Primary endometrial natural killer (NK)/T cell lymphoma: case report and review of literature

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Summary

Primary natural killer (NK)/T cell lymphoma of the uterus is extremely rare. A case of primary NK/T cell lymphoma arising from the endometrium of the uterus was diagnosed by curettage which demonstrated the typical pathological characteristics of NK/T cell lymphoma. The patient received induction chemotherapy but refused hysterectomy. Later she developed bone marrow infiltration and eventually died on day 76 after diagnosis. The natural course of primary endometrial (NK)/T cell lymphoma was very aggressive. Conventional cytotoxic chemotherapy may be ineffective for this aggressive disease.

Key words: Endometrium; NK/T cell lymphoma; Extranasal type.

Introduction

Primary lymphoma of the female genital tract is uncommon with a frequency of 0.002% in all patients with extranodal lymphoma [1]. NK/T cell lymphomas are rare and often occur in the nasal or nasopharyngeal region. They are occasionally present in the upper digestive tract, skin, soft tissue and spleen. Involvement of the gynecological tract by NK/T cell lymphomas is extremely rare. A few cases of NK/T cell lymphoma arising in the uterus have been reported [2-6] and only one case with primary NK/T cell lymphoma involving the endometrium of the uterus has been reported in the English literature [2]. In this report, we describe a rare case of primary NK/T cell lymphoma arising from the endometrium which later progressed to bone marrow infiltration.

Case Report

A 36-year-old female was admitted with signs of intermittent vaginal bleeding and mild fever for two weeks. Her medical history indicated no suspicious signs (including Epstein-Barr virus-related disease history and past gynecological history). She had normal menstrual cycles. Physical exam demonstrated a mildly elevated temperature of 38.0°C. No visible skin lesions were found. Gynecological examination revealed hardness and swelling of the cervix. A 6 cm × 5 cm mass was palpable at the posterior aspect of the vagina fornix. The white blood cell count was 3.16×10^9/l with 53.8% neutrophils and 36.4% lymphocytes. Her serum lactase dehydrogenase (LDH) was 345 U/l (normal value: 114~240 U/l). Chest computerized tomography (CT) and nasal sinus CT scan were normal. Enhanced CT of the abdomen and pelvis showed enlargement of the uterus without significant density change. Transvaginal ultrasonography demonstrated a mass occupying the middle and lower uteral segment and upper cervix (Figure 1: a-b). Endometrial biopsy indicated NK/T cell lymphoma. The neoplastic cells exhibited an isomorphic pattern with extensive necrosis, small to medium-sized atypical, lymphoid cells with irregular nuclear contours and scanty, moderately basophilic cytoplasm (Figure 2: a~b). Lymphoid cells showed positively of T cell- and NK cell-associated antigens like CD3, CD56, granzyme B and CD8 (Figure 2:c~e), and were negative for CD4, CD20 and CD5 based upon immunohistochemical stain. In-situ hybridization for EBV-encoded small RNAs (EBER) indicated strong positivity in the tumor cells (Figure 2: f). No abnormality was found in her bone marrow cytology (Figure 3: a) or biopsy (Figure 3: b). Neither monoclonal T-cell receptor (TCR)-γ rearrangement gene nor immunoglobulin heavy chain-H (IgH) was detected on the bone marrow sample. The diagnosis of primary endometrial NK/T cell lymphoma was established based on the above findings and was classified as Ann Arbor Stage I B, International Prognostic Index (IPI) 2 or International Federation of Obstetrics and Gynecology (FIGO) Stage I.

The patient refused having a total hysterectomy and was treated with two courses of induction chemotherapy (CHOP regimen: cyclophosphamide, vincristine, daunorubicin and dexamethasone). The mass had markedly decreased at the on follow-up study (Figure 1: c). However, her fever had not receded but was aggravated. She did not respond well to broad-spectrum antibiotics. No evidence of any infection was found in her body. Follow-up bone marrow aspirate revealed progression of lymphoma with 24% lymphoblasts (POX staining was negative) (Figure 3: c). Flow cytometry of bone marrow cells indicated that 65.8% NK cells (CD3-CD56+) and 44% T cells (CD3+) took up the lymphocytes. The CD3-CD56+NK cells expressed CD2, CD7, CD8, CD56, CD26, HLA-DR and did not express CD5, CD57 and CD16. Among CD3+T cells, the percentage of CD2-CD7+ T cells was 46.78%. Monoclonal TCR-γ rearrangement gene could be detected on the follow-up bone marrow sample. The disease was restaged as Ann Arbor Stage IVB, IPI 3 or FIGO Stage IV. The patient eventually passed away due to multiple organ failure 76 days after diagnosis.

