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LETTERS AND CORRESPONDENCE

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Interferon-Alpha 2b Interaction With Acenocoumarol

To the Editor: Several well-described side effects are ubiquitous among patients receiving interferon-alpha [1]. A possible interaction between interferon and warfarin increasing the prothrombin time has been recently reported [2]. We report the first case of potentiation of acenocoumarol by interferon.

A 46-year-old-woman was admitted for treatment of chronic C hepatitis. She had received acenocoumarol since 1979 after a mitral valve replacement. Her maintenance dose alternated between 2 and 1 mg daily. Thrombotest was stable between 30 and 35%. In February 1995, thrombotest was 35%. Six weeks after she was given interferon-alpha 2b, 3 million units three times a week, we observed increased anticoagulation with a thrombotest of 19% and gingival bleeding. The patient required a reduction dose of acenocoumarol to achieve appropriate prolongation of the prothrombin time. She was prescribed acenocoumarol 1 mg daily, as opposed to an alternating schedule required before admission. Subsequent thrombotests have remained between 25 and 40%. In October, as hepatitis C virus infection was in remission, interferon was tapered to 3 million units twice a week. Three weeks later we observed decrease anticoagulation with a thrombotest of 69%. Anticoagulation returned to its initial value after the patient was given a dose alternated between 2 and 1 mg daily. However, when prothrombin time was controlled at a different time after interferon therapy, we observed differences in the degree of anticoagulation. Thrombotest increased from 27 and 35% one day after the injection of interferon to 64 and 72% two or three days later.

Liver function tests were normal, except for mild cytolysis, and no other therapy than interferon can account for the fluctuation of anticoagulation observed in this patient. Potentiation of oral anticoagulant by interferon has been reported recently in 5 patients receiving warfarin, resulting in increased anticoagulation with an increased serum warfarin concentration necessitating a reduction in dose [2]. Our observation suggests that potentiation can also occur with acenocoumarol. An inhibition of hepatic microsomial enzymes by interferon can be suspected [3]. Indeed, interferon depresses cytochrome P-450 in mice [4], and has been shown to reduce the activity of drug-metabolizing enzymes in the human liver [3].

When interferon is given to patients receiving oral anticoagulant, the degree of anticoagulation should be carefully monitored.

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Atypical Presentation of Post-Partum Visceral Leishmaniasis

To the Editor: A thirty-one-year-old woman was referred because of fever, anorexia, and malaise of fifteen days' duration. Fever was double quotidian, and was accompanied by profuse sweating. Twenty days before admission she had given birth to a healthy child. Her husband was a military officer and they lived across the Greek-Albanian border the last 20 months.

On admission temperature was 37.6°C, blood pressure 110/70 mmHg, pulse rate 90 per min, and respiration rate 18 per min. Physical examination revealed a palpable spleen 3 to 4 cm below the left subcostal margin. There was neither lymphadenopathy nor hepatomegaly.

On complete blood count she proved to be pancytopenic: the hematocrit was 29%, the white cell count 3,450/μL (with neurtophils 44%, lymphocytes 38%, monocytes 15%, and eosinophils 3%), and the platelet count 110,000/μL. C-reactive protein was 32 mg/dL, and erythrocyte sedimentation rate 55 mm per hour. There was a polyclonal hypergammaglobulinemia on protein electrophoresis. Biochemical tests and urinalysis were within normal limits except for an increase in lactic dehydrogenase (560 IU/L, with an upper limit of 450 IU/L). A chest X-ray and an electrocardiogram were normal. An abdominal ultrasound confirmed the splenomegaly. Tuberculin skin test and serological tests for syphilis, brucella, CMV, EBV, HIV, and hepatitis viruses were negative. Serum direct agglutination test for Leishmania was also negative.

