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Treatment and Prophylaxis of Hypermenorrhea With Leuprorelin in Premenopausal Women Affected by Acute Leukemia at Diagnosis

To the Editor: Women affected by acute leukemia (AL) often show hypermenorrhea at diagnosis or after chemotherapy [1], increasing supportive care and transfusional needs and influencing performance status. The effect of leuprorelin, a Gn-rh analogue which induces profound amenorrhea, in premenopausal AL women showing vaginal bleeding at diagnosis is reported. Sixteen premenopausal women with AL were treated with standard chemotherapy, including antracyclines. Characteristics of patients are shown in Table I. Eight of them received oral contraceptives (OC) (gestodene, 0.075 mg, and ethynil estradiol, 0.03 mg, daily; group A) until resolution of thrombocytopenia or when toxicity occurred (median days 17.5). When leuprorelin (Enantone Depot, Takeda, Osaka, Japan) became commercially available, it was administered, after informed consent, to eight patients (3.75 mg/q 28 days sc) in combination with OC (median days 16) to prevent leuprorelin "flare-up" (group B).

Results were expressed as median values. Probability of significant differences between groups was assessed by Mann-Whitney U test for unpaired groups and $\times 2$ test on 2×2 tables. Statistical significance was $P = 0.05$.

Results are summarized in Table 1. Vaginal bleeding lasted a median of 3 and 5 days in groups A and B (P = NS), respectively. There was no statistically significant difference in supportive measures (median values: group A 7 red blood cell units [RBCu] and 5.5 single donor platelet units [SDPu]; group B 10 RBCu and 9.5 SDPu).

Liver toxicity grade I–II was observed in two of eight patients in group A and in five of seven in group B; three of eight patients in group A developed grade III–IV toxicity (P = NS). OC discontinuation was necessary in three of eight patients in group A and in five of seven patients in group B with resolution of liver damage. Three patients in group A discontinued OC for concomitant therapy with L-asparaginase. No side effects attributable to leuprorelin were encountered in group B. Upon OC withdrawal, vaginal bleeding occurred in six of eight patients in group A; no patient in group B developed vaginal bleeding ($P = 0.009$).

In premenopausal leukemic patients, significant blood losses may derive from uncontrolled vaginal bleeding, which per se determines an important discomfort and may increase susceptibility to infections due to lack of mucosal integrity [2]. The use of OC, despite a rapid control of vaginal bleeding, may adversely affect liver function [3], potentiating toxicity related to chemotherapy or antibacterial or antifungal agents; OC may affect the hemostatic system, inducing a prothrombotic effect [4] amplified by the use of specific antitumor drugs like L-asparaginase [5]. The compliance of oral administration is poor. Our data confirm that early discontinuation of OC may be necessary. Leuprorelin determines a profound amenorrhea acting on the hypothalamic–gonadal axis, but its effect is not as rapid as that of OC. The temporary agonist effect requires OC in combination early during thrombocytopenia. Our experience showed the feasibility and efficacy of leuprorelin. Compliance was optimal and safety profile good. No statistical differences were observed in the two groups in terms of toxicity, likely related to the contemporary use of OC or in length of vaginal bleeding and transfusional support. A significant difference occurred in resumption of vaginal bleeding upon OC discontinuation, reflecting the different biological mechanism of amenorrhea induced by leuprorelin, which is profound and long-lasting. Further reduction of liver toxicity

TABLE I. Characteristics of Patients

	Group A	Group B	*P*
Age (years)	29.5 (13–43)	39 (26–41)	0.042
Diagnosis	AML 5; ALL 3	AML 7; ALL 1	0.56
Platelet count × 10e9/l	27.5 (7–49)	28 (12–83)	0.3
Vaginal bleeding	6/8	7/8	1
Length of VB	3 (1–26)	5 (2–34)	0.28
RBCu	7 (2–21)	10 (3–15)	0.35
SDPu	5.5 (1–15)	11 (1–16)	0.35
Liver toxicity	5/8	5/8	1
WHO grade I–II	2/8	5/8	NS
WHO grade III–IV	3/8	0/8	0.20
Bleeding resumption	6/8	0/8	0.009
Days to platelets >50 × 10e9/l	17 (6–25)	21 (6–34)	0.23

VB, vaginal bleeding; RBCu, red blood cell units; SDPu, single donor platelet units. Age, platelet count, length of VB, RBCu, PLTsu, and days to platelets >50 × 10e9/l are expressed as median values.

could be obtained by shortening the duration of OC administration. No interferences with hemostatic balance are documented.