Discussion

Primary extranodal lymphoma involving the female genital tract is rare [7]; the prevalence was reported to be as high as 1.1% in a study of 1,467 cases [8] and as low

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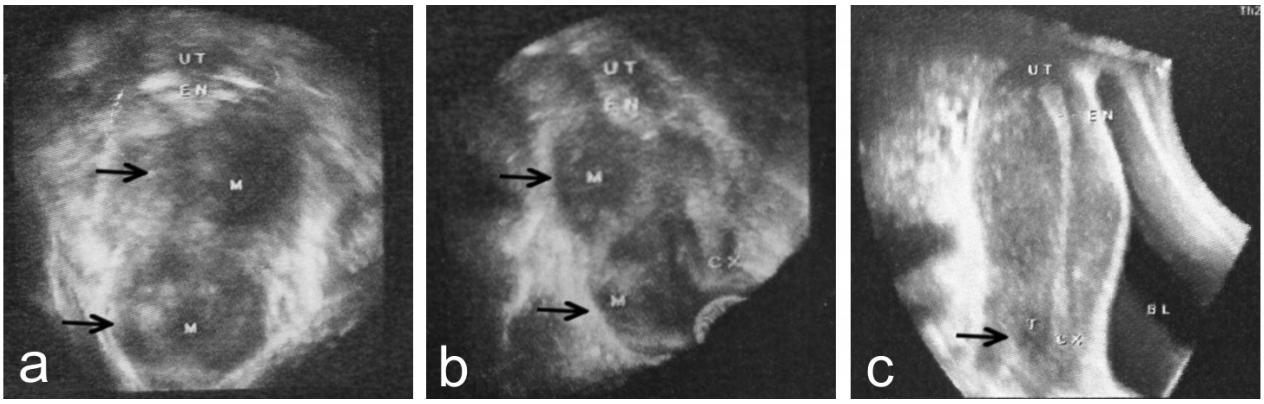

Figure 1. — Transvaginal three-dimensional ultrasonography: a, b 4.6 × 3.0 × 3.8 cm and 3.8 × 2.9 × 3.3 cm low echoes (arrows) can be detected on the posterior wall of middle and lower segment of uterus and posterior wall of cervix; disturbance blood flow signal was detected in the mass; resistance index (RI): 0.47-0.51. c the mass (2.2 × 1.6 cm, arrow) reduced significantly after chemotherapy.

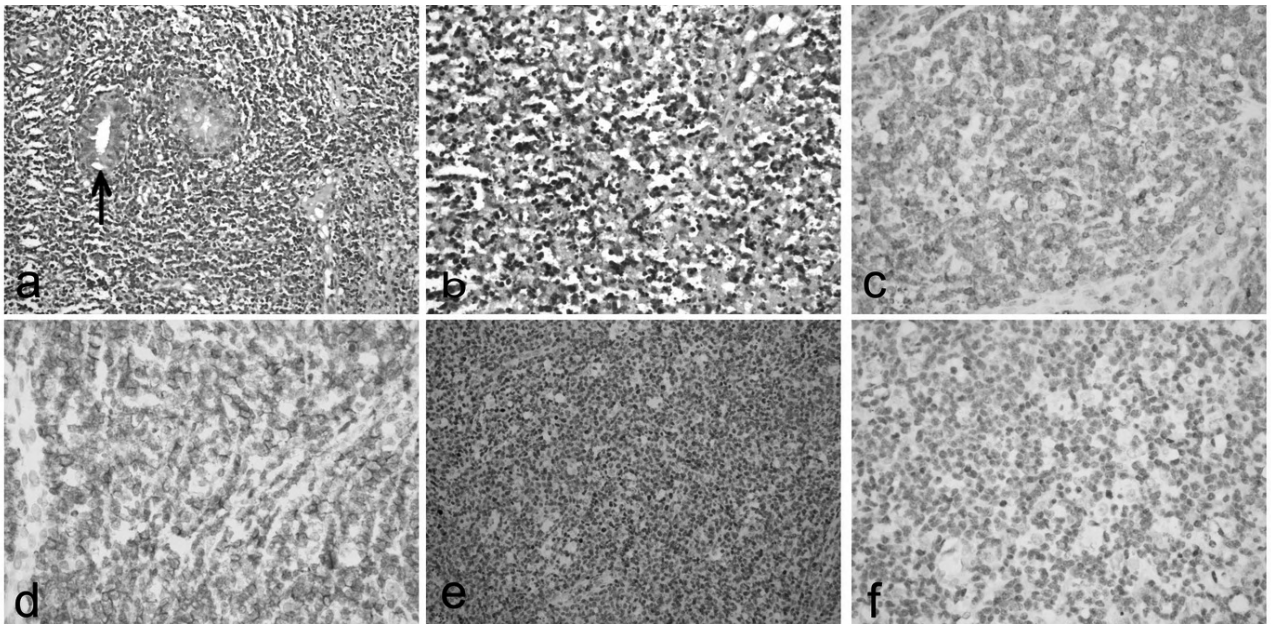

Figure 2. — NK/T cell lymphoma of the endometrium: a residual endometrial gland (arrow, a, × 200) can be found under the background of neoplastic cells. Higher magnification shows medium to large-sized lymphoid cells with irregular nuclear contours; piecemeal necrosis and lymphoid cells infiltration in endometrial tissues can be observed (b × 400). Immunohistochemical staining showed strong reactivity of lymphoid cells by antibodies against the T cell-associated antigen CD3 (c × 400) and the NK cell associated antigen CD56 (d × 400) and granzyme B (e × 200). In situ hybridization for EBER shows positive nuclear signals in many tumor cells (f × 400).

