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Rare disease

Primary malignant lymphoma of the uterine cervix

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Summary

Primary malignant lymphoma of the female genital tract is an extremely rare clinical entity. We report a case of primary non-Hodgkin lymphoma of the uterine cervix. An 85-year-old woman presented with abnormal genital bleeding. A colposcopic examination revealed a mass in the uterine cervix. No other lesions were detected by the whole-body CT, gallium scintigraphy and bone marrow examination. The histological examination and immunohistochemical staining of the cervical biopsy material confirmed a diagnosis of diffuse large B cell lymphoma of the uterine cervix, clinical stage 1E (according to the Ann Arbor Staging Classification for Lymphomas). The patient was treated with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (oncovin) and prednisone. Her family refused surgery and involved field irradiation. She was in good condition but after 5 months she expired due to myocardial infarction.

BACKGROUND

Non-Hodgkin's lymphoma (NHL) affects the extranodal regions in about one-third of patients. Extranodal lymphomas of the female genital tract account for only about 1% of all cases of NHL,[1] and involve the cervix more often than the uterus, vagina or vulva.[2] A review of the literature confirms the rarity of the disease since not many cases are reported and are mostly in the form of case reports and small case series. On the contrary, it demands particular attention because of the more frequent appearance of an intense inflammatory reaction in this site, such as cervicitis. Cervical lymphoma-like lesions mimic cervical lymphoma in histopathological features and immunohistochemical expression. The confusion is heightened by the fact that the management of this disease is not well defined in the literature. Here we report a case of diffuse large B cell lymphoma (DLBCL) of the uterine cervix managed with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (oncovin) and prednisone (RCHOP) and emphasise on the distinguishing features versus lymphoma-like lesions.

CASE PRESENTATION

An 85-year-old woman gravida 7, para 7, with postmenopausal vaginal bleeding of 1-month duration presented to the Department of Obstetrics and Gynaecology in our Hospital. She was apparently well prior to this complaint and her medical history was completely uneventful. She was not immunologically compromised nor was taking any immunemodulating medication. Physical examination revealed an old-aged woman with no abnormal finding on systemic examination. No palpable cervical, axillary or inguinal lymphadenopathy was found. Pelvic examination revealed a bulky, exophytic cervical mass measuring 7×4 cm in diameter along with a small-sized uterine corpus. No palpable parametrial mass was detected.

INVESTIGATIONS

Punch biopsy of the cervical mass was performed. Histologically, there was diffuse infiltration of the stroma of the exocervical and endocervical tissues by monomorphic population of malignant lymphoid cells. The cells had intermediate to large, round to ovoid and irregular nuclei surrounded by scanty neoplasm (figure 1). Neutrophilic infiltration and large foci of necrosis were also noted. Immunohistochemical study showed that the neoplastic cells were positive for B cell markers and negative for pancytokeratin (figures 2 and 3). A diagnosis of diffuse large B cell NHL was made. Chest radiography, bone marrow examination, blood and chemistry profiles, serum tumour markers and lactate dehydrogenase, abdominal ultrasonography, sigmoidoscopy and cystoscopy were unremarkable. Contrast-enhanced axial CT of the neck, thorax and abdomen were performed. No pathological lymphadenopathy, by the size criteria, was noted. Pelvic CT scan showed a diffuse, hypodense uterine cervical mass measuring 7×4 cm (figure 4). No evidence of involvement of parametrium and the adjacent organs was seen. The liver, spleen and kidneys were normal. In view

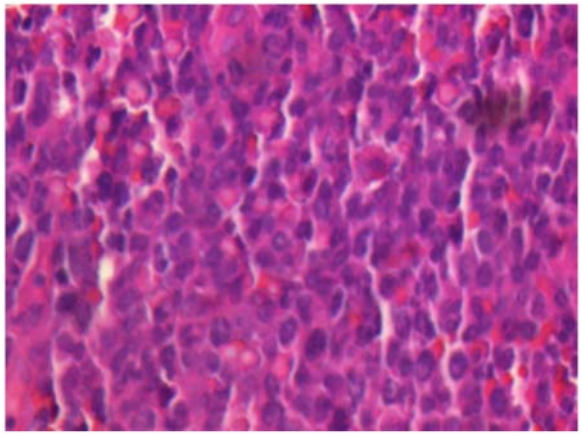

Figure 1 Section shows neoplastic intermediate to large cells with round to ovoid irregular nuclei surrounded by scanty neoplasm (H&E×40).

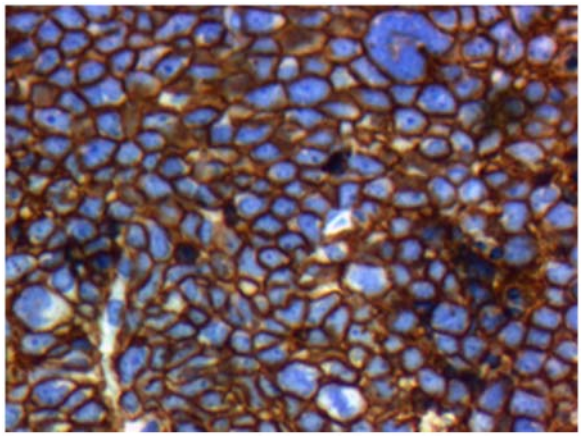

Figure 2 Section shows the neoplastic cells are positive for CD20 (×40).

of the histology and immunohistochemistry findings, a diagnosis of primary cervical NHL stage 1E was made.

