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Case

FAILURE OF GRANULOCYTE COLONY – STIMULATING FACTOR AND GRANULOCYTE – MACROPHAGE COLONY – STIMULATING FACTOR IN A PATIENT WITH KOSTMANN SYNDROME*

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SUMMARY: Hazar V, Ongun H, Yoşilipek MA,Yeğin O. (Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey). Failure of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in a patient with Kostmann syndrome. Turk J Pediatr 1999; 41: 117-120.

We present a seven-month-old boy referred to our hospital with a history of recurrent suppurative infections starting in his neonatal period. Anemia, absolute neutropenia absolute neutrophil count (ANC: 500 cells/µl), pneumonia, purulent otitis media and maturational arrest of granulocytes at promyelocyte-myelocyte level in bone marrow were detected on his admission. He was diagnosed as Kostmann syndrome and recombinant human granulocyte colony-stimulating factor (rhG-CSF) therapy was started at a dose of 10 µg/kg/d, gradually increasing up to 120 µg/kg/d in sequential seven-day courses. As there was no response, rhG-CSF was stopped and recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) was started subcutaneously with 2.5 µg/kg/d and was escalated by doubling the dose every seven days to 20 mg/kg/d. By this therapy absolute neutrophil count (ANC) transiently reached above 500 cells/µl, but eosinophilia developed with a total white cell count of 88.200 cells/µl, and a differential count showing 86 percent eosinophils. Since eosinophilia of this magnitude has deleterious effects, and neutrophil production did not significantly increase, we tried combined therapy with rhG-CSF and rhGM-CSF at doses of 10-20 µg/kg/d and 5-10 µg/kg/d, respectively, without any effect on absolute neutrophil count. The patient succumbed from sepsis eight months after the diagnosis.
Key words: eosinophilia, Kostmann syndrome, rhG-CSF, rhGM-CSF

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Kostmann syndrome (KS) (severe congenital neutropenia) is an autosomal recessive syndrome characterized by profound absolute neutropenia and maturation arrest of marrow progenitor cells at the promyelocyte-myelocyte stage, probably resulting from a defect in granulocyte colony-stimulating factor (G-CSF) binding receptor which transduces signals critical for the proliferation and maturation of granulocytic progenitor cells[1]. Patients with KS suffer from frequent episodes of severe bacterial infection starting in the first months of life. To stimulate differentiation of myeloid progenitor cells, clinical trials with recombinant human granulocyte colony-stimulating factor (rhG-CSF) and recombinant human

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granulocyte-macrophage colony-stimulating factor (rhGM-CSF) have been reported[2-4]. In this report a patient with KS suffering from severe infections since the neonatal period is presented.

