
Congenital Agranulocytosis (Kostmann's Syndrome) and G-CSF Therapy in an Infant

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ABSTRACT

Congenital agranulocytosis (Kostmann's Syndrome) is a rare autosomal recessive inherited disorder characterised by severe neutropenia, recurrent infections, and death in early life, with the bone marrow showing a maturation arrest of myeloid cells at the myelocyte stage. The treatment of Kostmann's Syndrome with G-CSF results in rapid improvement. However, a few unexpected results with the use of G-CSF, were reported. Here, we describe a 7-month-old female with Kostmann's Syndrome who had recurrent skin infections and a large pyogenic infection in the supravulvar region. The patient was treated with G-CSF successfully at low doses. The infectious process and the quality of life of the patient improved. There was no adverse effect due to the dosage and the duration. Currently bone marrow transplantation is the best way to treat Kostmann's Syndrome. Nevertheless, our experience showed that G-CSF treatment in Kostmann's syndrome was highly effective and successful on a short term basis.

Key Words: Kostmann's Syndrome, Infant, G-CSF therapy.

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In 1956, Kostmann described a condition of repeated bacterial infections in infancy which he termed "infantile genetic agranulocytosis"^[1]. This syndrome is a rare autosomal recessive disorder that is characterized by severe neutropenia due to impairment of myeloid differentiation in bone marrow, increased severe pyogenic infections, and

early death^[2,3]. In the literature, more than 200 cases have been reported^[4]. The etiology is not yet understood^[5]. In recent years, using recombinant growth factor (rHuG-CSF), a dramatic improvement in treatment has been achieved^[6,7]. Here, a typical case of Kostmann's Syndrome (KS) in an infant and its treatment using rHuG-CSF (Filgras-

tim) was evaluated.

CASE REPORT

A 7-month-old girl was admitted to our pediatric clinic with complaints of recurrent pyogenic skin infections. Since the fourth month of her life, the patient had suffered from three pyogenic attacks. With appropriate antibiotic use the lesions had healed. The last attack of a pyogenic lesion appeared three months ago in the supravulvar region and it progressively increased in size.

Her prenatal and natal history was unremarkable. There is first degree consanguinity in her parents and the other family members were healthy.

On physical examination, the body temperature was 37°C, the pulse rate 140/min, the respiratory rate 40/min. In the supravulvar region, a large pyogenic lesion, 6x7 cm diameter, extending to the labium and invading subepidermal layers, was found (Figure 1). Crackling rales were heard in both lung fields. There was no hepatosplenomegaly and lymphadenopathy. Laboratory studies revealed; hemoglobin 6.8 g/dl, mean corpuscular volume 70 fl, thrombocytes $263 \times 10^9/L$, leukocytes $9.4 \times 10^9/L$ with 52% lymphocytes, 36% monocytes, 12% eosinophils and no neutrophils were seen. The serum iron and iron binding capacities were 18 mg/dl and 410 g/dl, respectively. A flow



Figure 1. The large pyogenic infection extended to a deep layer of the dermis.

analysis of the peripheral blood yielded 33% CD4, 21% CD8, 63% CD3, 33% CD19, and 9% CD56, 19% CD23. Serum levels of immunoglobulins (Ig),

folic acid, vitamin B12, and zinc were within in normal ranges, except for the IgA and IgG, at 167 mg/dl and 1836 mg/dl, respectively, which were slightly higher than normal levels.