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Waldenstrom's Macroglobulinemia Transformed Into Immunoblastic Lymphoma Presenting With Malignant Ascites

To the Editor: On rare occasions, Waldenstrom's macroglobulinemia (WM) may transform into immunoblastic lymphoma (IL), a phenomenon analogous to Richter's syndrome occurring with chronic lymphocytic leukemia [1]. Transformation is signaled by diffuse lymphadenopathy, fevers, night sweats, and weight loss [2]. To our knowledge, we report the first case of a patient with malignant ascites as a presenting manifestation of WM that transformed into IL.

A 57-year-old male with a history of WM presented with 2 weeks of progressive abdominal distention, cervical adenopathy, fevers, night sweats, and weight loss. Ten years previously, he was diagnosed with WM. Immunocytochemistry of a marrow specimen demonstrated the majority of cells to be IgM kappa-positive. He received multiple agents, including cyclophosphamide, vincristine, prednisone, and chlorambucil. He had no history of ethanol use or liver disease.

Physical examination revealed left-sided cervical, supraclavicular, and axillary adenopathy. The abdomen was distended with shifting dullness. Serum lactate dehydrogenase (LDH) was 1,817 units/l and plasma viscosity was 2.87 (nl 0.99–1.55). White blood cell count was 24,000 cells/mm^3 with 30% immunoblasts, suggesting transformation of WM into a more aggressive neoplasm. Flow cytometry of these cells was consistent with WM. Paracentesis revealed numerous cells similar in morphology to the immunoblasts in the peripheral blood (Fig. 1); the culture was sterile. Ultrasound of the liver was normal. Computerized tomography scan showed massive thoracic and abdominal lymphadenopathy. A cervical lymph node biopsy was consistent with IL and stained positive for IgM kappa, supporting clonal transformation. The patient denied further intervention and died 13 days after admission.

Transformation of WM into IL is a rare event, occurring in approximately 1.7% of cases of WM [3]. The mean survival once transformation occurs in 2 months [2]. Prior therapy with alkylating agents may predispose to transformation, though this remains to be proven [3]. IL is characterized by the monomorphous proliferation of immunoblasts, which are large cells with plasmacytoid features [1]. Both WM and IL are clonal diseases, and the change in histologic appearance of the cells characteristic of WM into the larger cells of IL is believed to represent evolution of the same clone of cells. Furthermore, the appearance of identical heavy and light chains on both tumor cell types supports clonal evolution [4].

Ascites due to IL is very rare. Peritoneal lymphomatosis is much less common than peritoneal carcinomatosis and carries a dismal prognosis [5]. Runyon and Hoefs [5] reported on three patients with malignant ascites as

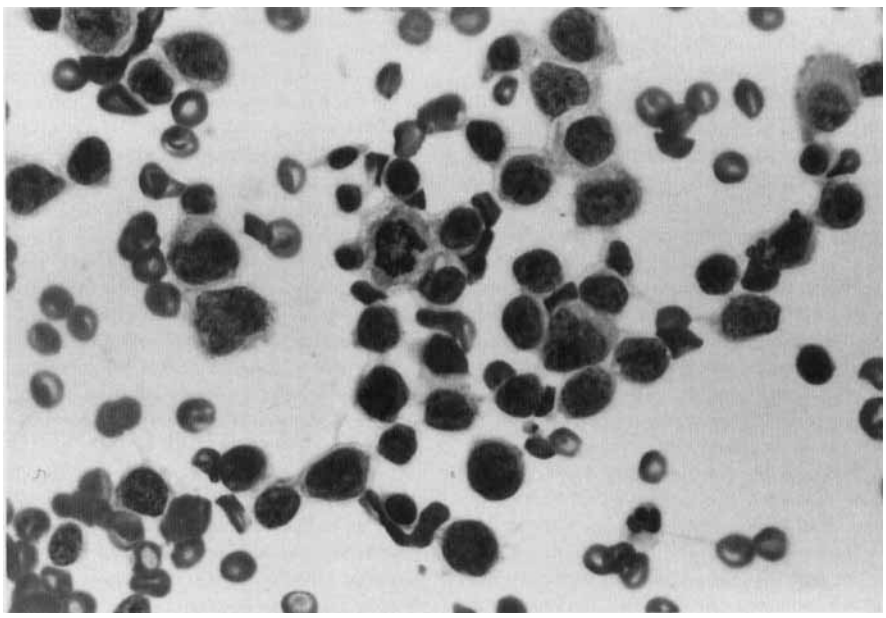

Fig. 1. Peritoneal fluid positive for immunoblastic lymphoma. Note mitotic figure in the center. Papanicalou cytocentrifuge preparation, magnification × 100, oil.