period of 6 weeks. After 2 months she developed malaise and persistent fever (38–38.5°C) without clinical or laboratory evidence of infection or hemolysis. Interferon-α-2b was ceased with resolution of fever, and she subsequently remains well on hydroxyurea.

A causal association between interferon-α-2a and intravascular hemolysis is suggested by the close temporal relationship of onset of symptoms with the first dose of the drug, the rapid resolution with its withdrawal, and the exclusion of other known causes of intravascular hemolysis. The mechanism by which interferon caused the hemolysis is unclear. Autoimmune hemolysis has been associated with interferon use, but is usually a long-term complication, occurring after a median of 14 months of treatment [1]. In our patient, hemolysis was not obviously immune-mediated, in view of the time course and the inability to detect either IgG or C3 on the red-cell surface. Furthermore, it is difficult to explain hemolysis with interferon-α-2a, but not α-2b, on an immunogenic basis when the biochemical difference between the two is confined to a single amino acid at position 22 [2].

Interferon-α-2a is cloned in an *Escherichia coli* strain, with a final purity >99% [3,4]. While it is theoretically possible that our patient reacted to a "contaminating" *E. coli* protein, we are not aware of reports of intravascular hemolysis associated with biological substances cloned in this way [5].

In the absence of other demonstrable causes, it is likely that the hemolysis was interferon-induced. Nonimmune intravascular hemolysis should be added to the list of potential complications of this drug.

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Acrocyanosis as a Heralding Sign of Ovarian Benign Teratoma

To the Editor: We report on the uncommon association of cryoagglutinins without hemolysis, which subsided following surgical ablation of an ovarian benign teratoma.

Case Report

A 22-year-old woman was admitted at our Institution for persistent acrocyanosis. Previous vascular (Doppler and capillaroscopy) investigations and present physical findings were unremarkable. Chest X-rays, bone-marrow biopsy, thyroid hormones, erythrocyte sodimentation rate (ESR), C-reactive protein, rheuma test, antinuclear antibody (ANA), immunoglobulin serum levels, lactate dehydrogenase (LDH), aptoglobin, Coombs' test, beta2 microglobulins, serum copper, and serum markers of viral infection were all normal or negative. Cryoagglutinins were 1:2,000. Computed tomography scanning showed the presence of a dermoid cyst 9 × 5 cm, close to her left ovarion. Following surgical ablation of this tumor (the pathological diagnosis being of ovarian benign teratoma), cryoagglutinins and acrocyanosis disappeared. The patient is well 18 months after surgery.

Discussion

The association of autoimmune hemolytic anemia and benign ovarian neoplasm is uncommon in adult patients [1,2]. Our case is exceptional in that the patient, although she had high-titer cryoagglutinins, never became anemic, and there was no evidence of hemolysis.

In our Medline-assisted literature search (for 1987–1995) we were unable to find any similar cases, and we believe ours to be the first report of acrocyanosis heralding an ovarian benign teratoma. We also tend to believe that the resolution of acrocyanosis and the disappearance of cryoagglutinins following surgery rule out a chance association among the three. Indeed, cryoagglutinins and acrocyanosis are known to be causally linked [3], and the development of autoimmune hemolytic anemia is a well-known paraneoplastic sign [4] in a variety of cancers (lymphomas, lung, ovary, tumors of the gastrointestinal tract, etc.). The absence of hemolymphopoietic tissue in the pathological specimen fits with the hypothesis that benign teratoma is not a site of direct cryoagglutinin production but that it serves as a stimulus for such production to occur in normal lymphoid tissue of the host. Once such stimulus was surgically removed, the cryoagglutinins disappeared. Our observation is worth further confirmation: owing to their subclinical manifestation, it is quite conceivable that cryoagglutinin production may have been overlooked in previous cases of teratomas. Accordingly, we propose that cryoagglutinins be systematically sought in benign ovarian teratomas to ascertain the hypothesis that their prevalence is increased in such patients as compared to a control population.

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Aplastic Anemia During Treatment With Albendazole

To the Editor: Albendazole is a benzoimidazole-carbamate compound whose use is rising in the medical treatment of hydatid disease [1]. Adverse

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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