the age of 17 years and succumbed during induction chemotherapy. The role of G-CSF in the pathogenesis of her malignant transformation to AML is complicated as this disorder has a propensity for myelodysplasia or AML as part of its natural history.

Key Words: Congenital, Neutropenia , Myeloid leukemia

Introduction

Severe congenital neutropenia (SCN) was first described by Kostmann in 1956 when he reported on an infant with congenital agranulocytosis. Currently, both autosomal dominant and recessive as well as sporadic forms have been recognized[1]. SCN is characterized by profound neutropenia, recurrent severe bacterial infections and maturation arrest in the myeloid lineage. The incidence has been estimated to be 1:1000 000 and affected children usually succumb before three years of age from severe bacterial infections unless they receive prophylactic granulocyte colony-stimulating factor (G-CSF). Over 90% of SCN patients respond to G-CSF with elevation of neutrophil counts and reduction in number of serious infections. Treatment with G-CSF is required for life. However, results from human leucocyte antigen identical sibling bone marrow transplant are good and this has become the treatment of choice in these patients. With prophylactic G-CSF, the majority of children can lead a reasonably normal life. However, there still remains a risk of mortality from transformation to myelodysplasia (MDS) or acute myeloid leukemia (AML). We illustrate the natural history of this condition in our case report below.

Case Report

TWS first presented to the University of Malaya Medical Centre (UMMC) in July 1990 at the age of three years with complaints of fever and progressive pallor of one weeks' duration associated with abdominal distension. She had had multiple skin infections since infancy but had not been hospitalised before. Clinically, she was found to have hepatosplenomegaly and a large perineal abscess. There were multiple furuncles on her trunk and limbs. There were no skeletal or skin abnormalities and no history of chronic diarrhoea. Her parents were non-consanguineous and there was no family history of a similar illness. FBC showed Hb 86 g/dL, platelets of 284 x 10^9/L and TWBC 8.2 x 10^9/L (differential count :

This article was accepted: 27 December 2005

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N 1%, L 51%, Mo 40%, E 8%, blasts 0%). The bone marrow examination showed markedly depressed granulopoeisis. The majority of the cells in the myeloid series were myelocytes and promyelocytes while neutrophils were conspicuously rare. These features suggested maturation arrest in the myeloid lineage. The erythroid series showed orderly maturation and there were adequate megakaryocytes (Fig. 1). Cytogenetic analysis was not available at that time. Serum immunoglobulins were : Ig A 105 mg/dL, IgG 1400 mg/dL and IgM 382 mg/dL. Screening for HIV was negative. These findings were consistent with a diagnosis of SCN (Kostmann's syndrome). She was treated with antibiotics and surgical drainage of the abscess.

Following this admission, she continued to have multiple episodes of infection (Table I). Bone marrow transplantation was not considered as she had no HLA-matched sibling. She commenced prophylactic therapy with subcutaneous G-CSF 5 mcg/kg/day at the age of eight years; after obtaining adequate funding for this agent. However, despite this, she continued to have repeated episodes of infection including a large liver abscess which required drainage via a laparatomy. After eight years, prophylactic G-CSF was stopped as it was noted that there was no reduction in the incidence of infections, including life-threatening ones.

In between these infection episodes, she was well and attended normal school. During a routine clinic follow-up at the age of 17 years, i.e. seven months after cessation of G-CSF therapy, she was noted to have an abnormal blood count. The FBC showed Hb level of 91 g/L, WBC 2.1 x 10^9/L (N 2%) and platelets 717 x 10^9/L. Bone marrow examination showed depressed erythropoiesis and granulopoiesis. Myeloblasts constituted 67% of total nucleated cells of the marrow. These blasts were heterogenous and had scanty to moderate amount of basophilic cytoplasm and conspicuous nucleoli. Many blasts showed cytoplasmic blebs and some blasts exhibited platelet budding [Fig. 2]. The blasts were myeloperoxidase negative. Immuno-phenoytyping revealed the blasts to be positive for CD13, CD33, CD34, CD61 and HLA-DR. They were negative for CD14, B- and T- lymphoid lineage markers. Karyotyping of the blasts revealed 45XX, +19, -7 del (16q). Real-time PCR screening for t(9;22)/bcr-abl fusion transcript was negative. A diagnosis of acute megakaryoblastic leukemia was made and she underwent chemotherapy. Unfortunately, she died of sepsis during induction chemotherapy.

Discussion

Until recently, the pathogenesis of SCN was largely unknown. Now it is acknowledged that mutations in the neutrophil elastase (ELA 2) gene are responsible for the majority of sporadic SCN cases; to date 30 different mutations have been reported[2]. The role of neutrophil elastase mutations in leukaemic transformation is not clear as both uninvolved and involved cases have been reported to transform[3].

