Primary lymphoma of the cervix uteri: a diagnostic challenge. Report of two cases and review of the literature

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Summary

Background: Primary non Hodgkin's lymphoma (NHL) of the cervix and vagina is uncommon; the incidence of uterine lymphoma is estimated to be less than 0.5% of all NHL.

Patients regularly present with vaginal bleeding. The diagnosis is made on biopsy but this can be difficult on small samples which may not be representative of the lesion. Immunohistochemical analysis and often molecular techniques are required to confirm the diagnosis.

Cases: We report two cases of primary diffuse large B-cell lymphoma of the cervix. In the first case, the diagnosis could only be made on repeat biopsies. The second case presented as a cervical polyp.

Conclusion: Gynecologists should be aware of this rare clinical entity in order to apply the proper treatment.

Key words: Malignant lymphoma; Cervix; Diagnosis.

Introduction

Secondary involvement of the uterus in cases of disseminated lymphoma is not infrequent. By contrast, primary lymphoma of the uterus is very rare. The histological diagnosis can be difficult due to small sample size, sampling error and crush artefact. In high-grade lymphomas the neoplastic nature of the infiltrate is often obvious. On the other hand, in low-grade lymphomas such as follicular lymphomas or MALT-lymphomas, the differential diagnosis with reactive conditions can be problematic and in such cases immunohistochemical analysis and molecular techniques to detect clonal rearrangements of the immunoglobulin heavy chain gene are required [1].

We present two cases of primary lymphoma of the cervix which presented a diagnostic challenge. In the first patient, the diagnosis of non-Hodgkin lymphoma was made only on a repeat biopsy after the initial diagnosis of lymphocytic cervicitis. In the second patient the histological examination of a cervical polyp revealed the presence of a malignant lymphoma.

Case Reports

Case 1

A 38-year-old nulligravid woman presented with a 4-month history of menometrorrhagia, lower abdominal pain and lumbalgia. After gynecologic examination and ultrasound scan a diagnosis was made of multinodular uterine myoma and total abdominal hysterectomy was proposed. The patient went to another gynecologist for a second opinion.

On repeat gynecological examination the cervix was normal. A cervical smear previously performed by her private physician was also normal. Bimanual palpation was painful and revealed a fixed bulky cervix and a central pelvic mass in continuity with bilateral tumoral adnexa. The right adnexal tumor extended nearly to the pelvic sidewall. Differential diagnosis was made between an extensive pelvic and ovarian endometriosis or a malignant tumor of the uterus and/or ovaries.

Examination under anesthesia confirmed the clinical findings. Diagnostic laparoscopy revealed uterine leiomyomata, a bilateral pyosalpinx and abnormally enlarged ovaries. Subsequently, biopsies were taken of the right ovary and peritoneum. The procedure was completed with a fractioned uterine curettage.

The initial biopsy of the cervix showed a dense lymphoid infiltrate of predominantly small cells. Immunohistochemical analysis revealed a heterogeneous infiltrate of T- and B-cells which rendered the diagnosis of chronic cervicitis. The biopsies of both the ovarium and peritoneum were small and revealed normal histological findings.

A repeat cervical biopsy, taken by another gynecologist on occasion of a third opinion, led to the diagnosis of diffuse large B-cell lymphoma. In this biopsy, the cervix was infiltrated by a polymorphous population of centroblasts (Figure 1). The tumor cells showed immunoreactivity for the B-cell marker CD20. There was no reactivity for CD10, CD138, BCL-2, BCL-6. The proliferation index was high (more than 60% of the tumor cells showed strong nuclear staining for Ki-67). EBV-in situ hybridisation was negative. Unfortunately, no fresh material was available for further molecular and cytogenetic studies. Computed tomography of the pelvis showed tumoral involvement of the cervix and both ovaries. The discrepancy between CT impression and biopsy findings of the right ovary, showing a normal ovarian cortex, can be explained by inadequate tissue sampling or sampling error. A gallium scan showed another focus in the right iliac fossa. Other investigations including full blood count, renal and liver function tests, computed tomography of the chest and mediastinum were normal. A bone marrow biopsy was negative for lymphoma. According to the Ann Arbor Classification this patient was staged as having IIE bulky disease.

