Extramedullary hematopoiesis in the uterine isthmus: A case report and review of the literature

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Summary

Extramedullary hematopoiesis (EH) is the ectopic production of myeloid, erythroid and megakaryocytic elements. In postfetal life it usually occurs in conditions with hyperactive, depleted or infiltrated marrow; it is extremely rare in the genital tract. We report a case of EH in the uterine isthmus (UI) which was found incidentally in a 40-year-old patient who presented with a right ovarian cyst and a history of a right modified radical mastectomy for infiltrating invasive lobular carcinoma one year earlier. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. Microscopic examination of UI revealed foci of hematopoiesis, consisting of white blood cell precursors confirmed by positive chloroacetate-esterase staining. Bone marrow biospy showed diffuse infiltration secondary to breast cancer. Further work-up, including a bone scan, showed multiple metastases suggesting that the high degree of bone marrow infiltration by neoplasmatic cells had stimulated the EH. In conclusion, the unusual finding of EH in UI heralded widespread infiltration of bone marrow.

Key words: Hematopoiesis; Extramedullary; Uterus; Bone marrow biopsy.

Introduction

Extramedullary hematopoiesis (EH) is the production of myeloid, erythroid and megakaryocytic elements at ectopic sites [1]. In postfetal life, it usually occurs in conditions with hyperactive, depleted or infiltrated marrow [2]. Paraosseous extramedullary hematopoiesis occurs more commonly in conditions with hyperactive bone marrow such as haemolytic anaemias. On the other hand, extraosseous extramedullary hematopoiesis is usually associated with bone marrow depletion or infiltration [2].

The most frequently involved sites of extraosseous extramedullary hemotopoiesis are the spleen, liver and lymph nodes; location in the genital tract is extremely rare.

We present a case of an asymptomatic 40-year-old woman with an incidental finding of EH in the uterine isthmus (UI) and diffuse replacement of bone marrow by neoplasmatic cells. The patient had had a right modified radical mastectomy for infiltrating breast cancer one year earlier. To our knowledge this is the first case reported in the English literature regarding EH in the UI.

Case Report

An asymptomatic 40-year-old gravida II, white Albanian woman presented to the District General State Hospital, "G. Chatzikosta", Ioannina, Greece in March 2000 with a two-month-old ultrasound report from a private clinic indicating a right ovarian cyst with maximum diameter 5.5 cm and without any heterogeneity or diaphragms within it. The patient reported regular menstruation every 28 to 30 days. Past medical history included infiltrating invasive lobular carcinoma of the right breast for which she had undergone a modified radical mastectomy and lymphadenectomy one year earlier in Albania. One of the four removed axillary lymph nodes had been positive for metastatic carcinoma and chemotherapy consisting of one cycle of cyclophosphamide, fluorouracil and methotrexate was given. This regime, however, had been discontinued because of adverse side-effects and the patient was started on oral tamoxifen therapy at a dose of 20 mg daily, which she was still taking when she presented at our hospital.

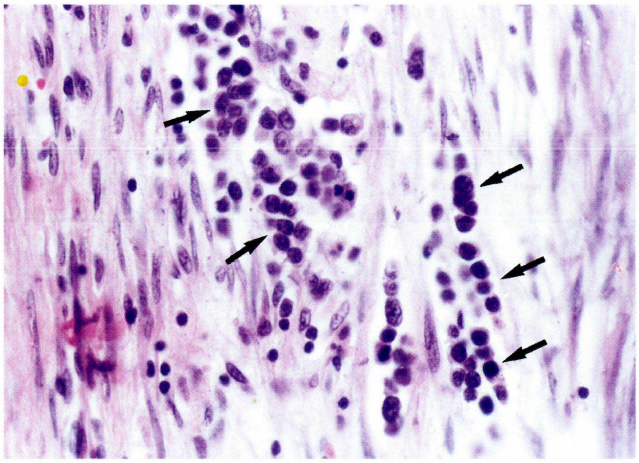
A repeat abdominal ultrasound scan at the March 2000 admission demonstrated no regression of the ovarian cyst and an exploratory laparotomy was considered. The preoperative hematological data was within normal limits: hemoglobin 12.9 g/dl, leukocyte count 9.74×10^9/l and platelet count 250×10^9/l. The blood chemistry values, serum CA125, urine test and chest X-ray were all normal. The patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. The fresh frozen biopsy of the right ovary with the cystic structure was negative for malignancy.

