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KOSTMANN'S SYNDROME WITH CHRONIC PNEUMONIA AND LYMPHOCYTOSIS: EFFECT OF RECOMBINANT HUMAN G – CSF*

*Sevgi Yetgin MD***, Namık Özbek MD***, Murat Tuncer MD****
*Ayhan Göçmen MD*****, Uğur Özçelik MD****

SUMMARY: Yetgin S, Özbek N, Tuncer M, Göçmen A, Özçelik U. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Kostmann's syndrome with chronic pneumonia and lymphocytosis: effect of recombinant human G-CSF. Turk J Pediatr 1994; 36: 87-91.

Kostmann's syndrome is a congenital disorder characterized by impairment of myeloid differentiation in bone marrow with severe absolute neutropenia. A 17-month-old girl was admitted to the hospital with complaints of recurrent skin infections since birth and severe pneumonia of the right lung which had been resistant to antibiotics since the patient was eight months old. Anemia, severe neutropenia and maturational arrest of granulocytes at the myelocyte stage in bone marrow were detected. At the age of 20 months, a right pneumonectomy was performed because of resistant cystic infection. Postoperatively, she was diagnosed with Kostmann's syndrome. Recombinant human granulocyte-colony-stimulating factor (rhG-CSF) was administered intravenously at a dose of 3 μg / kg / day, gradually increasing to 60 μg / kg / day in sequential seven-day courses to obtain a neutrophil count of more than 500 cells / mm^3. Absolute neutrophil counts increased to greater than 1000 cells / mm^3 at a dose of 60 μg / kg / day, and at that time bone marrow aspiration revealed an increase in neutrophilic granulocytic precursors beyond the myelocyte stage. In order to maintain the neutrophil response, a dose of 20 μg / kg / day rhG-CSF subcutaneously was continued successfully. The patient has tolerated rhG-CSF treatment without complications, and infectious attacks have significantly decreased. *Key words: congenital agranulocytosis, congenital neutropenia, Kostmann's syndrome, recombinant human granulocyte-colony-stimulating factor.*

Kostmann's syndrome is a congenital disorder usually detected in the first months of life. The syndrome is characterized by bone marrow morphology displaying maturational arrest of the development of neutrophil precursors with severe absolute neutropenia (500 neutrophils per microliter or less) and variable degrees of monocytosis, eosinophilia. thrombocytosis and hypergammaglobulinemia[1,2]. Children with this disorder suffer infections that may be either recurrent local infections or severe septicemia, thus accounting for the high morbidity and mortality associated with this syndrome.

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Professor of Pediatrics and Pediatric Hematologist, Hacettepe University Faculty of Medicine.
*** Pediatrician, Hacettepe University Faculty of Medicine.
**** Associate Professor of Pediatrics and Pediatric Hematologist, Hacettepe University Faculty of Medicine.
***** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

The etiology of the disease is not clearly understood. Anti-neutrophil antibodies and serum inhibitors have not been shown to be causative. Various approaches, including leukocyte transfusions or the administration of steroids, testosterone, lithium and vitamin B_6, have been used to stimulate neutrophil production[3-5]. Although bone marrow transplantation is the best treatment for this disease, several difficulties limit its successful application. Recent publications have described good results with the administration of granulocyte-colony stimulating factor (G-CSF)[6-9]. In this report, a patient with Kostmann's syndrome, who was diagnosed initially with tuberculosis because of chronic pneumonia and lymphocytosis, is presented along with the results of G-CSF treatment.

Case Report

A 17-month-old girl was admitted to the hospital with cough, weakness, and reported weight loss since the age of eight months, as well as recurrent skin infections since birth. At the age of nine months, she developed severe pneumonia which was resistant to antibiotics. At that time, the patient's immunoglobulin A,G,M levels were high. PPD test and acid fast bacterium staining of bronchial and gastric lavage specimens were negative. She was given antituberculous therapy because of the presence of consolidation in the upper part of her right lung as well as pleural effusion on chest radiograms, lymphocytosis in peripheral blood, and unsuccessful nonspecific antibiotic regimens.