as 0.2% in a study of 9,500 cases [9]. The cervix is the most involved site among the uterine lymphomas and lymphoma of the endometrium of the uterus is extremely rare [10, 11]. Most primary endometrial lymphomas are often reported to be of B cell lineage [10, 12]. Very few cases of primary or secondary NK/T lymphoma involving the gynecologic tract have been reported [3-6]. This is the second case of primary NK/T cell lymphoma originating from the endometrium in the English literature. Briese *et al*. reported the first case of primary endometrial lymphoma based on autopsy findings [2].

There is limited information about etiology, treatment and prognosis of primary endometrial NK/T cell lymphoma. General symptoms of uterine lymphoma include vaginal bleeding, fever of unknown origin and/or abdominal or pelvic pain [13]. EBV may play a causative role in some cases of lymphoma-like lesions of the cervix [14]. Its infection is closely related to nasal-type NK/T cell lymphoma as well as extranasal NK/T cell lymphoma as described in this case [15, 16].

Treatment of female genital tract lymphoma includes surgery, radiation, chemotherapy alone or a combination of these therapies. The optimal therapy is still unknown because of the rarity of primary uterine lymphomas. Many patients with early-stage cervical lymphoma received only local therapy in the form of surgery and

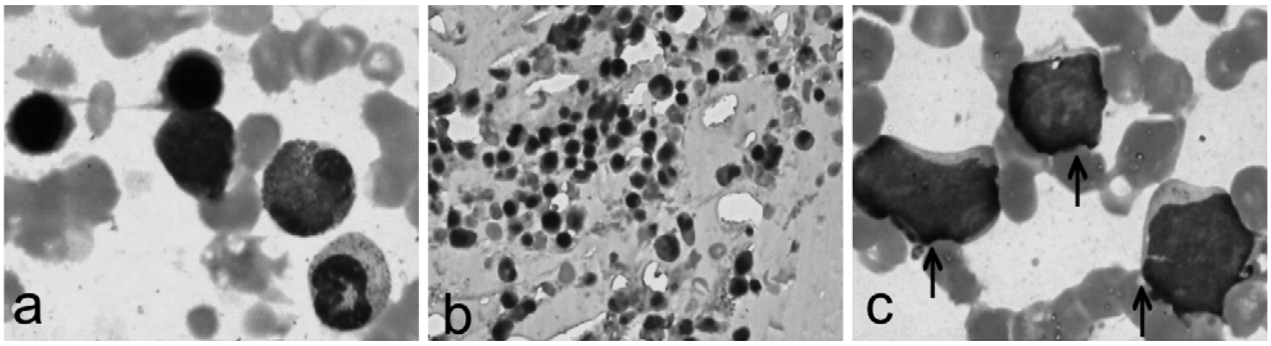

Figure 3. — Bone marrow cytology and biopsy: a. normal bone marrow smear at diagnosis (×400); b. normal bone marrow biopsy at diagnosis (×) c. lymphoma infiltration of bone marrow with 38% lymphocytes including 24% lymphocytoblasts (black arrows) on day 60 after diagnosis (× 400).

radiation but remained disease free for two or more years [11] so total hysterectomy may be one of the optimal treatments for a solitary uterine lymphoma at early stage. It was reported that both children and adolescents with early-stage extranodal nasal-type NK/T-cell lymphoma treated with primary radiotherapy had a favorable prognosis [17], but the role of radiotherapy in extranasal type NK/T-cell lymphoma remains to be defined. In this case, the patient does not respond to chemotherapy alone. Failure of chemotherapy may be due to the fact that this type of lymphoma was likely insensitive to solitary chemotherapy. A potential reason for the resistance in NK/T cell lymphomas is the high expression of p-glycoprotein which can lead to resistance of chemotherapy, particularly, the anthracyclines [18]. The L-asparaginase-containing regimens have been proposed to bypass the presence of p-glycoprotein and have shown excellent activity in refractory extranodal NK/T-cell lymphoma. Therefore, this type of agent can be considered as a second-line treatment option [19, 20]. More aggressive treatment or a combination of treatment options can be used in the future for patients with primary endometrial NK/T cell lymphoma.

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