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HIGH – DOSE METHYLPREDNISOLONE – INDUCED DRAMATIC MATURATION OF GRANULOCYTES IN IDIOPATHIC CHRONIC NEUTROPENIA*

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Idiopathic chronic neutropenia is characterized by a variable pattern of age at the onset of neutropenia, neutrophil counts, maturational arrest at the promyelocyte/myelocyte stage in the bone marrow, and recurrent pyogenic infections without any underlying disease or drug administration. There have been reports of lack of response to conventional-dose steroid therapy, but in recent studies it has been shown that high-dose corticosteroids are effective in several neutropenic states. Here we report an apparent response to high-dose methylprednisolone in a patient with idiopathic chronic neutropenia. *Key words: idiopathic chronic neutropenia, high-dose methylprednisolone.*

Idiopathic chronic neutropenia (ICN) is a form of neutropenia that may present at any age of life with neutropenia usually <500/mm^3 causing recurrent pyogenic infections involving the skin, mucous membranes, lungs and lymph nodes. Bone marrow examination reveals a variable pattern, usually with maturational arrest at the promyelocyte/myelocyte stage. A differential diagnosis of the several underlying diseases that may cause neutropenia should be done, and drug administration should be excluded in order to confirm the diagnosis of ICN[1,2]. These patients are usually responsive to a granulocyte-colony-stimulating factor. However, recent articles, have reported malignant transformation and some mutations in patients with different forms of neutropenia[3,4]. Although there are reports of a lack of response to conventional steroid therapy[1,2], here we report an apparent response to high-dose methylprednisolone in ICN.

Case Report

A two-year-old boy was admitted to our hospital with the complaints of recurrent bronchopneumonia and cough. On physical examination, his breath sounds were decreased on the left side of the thorax, and minimal hepatosplenomegaly was

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noted. The chest radiogram revealed cardiac enlargement and pleural effusion on the left side. The blood picture was compatible with absolute neutropenia (7% polymorphonuclear lymphocytes, 12% monocytes, 5% eosinophils and 66% lymphocytes). Bone marrow examination showed 24 percent erythroid cells, 46 percent myeloid cells, six percent monocytoid cells and 24 percent lymphoid cells. However, no myeloid element was noted beyond the myelocytic stage. There was no finding relevant to known causes of neutropenia. Because of the relatively late onset (two years of age), Kostmann syndrome was excluded in the differential diagnosis and the patient was finally diagnosed with ICN. He was given high-dose methylprednisolone (HD-MP) by the oral route in one morning dose for four weeks. His neutrophil count increased to normal levels in a week and remained greater than 500/mm^3 during this period. After cessation of therapy he became neutropenic again. To test the effect of short interval therapy, HD-MP (30 mg/kg) was given without any effect on the neutrophil count. After a month, the same four-week schedule was repeated successfully. His neutrophil counts were greater than 500/mm^3 with the dose of HD-MP tapered to 0.5 mg/kg/day every other day (Table I and Fig. 1). Improvement was also shown in the bone marrow. There were no side effects of HD-MP therapy except for a slight Cushingoid appearance.

TABLE I: Effect of HDMP in Different Doses

HDMP TREATMENT		WBC COUNT (mm^3)		PNL COUNT (mm^3)	
Dose (mg/kg)	Duration (weeks)	Initial	Last	Initial	Last
–	–	5800	–	406	–
30	1	3200	6000	128	2520
20	1	6000	5500	2520	1650
10	1	5500	4000	1650	1440
5	1	4000	5000	1440	1020
2	1	5000	4500	1020	1835
–	3	4500	4000	1835	480
–	2	5000	–	250	–
–	2	5600	–	280	–
30	3 days	5600	4800	280	288
–	3	4800	5000	288	250
20	1	5000	5400	250	1296
10	1	5400	5700	1296	2166
5	1	5700	7000	2166	560
2	1	700	5700	560	228
1	1	5700	5200	228	260
–	4	5200	6600	260	330
30	1	6600	4700	330	1786
20	1	4700	7700	1786	4125
10	1	7700	11100	4125	5600
5	1	11100	6100	5600	1880
2	1	6100	5900	1880	1062
1	1	5900	4000	1062	1200
0.5	1	4000	3800	1200	950
0.5*	3	3800	2800	950	634

* Given every other day.