G-CSF has had a major impact in the management of SCN where more than 90% of patients respond with increased neutrophil counts, reduction in infections and improved survival[1]. Data from over 400 patients with congenital neutropenia collected by the SCN International registry show that about 13% of these patients will undergo malignant myeloid transformation after approximately eight years of G-CSF therapy.

Table I : Infections experienced by the patient with severe congenital neutropenia

Date	Infectious complication
Aug 1990	Lobar pneumonia
Apr 1991	Scalp abscess
Sep 1991	Rt labial abscess
Apr 1992	Bronchopneumonia
Aug 1992	Clitoral abscess
Oct 1992	Bronchopneumonia
Jun 1993	Abscess on left foot
Nov 1993	Rt eyelid abscess and rt otitis media
Apr 1995	Rt gluteal abscess
May 1995	Lt inguinal cellulitis and perianal abscess
Sep 1995	Rt tibial cellulitis
	(Daily G-CSF 5mcg/kg/d commenced)
Oct 1995	Gluteal abscess
Nov 1995	Furuncle left thigh
Jan 1996	Lt foot cellulitis
Feb 1996	Rt eyelid cellulitis
Apr 1996	Lt inguinal cellulitis
Feb 1997	Lt calf cellulitis
May 1997	Abscess left thigh
Jan 1998	Liver abscess ; requiring laparotomy
Aug 1999	Abscess left thigh
Apr 2002	Periodontal abscess
Aug 2003	Cellulitis of left ear lobe
Mar 2004	Malignant transformation

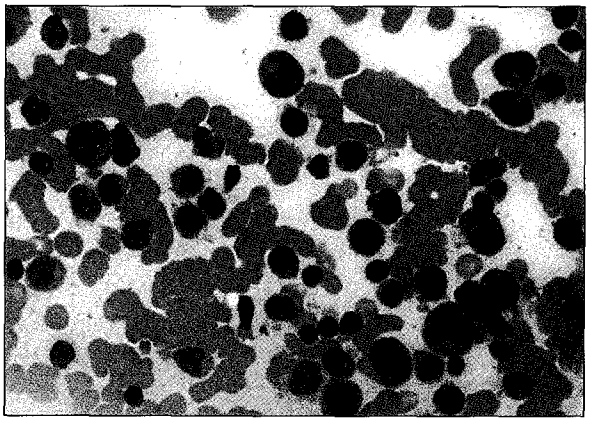

Fig. 1: Bone marrow at first presentation showing maturation arrest in the myeloid lineage; (x 40)

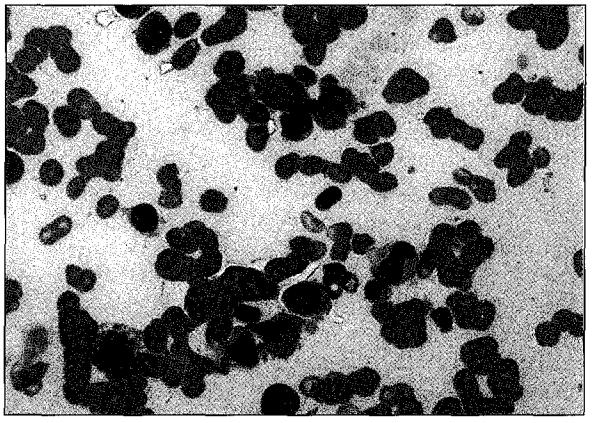

Fig. 2: Bone marrow at time of malignant transformation showing megakaryoblasts; (x 40)

However, no statistically significant relation between G-CSF dose used or duration of G-CSF therapy was found[4].

Although there is currently no means of predicting the likelihood of transformation, there are several genetic abnormalities associated with the event. G-CSFR mutations have been associated but the exact role has not been established. It is interesting that none of the non-Kostmann's syndrome patients e.g. with cyclical, chronic benign or idiopathic neutropenia developed malignant transformation despite being on GCSF prophylaxis.

There are some data postulating that mutations of neutrophil elastase impair survival of progenitor cells resulting in neutropenia and acquired G-CSFR mutations may initiate signaling events to override the pro apoptotic effect of mutant neutrophil elastase resulting in an expansion of the abnormal AML clone[5].

Monosomy 7, as was seen in our patient, is the most frequent cytogenetic abnormality associated with the transformation in SCN. However, it has been shown that not all patients with chromosome 7 abnormalities transform. Activating mutations in the oncogene ras has been described in patients with leukaemic progression. The stepwise acquisition of monosomy 7, ras oncogene mutations, and G-CSF receptor mutations in some patients with congenital neutropenia clearly indicate a genetic predisposition to malignant transformation. The most important genetic event(s) remains to be elucidated[3].

Thus, it is essential that all patients with SCN undergo full genetic analysis with screening for monosomy 7, ELA 2 and G-CSF receptor mutations. This information would help guide the overall management of these patients especially in relation to early intervention especially if a HLA–matched sibling donor is available for bone marrow transplantation before malignant transformation occurs.

References

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