Grossly, the uterus was slightly enlarged with two intramural leimyomas in the uterine body with maximum diameters of 1 and 1.5 cm. In addition, one submucosal leiomyoma with a maximum diameter of 0.7 cm was found at the level of the uterine isthmus. Microscopic examination of the right ovary revealed a functional ovarian cyst and an hemorrhagic corpus luteum. The left ovary and both fallopian tubes were normal. Sections taken from the uterus showed normal pathology. The endometrial mucosa was found to be at a deficient secretory phase. However, a few foci of hematopoiesis were found in the mucosa and inside the capillary vessels (Figure 1) corresponding to the UI. The cells had intense mitotic activity. Their nuclei were round, oval or slightly indented and the cytoplasm was basophilic and granulated. Histochemically, the cells were positive for chloroacetate esterase (Figure 2), while immunohistochemically they were negative for the common leucocyte

Revised manuscript accepted for publication November 5, 2001

antigen and polyclonal keratin. In sum, the cells were indicative of white blood cell precursors, namely promyelocytes, suggesting bone marrow infiltration.

In order to confirm this and also to determine the histological type of neoplasmatic cells we performed an osteomedullary biospy some days after the operation. On the day of the bone-marrow biopsy, the patient had mild anemia (hemoglobin = 12.1 g/dl), with normal leukocyte (4.56×10^9/l) and platelet (184×10^9/l) counts. The maximum diameter of the bone cylinder was 1.1 cm. Microscopic examination of the bone marrow biopsy revealed a metastatic adenocarcinoma. Considering the patient history, the most probable site of the primary adenocarcinoma was the breast. The myelospaces of the bone marrow were infiltrated by many neoplastic cells which were either diffused between the myeloid elements, or formed either trabecules or nests that were circumvallated by reactive lymphocytic infiltrations. Most of these cells had peripherally placed nuclei resembling signet-ring cells (Figure 3). Histochemically the signet-ring cells were found to contain acid or neutrophilic glycocalyx with acid or neutrophilic endocytoplasmatic mucin droplet (Alcian blue/PAS stain) (Figure 4). Immunohistochemically, these cells were intensively positive to pancytokeratin (Figure 5) and epithelial membrane antigen (EMA).



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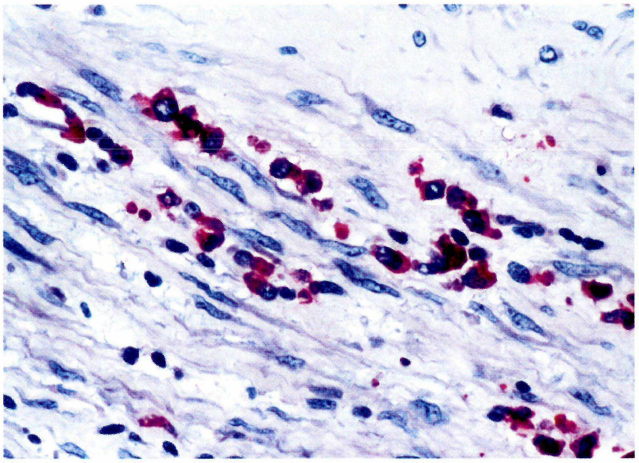