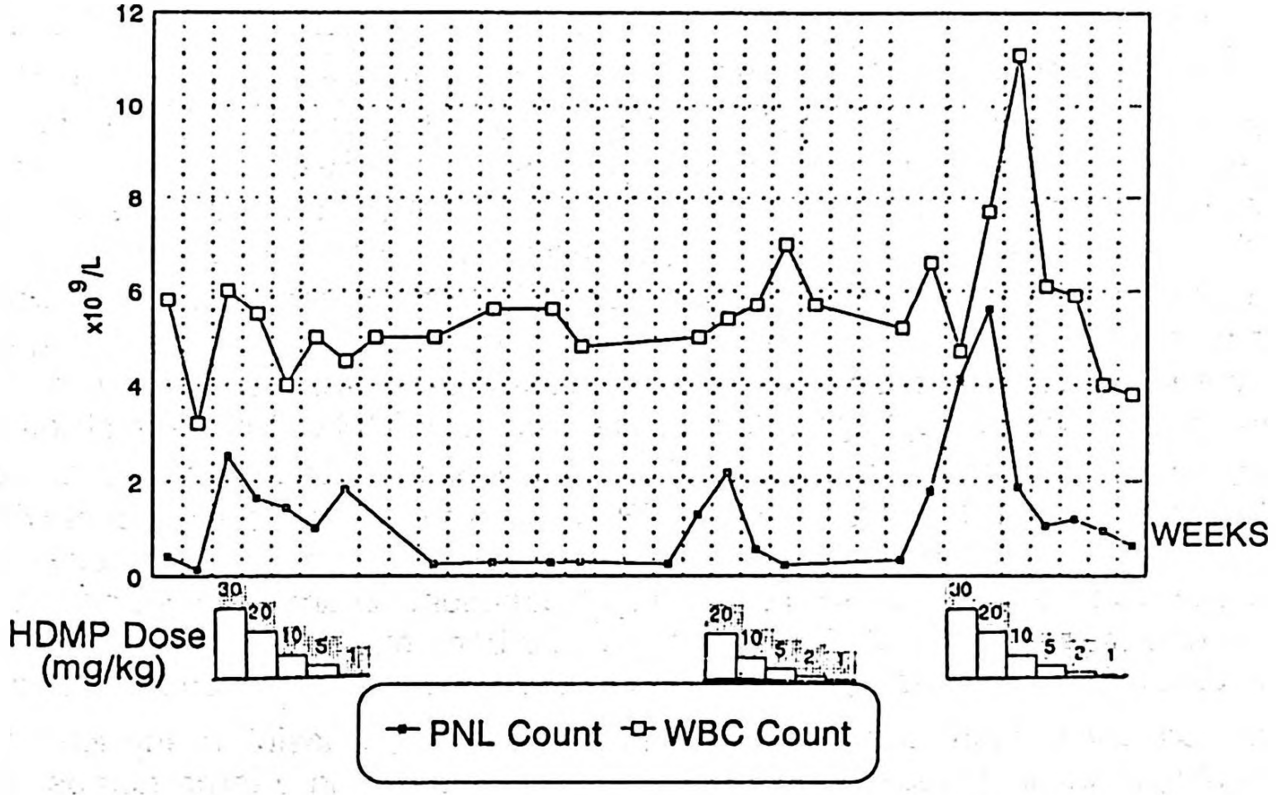

Fig. 1: Changes of WBC and neutrophil counts with HDMP.

Discussion

Chronic neutropenia of childhood is a group of disorders in which the blood neutrophil counts decrease below normal levels for a prolonged period. Although neutropenia can be caused by many definable disorders, there is a large group of patients in whom no clear cause can be identified. In our case, we excluded Fanconi's anemia, dyskeratosis congenita, cartilage-hair syndrome and Schwachman-Diamond syndrome on the basis of the normal phenotype. The age at onset and the course of the disease did not support a diagnosis of severe congenital neutropenia (Kostmann syndrome). Also, neither underlying disease or drug administration could be determined, and the patient was diagnosed to have ICN. Some patients with chronic neutropenia have anti-neutrophil antibodies; we could not study antineutrophil antibodies in our patient. However, in a recent article, it was shown that there was no relationship between the severity of symptoms of neutropenia and the presence or absence of antineutrophil antibodies in a group of patients with chronic neutropenia. Also, no other differences could be detected between groups when the patients were classified according to antineutrophil antibody results[1].

Dexamethasone and prednisolone can induce differentiation of some mouse myeloid leukemic cells into macrophages and granulocytes in vitro[5]. It has been shown that macrophage-granulocyte inducer and steroids have different sites

on myeloid leukemic cells for the induction of differentiation[6-8]. The effect of corticosteroids in increasing colony-stimulating activity in normal subjects[9], patients with aplastic anemia[10] and myelodysplastic syndrome[8-11] has been reported. Corticosteroid-induced leukocytosis is a well-known phenomenon, and leukocyte recovery has been observed in different patient groups such as idiopathic thrombocytopenic purpura, aplastic anemia, myelofibrosis, refractory anemia and acute lymphoblastic leukemia by HD-MP[12]. Hiçsönmez et al[8] showed a potential role of HD-MP in the maturation of myeloid leukemia in children in consecutive studies. It has also been shown that HD-MP treatment may increase the granulocyte-macrophage-colony stimulating factor (GM-CSF) level in children with acute leukemia[13]. In support of the above studies and their results, we have treated an ICN patient with HD-MP. As shown in Table I, the effect of HD-MP on the maturation of granulocytes was clear and depends on the doses of prednisolone and the duration of therapy. Maturational changes were observed not only in the peripheral blood but also in the bone marrow. It was shown that not the conventional dose, but high-dose steroids have an effect on maturation.

In conclusion, high- dose methylprednisolone may be useful in any form of neutropenia. Serial testing of the effect of this therapy on a large number of patients will clarify whether or not this effect is universal.

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