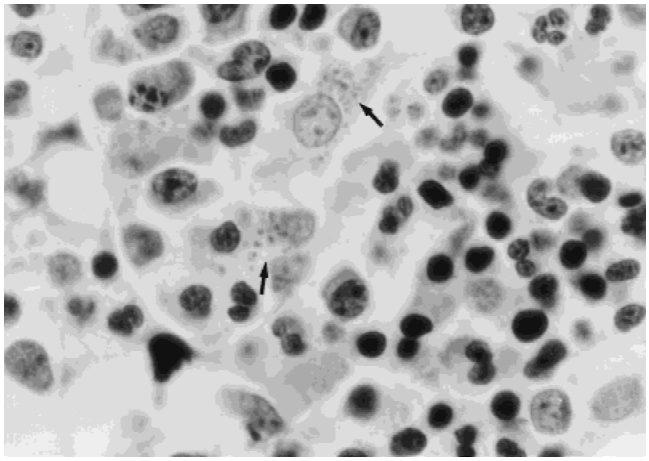

Fig. 1. Bone marrow biopsy. Intracellular amastigotes of Leishmania (Leishman-Donovan bodies) within mononuclear marrow cells (H&E, ×100).

Bone marrow aspiration smear examination showed atypical lymphoid cell infiltration, and a presumptive diagnosis of lymphoma was made at first. Trephine biopsy disclosed intracellular amastigotes of Leishmania species within marrow mononuclear phagocytes (Fig. 1).

The patient was treated with meglumine antimoniate at a dose of 20 mg/kg/day for 20 days with periodic electrocardiographic monitoring. Three months later she was feeling well and the hematological abnormalities were resolved. Her little child was also healthy.

Visceral Leishmaniasis (VL) is included in the differential diagnosis of fever of unknown origin, especially when splenomegaly is present [1]. In such cases serological tests and bone marrow aspiration prove to be valuable tools for the diagnosis of the disease [2,3]. However, in our case the direct serum agglutination test, although considered a sensitive indicator of acute disease in the majority of patients, was negative, and bone marrow aspiration smear examination was misleading, while only trephine biopsy was the definite procedure for establishing the correct diagnosis. The incubation period of VL is 3 to 8 months. Our patient must have contracted the parasite during gestation. Thus, we report this case first to underline the importance of trephine biopsy in the diagnosis of VL, and second to emphasize the possibility of presentation of the disease during the puerperium. Interestingly, it has recently been shown that pregnancy alters the equilibrium of cytokines towards Th2 and away from Th1 pattern during the antiparasite response in pregnant mice (T cell-mediated immune-response patterns, Th1 secreting IL-2, INF-γ, and TNF-β, and Th2 secreting IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, identified among mouse CD4 Th clones). This shift in cytokine patterns provides an explanation for the increased susceptibility to Leishmania infection in pregnant mice and possibly in pregnant women, as was the case in our patient [4,5]

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Unusual Leukocytosis With Eosinophilia by an Allergic Disease

To the Editor: Eosinophilia occurs in the idiopathic hypereosinophilic syndrome (HES), eosinophilic leukemia, and various etiologies such as parasitic infections and allergic diseases. Total leukocyte counts are mostly less than 25×10^9/l with between 30 and 70% eosinophils [1]. Increasing eosinophil stimulating cytokines (IL-5, IL-3) indicates that eosinophilia may be reactive to allergens [2]. The presence of chromosomal abnormalities and of myeloblasts in the peripheral blood with normal IL-3 and IL-5 levels indicates a myeloproliferative disorder [3,4]. High leukocyte counts with eosinophilia are believed to develop only in patients with HES or eosinophilic leukemia and are associated with poor prognosis [5]. We report here a case with a white blood cell count of 49.8×10^9/l with 72% eosinophils due to allergy for bird.

