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MARROW APLASIA DURING HIGH DOSE MEBENDAZOLE TREATMENT

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Abstract. A patient with chronic liver disease was treated with large doses of mebendazole for a hepatic hydatid cyst. Eighteen days after beginning treatment he developed marrow aplasia which reverted to normal after the drug was stopped. This is the sixth patient described as developing marrow aplasia when treated with large doses of mebendazole. We suggest that the aplasia is related to the dose of the drug, and that the patient's chronic liver disease was an important factor in its genesis. Patients treated with large doses of mebendazole should have their blood counts monitored during treatment.

Mebendazole is a broad spectrum anthelmintic drug which, in low doses, has been used a great deal with few adverse effects.[1,2] In large doses it is useful in the treatment of human hydatidosis,[3,4] but marrow aplasia may occur during treatment.[5–7] We describe a case of marrow aplasia due to mebendazole in a patient with chronic liver disease.

CASE STUDY

A male aged 65 years had undergone splenectomy at the age of 62 for idiopathic thrombocytopenic purpura. At 64 years a diagnosis of chronic liver disease was made. When admitted to our department because of pain in the right hypochondrium he had jaundice, hepatomegaly and a right pleural effusion. The effusion was an exudate rich in eosinophils. Analyses showed peripheral eosinophilia (1.24 × 10^9/l), hematocrit 37%, hemoglobin 13 g/dl, leukocytes 11.4 × 10^9/l, platelets 149 × 10^9/l, prothrombin time 50%, alanine aminotransferase 104 U/l, aspartate aminotransferase 106 U/l, alkaline phosphatase 180 U/l, bilirubin 89 μmol/l, albumin 27 g/l, globulin 51 g/l, HBsAg and anti-HBs negative. An abdominal computerized tomograph revealed a mass in the right lobe of the liver suggestive of a hydatid cyst. Serology for *Echinococcus* was positive (indirect hemagglutination $\frac{1}{2,560}$, latex agglutination $\frac{1}{5}$). Surgical resection was impossible because of his poor general health. Mebendazole therapy was started at a dose of 1,500 mg/day. Eighteen days later he presented with abdominal distension, fever, chills and right submandibular pain. Examination revealed erythema with congestion of the posterior fold of the soft palate and mucocutaneous pallor. The hematocrit was 24%, hemoglobin 7.8 g/dl, leukocytes 2.7 × 10^9/l (eosinophils 28%, neutrophils 28%, lymphocytes 44%), and platelets 180 × 10^9/l. The hematocrit and leukocyte counts fell further over the next 5 days. Marrow aspirate and biopsy showed hypocellular bone marrow, with severe diminution in both white and erythrocyte series and slight diminution in the megakaryocyte series. There was moderate lymphocyte and plasma cell infiltration of reactive character, depletion of iron deposits and toxic changes in the stroma manifested by hemorrhage and edema. *Staphylococcus aureus* was isolated in 2 blood cultures. The patient's progress was good after antibiotic therapy, transfusion of 4 U of blood and suspension of mebendazole therapy; after 17 days the leukocyte count was 8.3 × 10^9/l (eosinophils 5%, band forms 2%, neutrophils 54%, lymphocytes 28%, monocytes 11%).

DISCUSSION

This patient is the sixth described in the English language literature who developed neutro-

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TABLE 1

Reported cases of neutropenia due to mebendazole in English language literature

Author	Dose mg/kg/d	Days of treatment	Hematocrit %	WBC × 10⁹/l	Platelets × 10⁹/l	Bone marrow	Liver disease	Evolution
Miskovitz et al.[5]	50	19	27	2.2	210	Hypocellular	None	Recuperation in 14 days
Wilson et al.[6]	50	14	27	0.3	88	Aplasia of erythroid and myeloid series	Alcoholic hepatitis	Sepsis; death
Harris*	50	18	—	—	—	Not reported	—	Recuperation
Levin et al.[7]								
1st case	50	19	—	1.5	Adequate on smear	Not done	None	Recuperation in 12 days
2nd case	40	26	22	0.2	32	Hypocellular	None	Bacteremia; recuperation in 16 days
Present case	30	23	19	1.7	180	Hypocellular	Chronic liver disease	Bacteremia; recuperation in 17 days

* Personal communication, cited by Wilson et al.[6]

penia after treatment with large doses of mebendazole. The data which suggest the drug as the cause of marrow aplasia in our patient are: 1) the appearance of anemia and leukopenia 18 days after the start of treatment; 2) signs of bone marrow toxicity manifested by hemorrhage and edema in the stroma; 3) remission 17 days after stopping treatment; and 4) the absence of other etiological factors.

Our patient presented characteristics which were similar to those of the 5 cases previously described,[5–7] with the same changes in the marrow biopsy and the same latency period (Table 1). We draw attention to the fact that this is the second patient with liver disease who has developed aplasia. We postulate that aplasia is dose-related since: 1) there have been no reported instances of aplasia in any of the thousands of patients with intestinal parasitosis treated with low doses of mebendazole (the most widely used schedule is 100–300 mg twice daily for 3 days); 2) it has appeared only in patients treated with large doses; and 3) it has been reversed in almost all of them. In the only case in which plasma levels of mebendazole were measured they were very high,[7] giving further support to the hypothesis of dose-related toxicity. The chronic liver disease in our patient, with possible alteration in the metabolism of mebendazole and thus a possible increase in its plasma levels, could be an important factor in the genesis of the aplasia.

In conclusion, we recommend frequent monitoring of blood counts during high dose mebendazole treatment, especially in patients with liver disease.

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