effects include transient mild neutropenia, prolonged cephalin time (lupus anticoagulant was detected), and reversible elevation of liver-cell enzymes [2,3]. We report on a patient who presented aplastic anemia that, as far as we know, has not been previously described.

E.G.C., a 71-year-old woman, was diagnosed as having hepatic hydatidosis and portal hypertension, with low white blood cell (3.5×10^9/l) and platelet count (60×10^9/l) and a normal hemoglobin (Hb) level in April 1995. Albendazole (800 mg daily) was started on April 25, 1995, and on May 10, 1995 a blood count showed pancytopenia: leucocyte count, 0.8×10^9/l (neutrophils, 0); Hb, 6 g/dl; platelet count, 15×10^9/l, and anodine blood smear. Serologic test for viral hepatitis was HBsAg-negative, HBcAb-positive, HBsAb-positive, and anti-HCV-negative. Aspiration from marrow cavities yielded a few spicules; films made from spicules revealed fatty material with sparse populations of lymphocytes and plasma cells. A marrow biopsy showed severe hypoplasia and fatty replacement. Albendazole therapy was withdrawn, but without beneficial effects, and large doses (25 g/day for 5 days) of intravenous gamma globulin (IVIG) and G-CSF were given on the fifth day. She becomes nearly hematologically normal in 7 days, without developing dependency on any medication.

IVIG administration has been described successfully in pure red cell aplasia, parvovirus B19-induced aplastic crisis, and recently in idiopathic aplastic anemia [4]. Because of the patient's advanced hepatic hydatidosis, nonaggressive therapy was chosen, i.e., IVIG.

This is the first report of albendazole-associated bone marrow aplasia. Although neutropenia is described as a side effect of albendazole, this is infrequent (5% of cases) and clinically uneventful, resolving spontaneously either on discontinuation of the drug or after completion of the treatment period [2]. No other alterations of blood cells by albendazole therapy have been described in the medical literature (MEDLINE, 1983–1995).

Our contention is that this potential adverse effect of albendazole should be kept in mind during its use. Further studies about IVIG and cytokines are required in bone-marrow aplasia secondary to drugs, although a delayed spontaneous recovery of bone-marrow function cannot be ruled out in this case.

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Secondary Acute Myelogenous Leukemia Following Treatment With Oral Etoposide

To the Editor: We report on a 71-year-old male who, in January 1990, was diagnosed as having stage IV adenocarcinoma of the prostate. He was initially managed with leuprolide until 1991, when progressive painful pelvic metastasis required pelvic irradiation (4,000 cGy). He received goserelin and flutamide until March 1993, when progression prompted a referral to our institution. He was treated on a phase II trial for hormone refractory prostate cancer, consisting of oral etoposide 50 mg/m^2/day and estramustine 10–15 mg/kg/day for 3 weeks, repeated every 4 weeks [1]. He received 17 courses of treatment. In November 1994, he was noted to have pancytopenia with circulating blasts. A bone-marrow biopsy revealed acute myelogenous leukemia, French-American-British (FAB) classification system M2, with dysplastic changes in all cell lines. Cytogenetic examination revealed 46 XY t(8;21)(q22;22).

Induction was attempted with cytosine arabinoside and daunorubicin, but the patient died 3 weeks later, secondary to neutropenic sepsis.

Our patient developed acute myelogenous leukemia (AML) 18 months after initiation of treatment with oral etoposide and estramustine for hormone refractory prostate carcinoma, and $3\frac{1}{2}$ years after pelvic irradiation of 4,000 cGy. His bone marrow showed dysplastic changes, although he did not have a clinical preleukemic phase. Cytogenetics revealed a t(8;21). Quensel et al. [2] reported 26 cases of secondary AML with t(8;21) and a short latent period. Five patients had prior epipodophyllotoxin treatment (3 with etoposide (VP-16), and 2 with teniposide (VM-26). Four patients had prior radiation therapy as well [2]. Therapy-related AML secondary to epipodophyllotoxins is a well-recognized entity. The cancer therapy evaluation program (CTEP) of the National Cancer Institute (NCI) has developed a monitoring plan to obtain reliable estimates of the risk of treatment-related AML, following epidodophyllotoxin treatment at low ($<$1,500 mg/m^2), moderate (1,500–3,999 mg/m^2), and high cumulative doses ($\geq$4,000 mg/m^2) [3]. Bioavailability of oral etoposide appears to be approximately 50%, although the range of values noted in individual patients varies widely (25–75%). Our patient had received a total cumulative dose of 16,800 mg/m^2 of oral etoposide, which is comparable to at least 4,200 mg/m^2 of parenteral etoposide, which is a high cumulative dose. The CTEP plans to detect the frequency of secondary leukemia and will also address the importance of cumulative dose. Etoposide-related secondary leukemia is characterized by a short latent period of only 2–3 years after treatment, the absence of a preleukemic myelodysplastic phase, predominantly M4 or M5 type AML, and translocations involving chromosome 11 at locus 11q 23.