On admission, her weight was 10.5 kg and height 80 cm. Physical examination revealed oral angular cellulitis, furuncles on the face, clubbing, and no breath sounds in the upper part of the right lung. Hematological findings were as follows; Hb 5.8 g / dl, WBC 8200 / mm^3, reticulocyte 3%; the peripheral blood smear revealed hypochrome microcytic red cell morphology with 3% neutrophils, 16% eosinophils, 17% monoytes, 64% lymphocytes and thrombocytosis. Red cell mean corpuscular volume (MCV) was found to be 56 fl, serum iron level 12 µg / dl and iron binding capacity 270 µg / dl. Bone marrow aspiration revealed maturational arrest at the myelocyte stage. Immunophenotyping of bone marrow monocytes revealed 3% CD-34, 8% CD-19, 2% CD2, 2% CALLA, and classification as null-cell type. Immunoglobulin levels were as follows: IgG 6660 mg / dl (N: 889 ± 223), IgM 353 mg / dl (N: 118 ± 24), IgA 496 mg / dl (N: 659 ± 159). Nitro blue-tetrazolium dye test was low but within normal limits. Liver and renal function tests and coagulation parameters (PT, PTT, fibrinogen and fibrin split products) were within normal limits, and RAST tests for cow's milk and egg were negative. Chest x-ray, tomography and bronchoscopy showed signs of chronic pneumonia. The patient was diagnosed with Kostmann's syndrome and chronic pneumonia. Tuberculosis was ruled out since the diagnostic tests for tuberculosis were negative and the antituberculosis treatment was unsuccessful.

At the age of 20 months, a right pneumonectomy was performed. Pathological examination showed pneumonia with abscess formation and reactive hilar lymphadenopathy.

Postoperatively, the patient was given rhG-CSF (Roche) initially at a dose of 3 µg / kg / day by intravenous infusion over 30 minutes. Thereafter the bolus doses were increased to 10, 30, and 60 µg / kg / day in sequential seven-day courses. A response to therapy was achieved at a dose of 60 µg / kg / day with an increase in the absolute neutrophil count to greater than 1000 cells per microliter. At that time, bone marrow aspiration revealed an increased number of neutrophilic granulocytic precursors beyond the mylocyte stage. One third of the maximum dose (amounting to 20 µg / kg / day) was continued daily by subcutaneous injections and was found to be sufficient to maintain the neutrophil response (Fig. 1, Table I).