A 40-year-old female was referred to our hospital in June 1992 because of bilateral cervical lymph node swelling and leukocytosis with marked eosinophilia. Physical examination showed bilateral cervical lymph node swelling with mild tenderness. Laboratory tests were as follows: white blood cell count (WBC) 49.8×10^9/l, hemoglobin 14.1 g/dl, platelets 366×10^9/l. The differential showed 72% eosinophils (36×10^9/l), 17% neutrophils, 8.5% lymphocytes, 2% monocytes, and 0.5% basophils. LDH was mildly raised up to 434 U/l. Erythrocyte sedimentation rate was 10 mm/h. Autoantibody screening, immunoglobulins, and repeated stool examinations for ova and parasites were all negative. IL-5 level was increased to 42 pg/ml (normal values; <10 pg/ml). Bone marrow aspirate from the sternum showed a marked eosinophilic hyperplasia with a left-shifted eosinophilic series. The percentage of myeloblasts in the bone marrow was <3%. Chromosome analysis on bone marrow aspirate showed normal karyotype in all metaphases analyzed. Gastroscopy, ECG, heart ultrasound, and chest X-ray tests were all normal. Without any treatment, bilateral cervical lymph node swelling regressed. In October 1992, laboratory findings were as follows: WBC 8.8×10^9/l, hemoglobin 14.4 g/dl, platelets 325×10^9/l. The differential showed 51.3% neutrophils, 8.4% eosinophils (0.7×10^9/l), 25.4% lymphocytes, 8.4% monocytes, and 0.4% basophils. IL-5 level at this time was quite normal. In March 1993, leukocytosis was again observed with eosinophilia. At that time her peripheral blood showed: WBC: 36.5×10^9/l (67% eosinophils, 22% neutrophils, 7% lymphocytes, 4% monocytes), hemoglobin 15.3 g/dl, and platelets 385×10^9/l. The bone marrow aspirate revealed a marked hyperplasia with 72% eosinophilia and less than 3% myeloblasts. Spontaneous regression of eosinophilia occurred again in September 1993.

Eosinophilia was observed only in spring in this patient. Careful review of her present illness found the evidence that her daughter took care of a parrot that lost its feathers in spring. As the allergenic test for bird feathers was positive in this case, they gave up taking care of the parrot. Then the patient was well without any evidence of eosinophilia.

Etiologies for marked leukocytosis with severe eosinophilia are mostly HES or the eosinophilic leukemia. Our case implies an important suggestion that a marked increase in the absolute eosinophil count more than 30×10^9/l should also be considered an allergic disease.

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Effect of Omeprazole in Chronic Idiopathic Thrombocytopenic Purpura

To the Editor: In adult patients with chronic idiopathic thrombocytopenic purpura (ITP) who are resistant to steroid treatment and splenectomy, or in whom they are contraindicated, treatment options other than intravenous immunoglobulin are quite limited. There have been several reports describing temporary recovery of platelet counts after treatment with azathioprine, cyclophosphamide, vinca alkaloids, or heparin, but overall results were unsatisfactory [1,2]. We present a case of ITP whose platelet count increased 2- to 3-fold, as compared to baseline, after omeprazole treatment for peptic ulcer disease.

A 69-year-old Japanese woman had been diagnosed as having ITP 13 years previously when her platelet count was 14.0×10^9/L, the white blood cell count 9.1×10^9/L, and hemoglobin 145 g/L. C reactive protein, antinuclear antibody, and rheumatoid factor were negative. Bone marrow examination revealed a nucleated cell count of 89.0×10^9/L and a megakaryocyte count of 75×10^6/L. The patient was started on 0.5 mg/kg of prednisolone daily to which her platelet count responded by rising to 134×10^9/L. Although the platelet count later decreased with tapering of the dose of prednisolone, her platelet count had been maintained at 30 to 60×10^9/L with 7.5 mg of prednisolone every other day for 10 years.

In 1991, she started complaining of epigastric pain and endoscopic examination revealed a gastric ulcer. Famotidine was started with no change in her platelet count. At the end of 1993, due to worsening of her peptic ulcer disease, she was started on omeprazole. After the omeprazole had been started, her platelet count increased from 73 to 232×10^9/L with no change in white blood cell counts. Her platelet count decreased shortly after the discontinuation of omeprazole, falling to 72×10^9/L (Fig. 1A). Medications had never been changed meanwhile, which included danazole and prednisolone. After this experience, she was successively treated with omeprazole three times, including two times without danazole, with a washout period of at least 3 months between each exposure. On each occasion, her platelet count increased 2- to 3-fold, as compared to the baseline value (Fig. 1B).