In reviewing the literature, we came across only one case of therapy-related AML secondary to oral etoposide. The patient received 21 cycles of oral etoposide over 2 years for metastatic nonsmall-cell lung cancer [4].

Our patient also received estramustine, an alkylating-agents derivative. It is unlikely that leukemia developed secondary to estramustine, since secondary leukemia reported after the use of alkylating agents occurs after an average interval of 5–7 years. This secondary leukemia is preceded by a preleukemic myelodysplastic phase, and usually involves cytogenetic abnormalities of chromosomes 5 and 7 [5].

Oral etoposide is increasingly used for metastatic small- and nonsmall-cell lung cancer, and is an active agent in hormone-refractory prostate carcinoma. Careful follow-up of patients treated with oral etoposide is important for the detection of secondary AML.

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Severe Vitamin K Deficiency Induced by Occult Celiac Disease BR96-026

To the Editor: This report describes the clinical course of an elderly woman in whom celiac disease was diagnosed, in the absence of gastrointestinal symptoms, after she developed ecchymoses due to vitamin K deficiency. After 1 year of receiving a gluten-free diet, she continued to have subclinical malabsorption, based on a warfarin requirement of <1.3 mg daily for anticoagulation following a cardiac valve replacement. This report and other studies [1,2] suggest that occult malabsorption may be a likely etiology for vitamin K deficiency or low warfarin requirements in elderly patients.

Case Report

A 68-year-old woman was admitted for evaluation of diffuse ecchymoses, which developed after outpatient therapy for sinusitis consisting of ampicillin (10 days) followed by trimethoprim-sulfamethoxazole (2 days). The patient had no history of liver disease or unusual diet, and was not receiving warfarin. She noted a 4-lb weight loss in the previous 2 months, but denied diarrhea or abdominal pain. A gastrointestinal evaluation performed 1 year earlier for iron-deficiency anemia was normal, and the anemia resolved with iron supplementation.

Other medical problems included: idiopathic hypoparathyroidism, hypocalcemia, low-normal vitamin D levels, and osteoporosis treated with calcitriol and calcium; hypothyroidism treated with levothyroxine; rheumatic heart disease and chronic atrial fibrillation, treated with triamterene/hydrochlorothiazide and digoxin; and a seizure disorder treated with phenytoin.

The patient, who was 58 inches tall and weighed 40 kg (88 lb), had ecchymotic lesions on her extremities but did not have mucosal bleeding, lymphadenopathy, or hepatosplenomegaly. The stool tested guaiac-negative. Initial laboratory data (Table I) revealed anemia and deficiency of vitamin K-dependent factors. The deficiency of vitamin K-dependent factors was rapidly corrected with subcutaneous vitamin K (10 mg). Small-bowel biopsy revealed villous atrophy with chronic inflammation, consistent with celiac disease. A gluten-free diet was initiated and the patient gradually gained 9 kg (20 lb). Her coagulation studies remained normal, her bone density improved, and she no longer required calcium or calcitriol. One year later, after undergoing cardiac valve replacement, the patient's warfarin requirement was 9 mg/week (<1.3 mg/day), which suggested residual occult malabsorption.

TABLE I. Summary of Laboratory Data at Presentation (Time 0), and 18 Hr After Vitamin K Administration*

Test	Time 0 hr	After 18 hr	Normal
Platelets/μl	173,000		150–450,000
Hematocrit (%)	24		37–47
MCV (μ^3)	99		81–99
PT (sec)[a]	45.5	14.5	11–14
aPTT (sec)[a]	102.6	32.9	22–34
Fibrinogen (mg/dl)	530		200–400
Factor II (%)	45	55	50–150
Factor VII (%)	5	97	50–150
Factor IX (%)	4	61	50–150
Factor X (%)	2	34	50–150
Factor V (%)	148		50–150
Thrombin time (sec)	12.2		11–14
Reptilase time (sec)	12.0		10–13

*MCV, mean cell volume; PT, prothrombin time; aPTT, activated partial thromboplastin time.
[a]Studies corrected when patient plasma was mixed with normal plasma in 1:1 ratio.

Discussion

Hematologic manifestations of celiac disease (or malabsorption in general) are usually limited to iron or folic acid deficiency [3]. Subclinical vitamin K deficiency is common in malabsorption but rarely results in an overt coagulopathy [2,4].

Although the patient improved clinically on a gluten-free diet, her warfarin requirement was extremely low, suggesting that the gastrointestinal tract may not have undergone complete healing. The prevalence of occult malabsorption in elderly patients who require minimal doses of warfarin to achieve anticoagulation may be higher than currently recognized.

Immunofluorescence assays for endomysial and antireticulin antibodies, and an enzyme-linked immunosorbent assay for antigliadin antibodies, can now be used to exclude celiac disease as a cause for malabsorption [5]. If these tests are positive, small-bowel biopsy should still be performed, since there is an increased risk of intestinal lymphoma associated with celiac disease [3].

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