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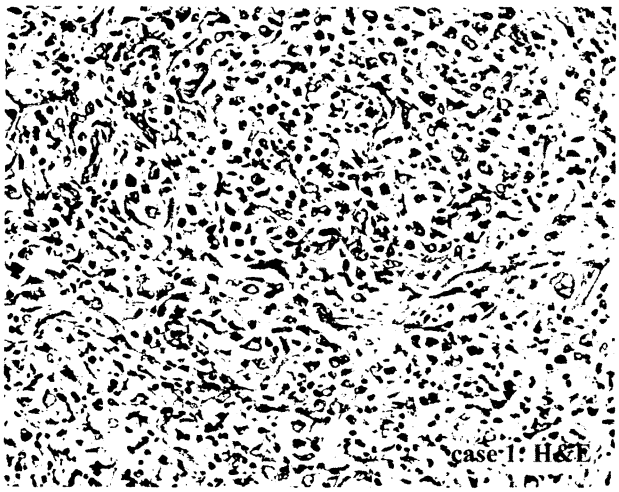

Figure 1. — Diffuse polymorphous infiltration by blasts admixed with small lymphoid cells (Case 1, H&E x40).

She received three courses of CEOP (Cyclofosfamide, Epirubicine, Vincristine and

Prednisolone). Because of partial remission, local radiotherapy with 28 Gy in 20 fractions needed to be added. This treatment resulted in complete remission.

There was no evidence of recurrent disease 48 months later.

Case 2

A 45-year-old woman with a history of Hodgkin's disease 23 years before, presented with a malodorous watery discharge and spotting as the main complaints.

A cervical smear two years earlier had shown AGUS; a repeat smear six months later was normal.

On inspection of the cervix an ectropion and multiple polyps were seen. A smear was taken and the polyp was resected. The smear was normal but histological examination of the polyp showed infiltration by a diffuse large B-cell non-Hodgkin's lymphoma. The large cervical polyp was partially infiltrated by a monomorphic proliferation of large to medium-sized cells of B-cell phenotype (B-cell marker CD79α positive). Other markers like CD10, CD138, BCL-6, BCL-2 were negative. Again, the proliferation index was high (more than 60% of tumor cells showed nuclear labelling for Ki-67) and EBV-in situ hybridisation was negative. Computed tomography of the pelvis revealed a mass at the uterine isthmus. Other investigations including full blood count, renal and liver function tests, bone marrow aspirate, computed tomography of the chest and a gallium scan were normal. According to the Ann Arbor Classification this patient was staged as having IEa disease.

The patient was treated by chemotherapy (3 courses of ACVBP, Adriamycine, Cyclofosfamide, Vincristine, Bleomycine, Prednisolone) followed by consolidation with Methotrexate IV, Itostamide VP 16 abd Ara-C subcutaneously and remains well 18 months later.

Discussion

Primary malignant lymphoma of the cervix and vagina is a rare condition.

However, in a review of 12,447 cases of NHL lymphoma, 1,467 (12%) presented only with extranodal involvement without evidence of disseminated disease (the so-called extranodal lymphomas) and eight of them (0.5%) arose in the uterus [2].

Nevertheless, awareness of this rare clinical entity is important because these tumors can mimic squamous cell carcinoma both clinically and histologically. The treatment of these two conditions is fundamentally different as in cervical lymphoma radical gynecologic surgery is unnecessary and should be avoided [3].

These tumors may be sessile, polypoid or present as a barrel shaped thickening of the cervical wall without obvious mucosal lesions.

Histologically most tumors are high-grade lymphomas (diffuse large B-cell lymphomas) but low-grade lymphomas, especially follicular lymphomas and MALT-type lymphomas, do occur. These lymphomas are morphologically difficult to distinguish from benign reactive lesions such as severe chronic cervicitis or follicular cervicitis. Unlike malignant lymphomas, florid reactive hyperplasias of the female genital tract are superficial and do not form tumor masses. The reactive infiltrates are heterogeneous and composed of a mixture of small T- and B-cells admixed with histiocytes and plasma cells and are sometimes accompanied by erosions or ulcerations.

We have reported two cases of diffuse large B-cell lymphoma with identical immunohistochemical profiles (CD20 or CD79α positive, CD10-, BCL-6-, BCL-2-, CD138-, with a high proliferation index and no evidence of assiociation with EBV). Morphologically, however, the tumors were different. The first case showed a polymorphous blast proliferation where in the second case the infiltrate was monomorphic.