A chromosome study of bone marrow cells revealed a normal karyotype. The platelet-associated immunoglobulin level was 20.2 ng/10^7 platelets while on omeprazole but 61.4 when off.

Omeprazole is one of the proton pump inhibitors indicated for peptic ulcer disease and esophageal reflux [3,4]. This medication is reportedly

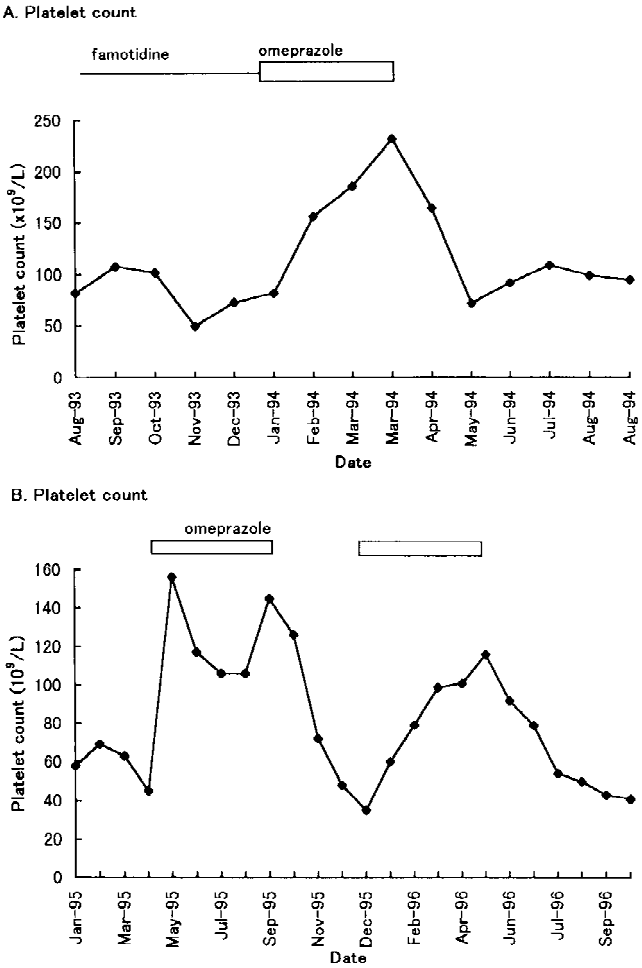

Fig. 1. Effects of omeprazole on platelet counts. Initial (A) and subsequent (B) treatment with omeprazole.

associated with the development of thrombocytopenia but no cases of thrombocytosis have previously been reported. The mechanism underlying the increase in the platelet count in this patient while being treated with omeprazole remains unclear and merits further evaluation. Proton pump inhibitors may have some effects on the immune system but, in one report the functions of monocyte-macrophages were enhanced rather than inhibited by omeprazole [5].

Omeprazole has not previously been reported to be an effective treatment for chronic refractory ITP but an evaluation of its effects may be worthwhile because of its well-established safety profile and cost-effectiveness.

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Modulation of Macrocytosis in Aplastic Anemia

To the Editor: The recent letter by Altay and Gurgey [1] regarding the modulation of macrocytosis in Fanconi's anemia by β-thalassemia trait leads me to point out that any cause of microcytosis would have the same effect. There are allusions to the same observation in the older Fanconi's anemia literature [2,3] as well as the one cited by them [4]. In addition, iron deficiency may result in the same finding; I have seen a patient with Fanconi's anemia with a normal MCV, in whom macrocytosis appeared when his iron deficiency was adequately treated. In fact, perhaps their patient actually developed iron deficiency when she responded to androgens. Furthermore, I have seen unexpectedly normal MCVs in patients with Diamond-Blackfan anemia who have concomitant β- or α-thalassemia trait. We also published the results of bone marrow transplantation from β-thalassemia trait to β-thalassemia major, in which the expected transient phase of macrocytosis during fetal-like erythropoiesis was masked by the microcytosis of the donor erythrocytes [5]. Thus, so-called macrocytic anemias may not be macrocytic in the face of microcytosis, be it genetic or acquired.

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