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CASE REPORT

Cataract associated with high-dose hematopoietic colony stimulating factor, case report and literature review

Soad K. Aljaouni *, Hanadi M. Aljedani

Haematology Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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KEYWORDS

Congenital neutropenia;
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Side effects of G-CSF therapy

Abstract *Background:* Granulocyte-colony stimulating factor (G-CSF) is a lineage-restricted hematopoietic growth factor. It induces proliferation and maturation of neutrophilic precursors and progenitors and activates neutrophil functions. It is used to ameliorate or prevent profound neutropenia and its consequences. G-CSF therapy in neutropenic disorders increases neutrophil count and improves infectious complications. However, it is not without side effects. Here, we discuss the case of a 2 years old patient with Kostmann's disease who developed cataracts following high-dose G-CSF therapy. We also review the relevant literature on G-CSF-related complications.

1. Introduction

Granulocyte-colony stimulating factor (G-CSF) is a lineage-restricted hematopoietic growth factor that can induce proliferation, maturation and activation of neutrophils and their progenitors. Other cells like stromal and endothelial cells can also be activated (Bodey et al., 1966; Morstyn et al., 1988; Trillet-Lenior et al., 1993). G-CSF has been used to ameliorate and prevent profound neutropenia and its consequences. It is also used to enhance mobilization of peripheral blood progenitor cells for bone marrow transplantation, and accelerate reconstitution after both allogeneic and autologous bone marrow transplantation (British Society for Hematology, 2003). Congenital neutropenia, such as Kostmann's or Schwachmann-Diamond syndrome, are associated with severe neutropenia, which causes serious infectious complications that can be life threatening. G-CSF therapy has been approved for these disorders, as it has been found to increase the number of circulating neutrophils and improve infectious complications (Jakubowski et al., 1989).

2. Case report

A Yemeni boy was delivered normally to a 23-years-old mother with normal birth weight and Apgar scores. At birth, his examination was unremarkable and blood count was normal. He exhibited normal growth and development, had no history of any medications and received up-to-date vaccinations. His parents are first degree cousins and he has an

* Corresponding author. Address: Haematology Department, King Abdulaziz University Hospital, Jeddah, P.O. Box 80215, Post Code 21589, Saudi Arabia.
E-mail address: saljaouni@kau.edu.sa (S.K. Aljaouni).

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apparently healthy 2-years older brother. There was no family history of congenital or inherited disorders.

At the age of 7 months, he presented with high grade fever for 20 days and diarrhea for 1 week. There was no focus of infection, lymphadenopathy or organomegaly. Laboratory results showed persistent severe neutropenia with an absolute neutrophil count of 0.1×10^9/L and iron deficient anemia. The blood film confirmed severe neutropenia and revealed reactive lymphocytes; no blasts or dysplastic leukocytes were observed. Renal and liver function tests were normal. Blood sugar and electrolytes were within normal ranges. A septic screen was negative and a virology screen for HIV 1 and 2, parvovirus, and Epstein Bar virus antibodies was negative. The patient was positive for cytomegalovirus (CMV) IgG and IgM. The mother was negative for CMV antibodies. Septic screen was negative. CMV IgG and IgM levels remained positive. The patient received ceftriaxone (weight adjusted dose) and oral paracetamol as an antipyretic, and showed improvement. After being stabilized, he was discharged on oral penicillin for 10 days and a daily oral iron supplement. At discharge, his absolute neutrophil count was 0.68×10^9/L. One month later, he was admitted again with fever and cough. Examination revealed congested and enlarged tonsils, which were removed surgically. Histology revealed evidence of a chronic inflammatory process with no evidence of lymphoma. Laboratory tests showed persistent neutropenia of 0.2×10^9/L. The patient responded to intravenous antibiotics (cephalosporins).

Bone marrow aspiration was consistent with a diagnosis of Kostmann's disease. Immunophenotypic analysis of his lymphocyte profile revealed normal levels of T, B and natural killer lymphocytes. The patient had normal immunoglobulin levels with a normal count and ratio of CD4 and CD8 cells. Both parents and the brother were tested and had normal neutrophil counts and neutrophil morphology.