Case Report

A seven-month-old boy who experienced several episodes of purulent otitis media and suffered from frequent pneumonia and omphalitis since his second day of life was admitted to our hospital with a history of cough, fever, and purulent discharge from the ears. On admission, physical examination revealed bilateral perforated tympanic membranes, fine and crackling rales on both sides of lungs and minimal hepatomegaly. He had a normal total white blood cell count of 7,800/µl, with a differential count showing four percent neutrophils, two percent eosinophils, four percent monocytes and 90 percent lymphocytes. This profound neutropenia was accompanied by a hypochromic and microcytic anemia with a hemoglobin level of 7.1 g/dl and a normal platelet count of 309,000/µl. Immunoglobulin determination and immunoelectrophoresis showed polyclonal increase in all isotypes (IgA: 874 mg/dl, IgM: 527 mg/dl, IgG: 3712 mg/dl). Bone marrow aspiration showed maturation block between promyelocytes and myelocytes. A few bands and mature neutrophils were present. Anti-neutrophil antibodies were negative. Liver and renal function tests were within normal limits. Chest x-rays showed bronchopneumonic consolidation. The diagnosis of KS was established on the basis of profound neutropenia, maturation arrest of neutrophil lineage in bone marrow and frequent bacterial infections since his neonatal period. The patient was started on antibiotics and rhG-CSF (Neupogen, Roche) beginning with 10 mg/kg/d subcutaneously (SC) which was escalated by a dose of 10 mg/kg/d every seven days. When a dose of 120 mg/kg/d was reached, absolute neutrophil count (ANC) was still under 500/µl. Thereafter rhGM-CSF (Leucomax, Sandoz) was given initially at a dose of 2.5 mg/kg/d SC and doses were increased to 5, 10 and 20 mg/kg/d in sequential seven-day courses. A transient response to therapy was achieved at a dose of 20 mg/kg/d with an increase in ANC to greater than 1,000 cells/µl; however, at this level eosinophilia developed with a total white cell count of 88,200 cells/µl with a differential count showing 86 percent eosinophils and four percent neutrophils. Since eosinophilia of this magnitude has deleterious effects and neutrophil production did not significantly increase, we tried combined therapy with rhG-CSF and rhGM-CSF at doses of 10-20 mg/kg/d and 5-10 mg/kg/d, respectively, without any effect on ANC. Nevertheless, eosinophilia continued and echocardiography showed signs of hypertrophic cardiomyopathy. He was given rhG-CSF alone again at a dose of 20 mg/kg/d SC and the eosinophilia subsided. His parents did not accept suggestion of allogeneic bone marrow transplantation. He died from sepsis eight months after the diagnosis.

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Discussion

Patients with KS experience frequent episodes of fever, pneumonitis, and skin infections, usually beginning in early infancy and often leading to fatal infections despite antibiotics. Several therapeutical approaches, such as white cell transfusions, and administration of steroids, lithium and androgens have been attempted in the past[5-7]. Therapeutic alternatives today are either allogeneic bone marrow transplantation (BMT) or rhG-CSF. Both have resulted in correction of the neutropenia[2-4,7]. As several difficulties limit application of BMT, rhG-CSF seems to be the most applicable therapeutic approach. Therefore, our patient was first started on rhG-CSF. Because a majority of patients with KS need higher doses of G-CSF to promote neutrophil formation compared with the doses used in patients with chemotherapy-induced neutropenia, we reached high doses[2-4,8]. However, could not obtain an ANC above 500 cells/µl even at a dose of 120 mg/kg/d. This failure may be due to reduced responsiveness of neutrophil progenitor cells to G-CSF as reported before[9].

In contrast to rhG-CSF, rhGM-CSF induced an increase of blood granulocytes. However, this increase was due to eosinophilia. During this treatment period the eosinophils increased up to nearly 76,000 cells/µl, demonstrating the potent biologic activities of rhGM-CSF, yet there was still no increase in the ANC. Welte et al.[3] showed that an increase in absolute granulocyte count secondary to eosinophilia developed in four out of five patients with KS treated with rhGM-CSF. In addition, they commented that the high number of eosinophils activated by rhGM-CSF might be of clinical benefit because of no severe bacterial infections occurring in the patients during eosinophilia. But our patient had no clinical improvement during eosinophilia and on echocardiography we determined hypertrophic cardiomyopathy. This was due, we believed, to eosinophilia as reported before because his telecardiography on admission was normal and he had no prior symptoms of the cardiovascular system[10,11]. These results were in contrast to those in rhGM-CSF therapy in other neutropenic conditions such as myelodysplastic syndrome after BMT and idiopathic neutropenia, in which substantial increases in ANC have been noted[9,12-14]. This indicates that KS might have a different pathophysiology as compared with these conditions. The G-CSF receptor abnormality could explain the lack of response to this cytokine, but it remains to be seen if this abnormality is applicable to all patients with KS.

The patient presented here does not allow us to make definitive statements regarding the percentage of patients who may respond to rhG-CSF and/or rhGM-CSF therapy. It is possible that there are different mutations responsible for KS. In case there is no response to rhG-CSF and rhGM-CSF, allogenic BMT should be planned.

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