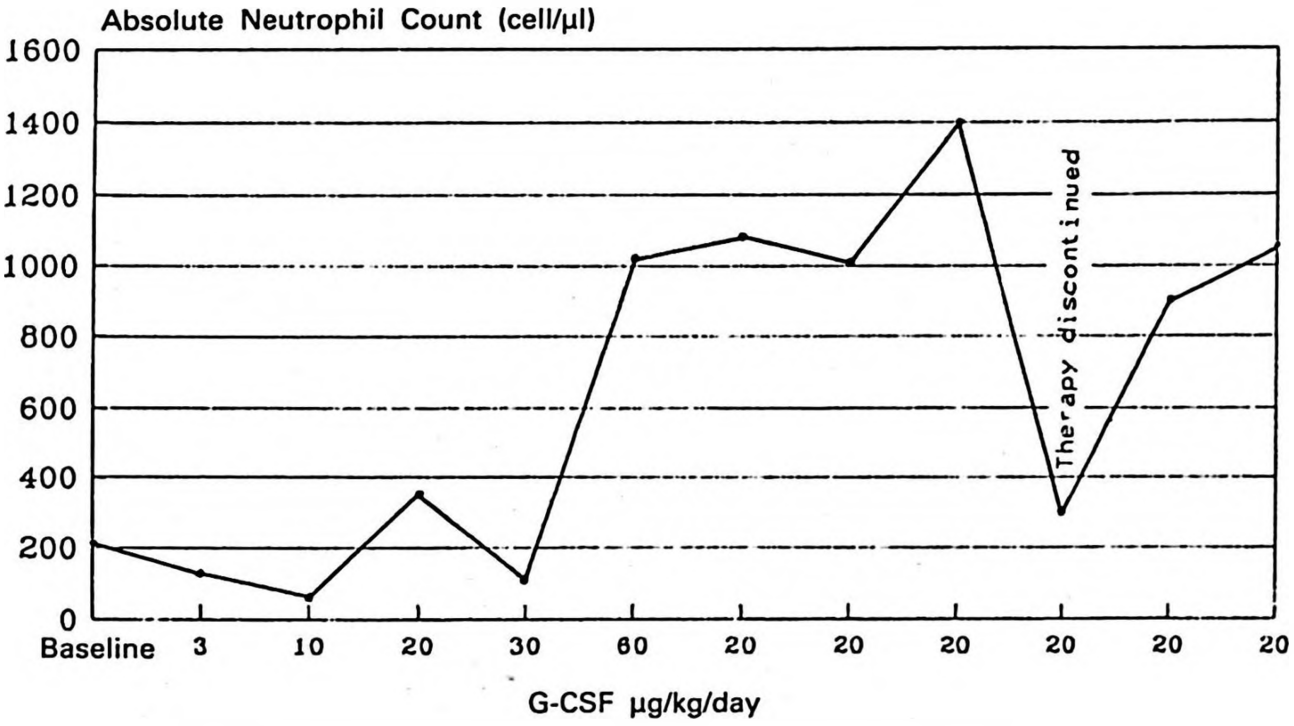

Fig. 1: The changes in the absolute neutrophil count releated to G-CSF dose

Discussion

The patient was diagnosed with Kostmann's syndrome because of progressive pulmonary infections resistant to antibiotics, recurrent skin infections, peripheral neutropenia, eosinophilia, and monocytosis with maturational arrest at the myeloid stage in the bone marrow. Allergic factors for eosinophilia were excluded in the etiology before the diagnosis of Kostmann's syndrome was made. The unremitting decreases in the level of absolute neutrophil count with recurrent infections in the follow-up period confirmed the diagnosis.

Table I: Hematological Findings Before and After G-CSF Treatment

	Hb (g/dl)	Ret (%)	WBC (10^9/L)	Neutrop (%)	Lymph (%)	Eosinop (%)	Basop (%)	Monoc (%)	Thromboc (10^9/L)
Baseline	5.8	3	8.2	64	16	17			433
G-CSF 20 µg/kg/day (Maintenance)	11.5		7.1	14	66	16	2	2	250

Hb : Hemoglobin.
Ret : Reticulocyte.
WBC : White blood cell.
Neutrop : Neutrophil.
Lymph : Lymphocyte.
Eosinop : Eosinophil.
Basop : Basophils.
Monoc : Monocyte.
Thromboc : Thrombocyte.

Although Kostmann's syndrome is a rare disease, it is a model for the design of therapy in different neutropenic states. G-CSF, which is a one of the recently purified, molecularly cloned hematopoietic growth factors, promotes the proliferation and differentiation of granulocytes, both in-vivo and in-vitro.

Our patient responded to G-CSF therapy, achieving a neutrophil count greater than 1000 cells per microliter in peripheral blood and the maturation neutrophil stage at a dose of 60 µg / kg / day. These results remained at the same level for six months while the patient was receiving subcutaneous therapy decreased to one third of the maximum intravenous dose. These findings are similar to those documented in the literature[8,9]. No clinical or laboratory side effects of G-CSF have been detected in our patient so far. Preexisting chronic infections have resolved clinically, and the number of infectious episodes have decreased. Our patient's favorable progress reflects the effect of G-CSF on the number and function of neutrophils in congenital severe neutropenia. We thus conclude that this therapy could be useful for patients with other types of neutropenia.

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