The bone marrow aspirate demonstrated normal megakaryocytic and erythroid maturation with mild erythroid hyperplasia. The distribution of white cells in the bone marrow were 62% lymphocytes, 9% myelocytes, 11% eosinophils and its precursors, and 18% monocytes. The arrest maturation of neutrophils at the myelocyte stage was determined (Figure 2a, b). The clinical and laboratory findings supported congenital neutropenia, thus KS was diagnosed. In addition to Vancomycin-Tobramycin treatment, Filgrastim was started at 3 g/kg/day on the 20th day of admission. The dose was increased at two week intervals to 6 g, 8 g and finally to 10 g/kg/day subcutaneously. At the dose of 8 g/kg/day of Filgrastim, a gradual increase in the absolute neutrophil count (ANC) was achieved, and at the dose of 10 g/kg/day the ANC was raised to 2200 cells/ L. The patient was treated successfully with the antibiotics and Filgrastim combination and her pyogenic lesion healed completely in three weeks. She is under Filgrastim treatment, at a maintenance dose of 8 g/kg/day three times a week, and she has been asymptomatic and afebrile during the last three months.

DISCUSSION

Kostmann's Syndrome is a rare autosomal recessive disorder^[3,8]. A few cases showing autosomal dominant inheritance of KS were reported^[9]. The male-to-female ratio of KS is about 0.8. At least 10 patients of KS were in consanguineous families and more than 20 had affected siblings^[3]. Our patient was a child of first degree consanguinity and the other members of the family were healthy, she does not have any siblings.

The origin of KS is not yet understood. Recently, most of the attention has been focused on the G-CSF receptor (G-CSFR) abnormality. There are increasing numbers of reports about mutations in the G-CSFR gene, disrupting its normal signaling functions and contributing to leukomogenesis^[9-11]. The association of KS with mono-

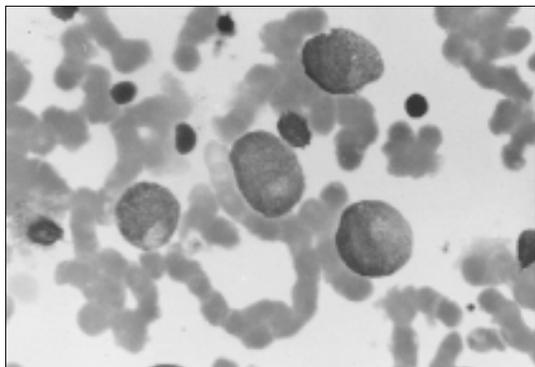


Figure 2. Bone marrow smear of the patient:
a. Absence of the mature neutrophilic cells

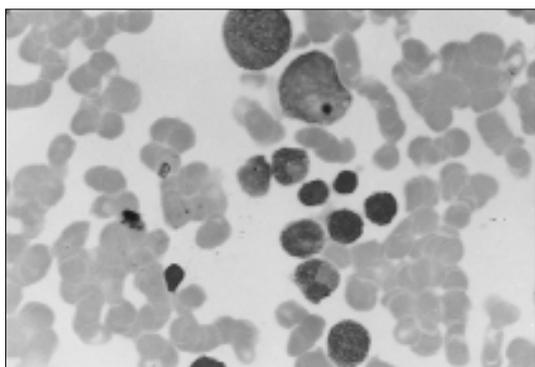


Figure 2. Bone marrow smear of the patient:
b. Increased eosinophilic cells and normal erythroid line (May-Grünwald-Giemsa, x 1000)

somy 7, trisomy 21, leukemia predisposition, mental retardation, cataracts, and microcephaly have been reported^[12]. Monosomy 7 also may be acquired during G-CSF therapy^[13]. In our case, no phenotypic and genotypic anomaly was determined.

Half of the patients were symptomatic within the first month, and 90 percent by 6 months^[3]. The prominent features of KS are recurrent fevers, severe relapsing infections including bacterial conjunctivitis, oropharyngeal ulcerations, periorbital cellulitis, periodontitis, mastoiditis, pneumonitis, and otitis media^[2,14]. The recurrent skin lesions in the present case had begun at the 4th month of age. Physical examination revealed a large cavitory skin lesion and also mild bronchopneumonia.

The average ANC in KS is fewer than 200 cells/ μ l, and in some cases, neutropenia may be absolute^[15]. Some infants have normal ANC in the first week, but then ANC declines rapidly^[4]. In our case, repeated full blood counts confirmed a persistent severe neutropenia. However, we did not have any information about the ANC of the patient in the neonatal period.