Diffuse large B-cell lymphomas, as they are now recognized in the WHO classification, are heterogeneous in morphology, immunophenotype and molecular genetic features.

Patients' ages ranged from 23 to 74 with a mean age of 50 years. In general, non-Hodgkin's lymphomas occur in an older age group. However, 60% of the non-Hodgkin's lymphomas of the cervix occur in women under 50 years of age [4].

These tumors frequently present with abnormal vaginal bleeding or discharge as in our second case, pelvic pain and dyspareunia as in our first case, but may be asymptomatic in 20% of cases [5]. Adnexal enlargement is frequent and can lead to inappropriate laparotomy. Bleeding and mass are grossly indistinguisable from carcinoma or sarcoma.

Initial detection on a cervical smear, although reported [6], is uncommon. Suspicion of malignancy on cytology can be concluded, but has to be confirmed by histological examination. Even on cervical biopsy the diagnosis may be difficult and repeat biopsies may be necessary to confirm the diagnosis, which was the case in our first patient.

In our second patient the histological examination of a polyp demonstrated the presence of a malignant lymphoma. This presentation stresses the need for removal of

cervical polyps for histological examination. One explanation for the apparent low sensitivity of the pap smear in the detection of this tumor may be its submucosal localization and rarity of surface ulceration [7].

Work-up should also include fractioned uterine curettage, diagnostic laparoscopy and computed tomography.

The morphologic differential diagnosis includes chronic lymphocytic cervicitis, chronic PID, undifferentiated adenocarcinoma of the endometrium, anaplastic squamous-cell carcinoma, mixed mesodermal tumor, poorly differentiated stromal sarcoma, cervical small cell carcinoma, tumors with neuroendocrine differentiation and also metastatic tumors [8]. The use of an adequate immunohistochemical panel of antibodies, including epithelial (different cytokeratins, epithelial membrane antigen, neuro-endocrine markers etc.), hematological and mesenchymal markers, lead to the correct diagnosis. Flow cytometry and cytogenetic studies (karyotyping, PCR and FISH studies, etc.) are also useful additional tools to help characterize lymphomas but these techniques require fresh material. In case of suspicion of lymphoma, it is therefore recommended to submit additional fresh tissue for further molecular analysis.

The management of these lymphomas depends, as in the management of all lymphomas, on the stage of the disease. All patients should be staged primarily according to the Ann Arbor Classification (Table 1) [9], however parallel use of the FIGO system does give useful information concerning disease bulk.

Table 1. — *The Ann Arbor Staging Classification for Lymphoma [9].*

Stage I	Involvement of a single node region (I), or of a single extralymphatic organ or site (IE).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE).
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

Each stage is further divided into A and B categories. B is for those patients with any (a) unexplained weight loss of more than 10% of the body weight over the previous six months, (b) unexplained fever with temperatures over 38°C, and (c) night sweats.

For localized (Ann Arbor Stage IE) and non-bulky disease (FIGO Stages I and II) of low and intermediate grade lymphomas, pelvic radiotherapy or combination chemotherapy is the appropriate treatment. For more extensive disease (Stage IIE), bulky locally advanced diseases (FIGO III and IV) or disease of high-grade malignancy, combination chemotherapy should be used, possibly in conjunction with radiotherapy, particularly if the initial disease was of high-grade malignancy or in case of partial response/remission. There is no evidence that radical gynecological surgery is advantageous in any way [3].

Many of the women were likely to have been sexually active when their disease presented and some might have wished to remain fertile. These considerations would favor combination chemotherapy as the sole modality of treatment, even for patients with localized disease.

The prognosis of lymphomas of the vagina and cervix remains unpredictable, but when it concerns a single pelvic lymphoma it is relatively favorable [10]. The overall 5-year survival rate has been reported to be 77% [11].

In summary, we have reported two patients with primary non-Hodgkin's lymphoma of the uterine cervix. Both were confirmed by histology as high-grade B-cell lymphomas although the initial cervical smear was normal. Repeat biopsies and immunohistochemical and molecular techniques may be necessary to make an accurate diagnosis. Gynecologists should be aware of this rare clinical entity in order to apply the proper treatment.

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