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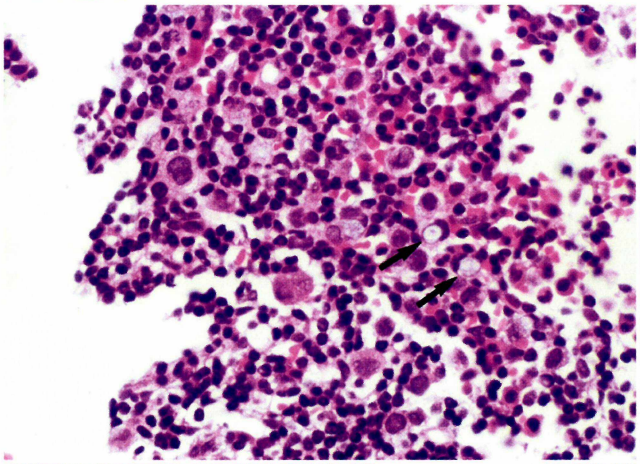

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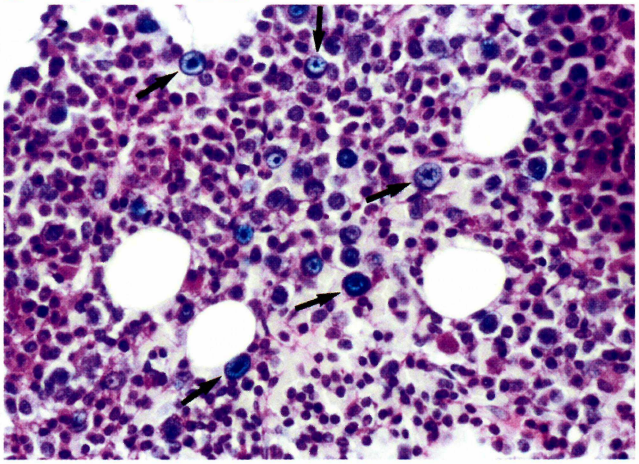

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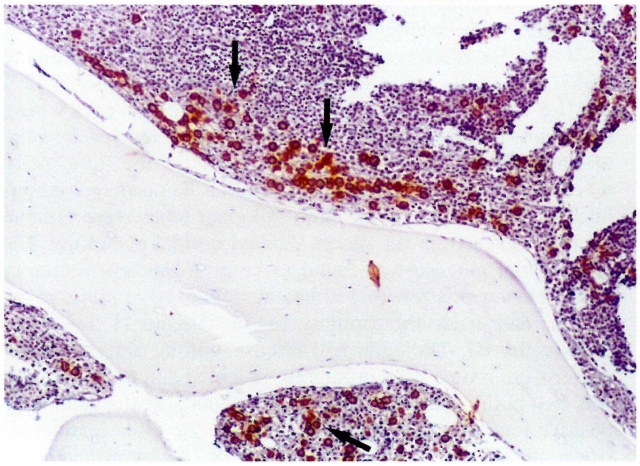

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Figure 1. — Focus of extramedullary hematopoiesis in the isthmus mucosa consisting of white blood cell precursors (arrows) [H&E x 400].

Figure 2. — Chloroacetate esterase positive white blood cell precursors [x 400].

Figure 3. — Infiltration of bone marrow by neoplastic signet ring-like cells (arrows) [H&E x 400].

Figure 4. — Signet ring-like neoplastic cells in bone marrow containing endocytoplasmatic acid mucin droplet (arrows), [Alcian blue/PAS stain x 400].

Figure 5. — Immunohistochemical demonstration of pancytokeratin-positive neoplasmatic cells in bone marrow (arrows), [x 200].

To determine the degree of bone marrow infiltration, a scintigram of the skull, clavicles, sternum, ribs, vertebral column and pelvis was done which showed multiple bone metastases.

Postoperatively tamoxifen, 20 mg/day, was administered orally. On follow-up in March 2001, no signs of disease progression was found by chest X-ray, CT scan of the upper and lower abdomen and ultrasound examination of the liver.

Discussion

EH can be discovered as an incidental microscopic finding, or as a macroscopically solid tumor mass that could be confused with carcinoma or sarcoma. Signs and symptoms of compression, bleeding or obstruction can also complicate diagnosis [3, 4].