Anemia due to KS is unusual. However, we thought our patient had both iron deficiency and chronic infection anemia. Eosinophils and monocytes may be very high, but they are not as effective phagocytes as are neutrophils. Increased immunoglobulins are often seen^[16]. In our case, there was a marked increase in the monocytic and eosinophilic series in the peripheral blood. Serum IgA and IgG levels were slightly increased.

The histopathologic hallmark of KS in the bone marrow examination is a normal cellularity with absent or markedly decreased myeloid precursors and a maturation arrested at the myelocyte or promyelocyte stages^[8]. In the present case, the bone marrow examination revealed markedly arrested maturation at the myelocyte stage and increased eosinophils. There were no neutrophils in the blood smear. These findings helped us to diagnose KS.

The prognosis in KS is poor, with more than half of the reported cases being fatal at a mean age of 2 years, median of 7 months, and range from 2 weeks to 20 years^[3]. Therefore, several therapeutic modalities have been tried for several years. As a therapeutic agent, lithium therapy is not effective in normal individuals with KS. Chan et al^[17], attempted to treat five children with chronic neutropenia, including one patient with KS, by lithium carbonate. But they did not observe any improvement in the neutrophil counts of the four patients including the KS patient. The development of recombinant human granulocyte-colony stimulating factor in clinical use had a major influence on the treatment of many diseases^[7,16]. This impact has perhaps been greatest in the treatment of severe and chronic neutropenic conditions^[16]. Mempel et al.^[18] reported raised serum levels of G-CSF in KS, but this G-CSF level was thought to be inadequate in KS. Rauprich et al.^[15]

reported that Filgrastim treatment lead to a significant increase in circulating neutrophils above 1000 cells/ μ l in most of the patients at a dose of 3 to 60 μ g/kg/day. It is evident that Filgrastim treatment almost always improves the course of KS and the quality of the patient. However, there is no agreement on the factors causing MDS/AML development in KS. Imashuku et al.^[19] reported the results of their national survey. In the long-term follow up of 123 pediatric neutropenic patients including 20 patients with congenital neutropenia they found that only four cases developed fatal MDS/AML with monosomy 7 in patients who had received Filgrastim administration. They also concluded that the incidence of MDS/AML, in patients with KS who were treated with Filgrastim, was the same when compared with earlier patients who did not receive Filgrastim. Welte et al.^[16] demonstrated a clinical cascade, in some severe congenital neutropenia, including G-CSF receptor mutation, monosomy 7, MDS, AML, and death. They did not find they did not find that Filgrastim treatment had any effect on this cascade any effect of Filgrastim treatment on this cascade. Also, Tidow et al.^[20] suggested that the G-CSF receptor point mutations were not correlated with the start, duration, or dose of Filgrastim treatment, but might be the result of genetic instability in the G-CSF receptor gene in severe congenital neutropenia. They also concluded in another study, the point mutations in the critical region of the intracellular part of the G-CSF receptor, occurred spontaneously and was not inherited, and the G-CSF receptor mutations did not alter the response to treatment with Filgrastim and was not the cause of severe congenital neutropenia. Whether Filgrastim accelerates this pathway or not is unclear.

Bone marrow transplantation (BMT) has been accepted as the preferred treatment approach for a long period to treat several immunologic and neoplastic disorders. In KS, the total success of BMT is over 50%^[3,21]. Some authors recommend BMT only for patients who do not respond to Filgrastim at a level of 100 μ g/kg/day or more. In our case, Filgrastim treatment greatly improved the of life quality of the patient and we achieved a good response with small doses. However, we believe

the best way to treat the patient is with BMT until the effectiveness of Filgrastim treatment is clearly determined. For this reason, studies involving the immunologic determination of the patient are continuing.

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