After confirming the diagnosis, the patient was started on Filgrastim (recombinant methionyl human G-CSF) at a dose of 5 μg/kg (mcg/kg) body weight subcutaneous (sc) on a daily basis during hospital admission periods, which usually lasted 7–10 days. Upon discharge, the patient received G-CSF 5 mcg/kg sc 1–2 times weekly for 10 weeks, with no apparent effect on neutrophil count. The dose was increased to 15 mcg/kg weekly for 5 weeks, again with no increase in neutrophil count, although episodes of febrile illness and hospital admissions were minimized. The patient was shifted back to a dose of 5 mcg/kg body weight once weekly for 3 months. Granulocyte monocyte (GM)-CSF at a dose of 5 mcg/kg sc was administered on three occasions when G-CSF was not available. Neutrophil count remained in the range of 0.3–0.5×10^9/L.

Four months after the initiation of high-dose G-CSF, the patient developed bilateral eye cataracts, more severely in the left eye, which required left lensectomy. Lens histology revealed chronic inflammation, many macrophages and some fibrosis. Cultures of the lens tissue were negative for bacteria, viruses and fungi. G-CSF was stopped, and the patient was put on prophylactic oral penicillin with close follow up. However, he was admitted on two occasions with respiratory tract infections treated as per febrile neutropenia protocol.

At the most recent clinical visit, a full blood count revealed a white cell count of 6×10^9/L with an absolute neutrophil count of 0.2×10^9/L; 10% monocytes; and 76% lymphocytes. Platelet count was 296×10^9/L and hemoglobin was 11.4 g/dL. A blood film showed no evidence of dysplasia and no blasts were noted. The family was counseled for stem cell transplantation. Therefore, patient and family moved back to their original country in order to arrange for transplantation and we lost contact with them. In terms of medication history, the patient did not receive any steroid therapy and never received non-steroidal anti-inflammatory drugs (NSAIDs). In addition to regular doses of G-CSF and intravenous antibiotics for neutropenia-related febrile illnesses during in-patient admissions, he was on regular prophylactic doses of oral penicillin, oral iron supplement and oral paracetamol, as required.

3. Discussion and literature review

Cataract is a term used for opacity of the lens that affects visual acuity. The pathology of cataracts involves enhanced protein carbonylation and glycation in the epithelial cells of the lenses of affected individuals (Balog et al., 2001). The most common causes of cataract are age, trauma, inflammation, metabolic and nutritional defects, corticosteroid therapy and radiation damage (Berson, 1993). Cataracts are increasingly reported in long-term survivors, particularly children, of bone marrow transplantation who received full-body irradiation prior to transplantation. In one study, cataracts occurred in 20% of children who were recipients of a bone marrow transplant (Barrett et al., 1987).

Kostmann's disease is a rare autosomal recessive disorder characterized by severe neutropenia that was first described by Kostmann in 1956 (Kostmann, 1956). Its prevalence is estimated to be 1–2 cases per million individuals. The disease is characterized by an absolute neutrophil count typically less than 0.2×10^9/L. The mortality rate of Kostmann's disease can be as high as 70% or higher within the first year of life in the absence of therapy, mainly due to bacteremia or septicemia, most commonly from streptococci, staphylococci, *Pseudomonas* and fungi (Baehner and Miller, 1995). Recently, intervention with G-CSF and hematopoietic stem cell transplantation has been shown to significantly improve clinical outcomes in patients with Kostmann's disease (Dale et al., 2003), although cases of severe congenital neutropenia that is unresponsive to G-CSF have been reported (Ryan et al., 1995; Dale et al., 1993; Imashuku et al., 1992).

The underlying etiology of Kostmann's disease is unknown, although defects in G-CSF-induced intracellular signal transduction have been implicated. A genetic defect a region of chromosome 1 (1p35–p34.3) that corresponds to the G-CSF receptor coding region has been reported (Dror and Sung, 2004). Using a positional cloning approach and candidate gene evaluation, a homozygous germline mutation in *HAX1* in many pedigrees of Kostmann's disease was recently identified. *HAX1* encodes the mitochondrial protein HS1-associated protein X-1 (*HAX1*), which functions in signal transduction and cytoskeletal regulation. *HAX1* is critical for maintaining the inner mitochondrial membrane potential and protecting against apoptosis in myeloid cells. Defects in *HAX1* have been shown to depress apoptosis, underscoring the importance of apoptosis in neutrophil development (Klein et al., 2006).

Currently, the mainstay of therapy for severe congenital neutropenia/Kostmann's syndrome is recombinant human (rHu)G-CSF. Treatment with rHuG-CSF results in increased granulocyte count within 7–10 days of administration, and is