The most frequently involved sites of extraosseous EH are the spleen, liver and lymph nodes, although many other sites can be affected including the breasts, thoracic cavity, abdominal viscera, lungs, bronchus, gut, central nervous system, thyroid gland, adrenal glands, renal pelvis, and genital tract [1, 2, 3].

EH of the female genital tract is extremely rare. To our knowledge, it has been described in the English literature in eight cases which were localized to the endometrium [4, 5] and in one case confined to the uterine cervix [6]. In addition, Glew *et al.* [7] has described a case of aggressive and widespread EH involging various organs including the cervix. As far as we know, we report for the first time EH in the UI.

The differential diagnosis of EH localized in the UI with the presence of promyelocytes alone includes leukemic and lymphomatous infiltrates, granulocytic sarcoma and metastatic carcinoma. In our case, the cells from the hematopoietic areas stained positively for chloroacetate esterase, confirming the presence of white blood cell precursors. In cases where megakaryocytes exist, immunohistochemistry is useful, because these cells stain positive for factor VIII. Also, the immunohistochemitry for the common leucocyte antigen is helpful in the differential diagnosis of lymphomatous infiltrates of the female genital tract. Immunohistochemistry for polyclonal keratin is also helpful in the differential diagnosis of carcinoma.

In our case, the finding of EH in the UI suggested bone marrow infiltration. To confirm this and to determine the histological type of the neoplasmatic cells a microscopic examination of the bone marrow biopsy was done. This examination showed the myelospaces of the bone marrow to be infiltrated by many metastatic adenocarcinoma cells probably due to the primary disease of breast cancer. Additional work-up including bone scan showed multiple bone metastases suggesting that the high degree of bone marrow infiltration by the neoplasmatic cells was enough to stimulate the onset of EH.

In the present case, after consulting with the patient and obtaining written consent, we performed a total abdominal hysterectomy with bilateral salpingo-oophorectomy. There were three main reasons for this decision. First, although the ultrasound scan and the preoperative serum Ca 125 levels were suggestive of a benign ovarian cyst, the size of the ovarian cystic structure was larger than 5 cm, without any regression after two months of observation. Therefore, the possibility of ovarian malignancy had to be excluded. Secondly, we believe that an oophorectomy would be beneficial for the primary disease of the patient. Bryant and Weir [8] have found that women aged less than 50 years with operable carcinoma of the breast and with positive axillary nodes benefited significantly from prophylactic oophorectomy, both in relapse-free status at five years and in survival and relapse-free status at ten years. In addition, Nomura *et al.* [19] have suggested that in premenopausal patients with oestrogen-positive breast caner, therapy with oophorectomy and daily oral administration of 20 mg tamoxifen may be equivalent in prolonging relapse-free survival and overall survival to chemotherapy or to chemotherapy and tamoxifen therapy. While in Albania, our patient had discontinued the combined chemotherapy cycles because of their adverse side-effects. Although we did not have information about the oestrogen receptor status of her breast cancer cells, we hoped that the tamoxifen therapy would be more beneficial in the absence of the ovaries. Finally, a hysterectomy would enable the patient to avoid the adverse effects of tamoxifen on the uterus. It is widely known that women with breast cancer have 1.72 times the risk of developing endometrial cancer [10]. Also, long-term tamoxifen treatment has been reported to increase the occurrence of endometrial polyps and hyperplasia [11]. Lahti *et al.* [12] found that the development of endocervical and endometrial polyps were, respectively, twice and three times as common in the tamoxifen group as in the control group and endometrial polyps generally have a 0.5% chance of malignant transformation [13]. Additionally, it has been suggested that tamoxifen use may increase the occurrence of endometrial sarcomas [14, 15].

In conclusion, we present a rare, incidental finding of EH in the UI that heralded widespread infiltration of bone marrow by neoplastic cells. This case confirms the importance of prompt investigation of EH in the female genital tract.

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