DIFFERENTIAL DIAGNOSIS

Cytological differential diagnosis can be difficult. Chronic lymphocytic cervicitis should be distinguished from cervical lymphoma. However, the bland appearance of cells in chronic lymphocytic cervicitis is helpful.[3] In rare occasion, the inflammatory reaction is so florid and contains large transformed lymphoid cells, making some problem in the differential diagnosis from malignant lymphoma.[4 5] Lymphoma-like lesion (LLL) of the uterine cervix is a known term in the literature that explains a florid lymphoid proliferation that can mimic lymphoma closely. Various causes of LLL have been purposed but the exact cause is unknown. It was first described in 1985 by Young *et al*.[4] Their report included 16 LLL: 10 of the cervix, 5 of the endometrium and 1 of the vulva. Histologically it can mimic diffuse large-cell lymphoma. Important diagnostic clues that can distinguish these lesions from typical cervical lymphoma include superficial distribution and heterogeneity of the lymphoid cells, the presence of various inflammatory cells and the absence of gross mass or ulcerations.[4] Our case had a bulky, exophytic cervical

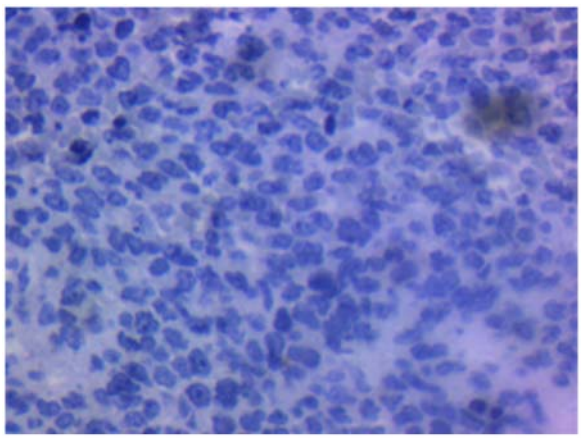

Figure 3 Section shows the neoplastic cells are negative for pancytokeratin (×40).

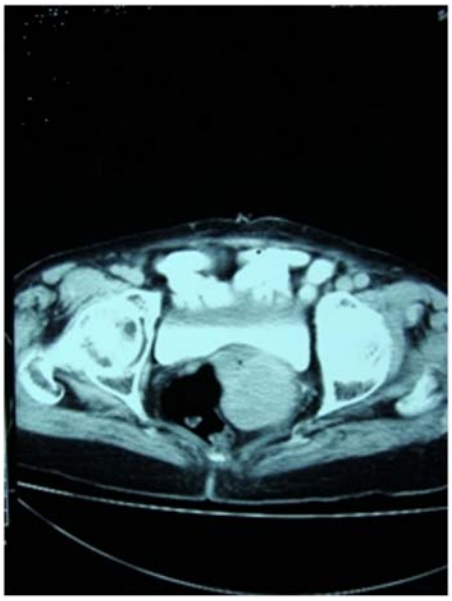

Figure 4 CT scan shows a diffuse, hypodense uterine cervical mass.

mass and on microscopic examination there was diffuse infiltration of monotonous lymphocytes with coarse chromatin in the cervix. Therefore, the diagnosis of an LLL was excluded. Assay for rearrangement of immunoglobulin H (IgH) gene may be helpful in differential diagnosis, though monoclonality can be detected in some benign lesions as well. One study showed for the first time that light chain restriction and clonal IgH rearrangement do not exclude the diagnosis of LLLs of the cervix.[6] Geyer *et al*[7] recently identified monoclonal IgH gene rearrangements in four (44%) of nine cases of LLL of the cervix. Differentiating cervical lymphoma from small-cell carcinoma can be problematic. Distinction between the two entities depends on careful evaluation of their cytological features. The cells of small-cell carcinoma have nuclear chromatin that is finely granular or smudged, and show nuclear moulding, features not described in the malignant lymphoma.[8] On the contrary, cervical lymphomas are mostly high-grade tumours and may exhibit cohesive growth, simulating poorly differentiated carcinoma. In these situations immunohistochemistry techniques are useful. Other lesions such as small cell variant of a melanoma, endometrial stromal tumours, lymphoepithelioma-like carcinomas and small-cell neuroendocrine cervical carcinoma should be considered in the differential diagnosis.[9] Again in this matter ancillary methods (immunohistochemistry markers) are helpful.

TREATMENT

She received three cycles of chemoimmunotherapy (RCHOP).

OUTCOME AND FOLLOW-UP

Post-treatment CT scan (figure 5) shows that the tumour decreased in size but did not completely get removed after three courses of chemotherapy. Although her family refused surgery and radiotherapy, she was in good

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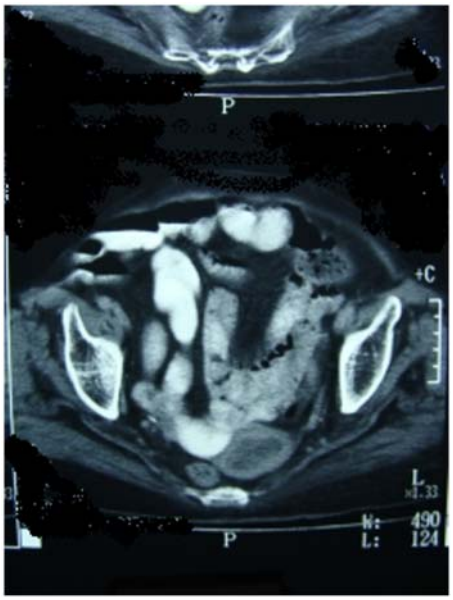

Figure 5 Post-treatment CT shows the tumour decreased in size but did not completely get removed.

condition for 5 months. Unfortunately she died due to myocardial infarction.

DISCUSSION

Primary NHLs of the cervical stroma are characterised by lymphomas that are restricted to the cervix without any evidence of myometrial involvement or leukaemia at the time of diagnosis.[10] According to Freeman *et al* [11] the incidence of extranodal lymphomas of female genital tract is 2% and Carr *et al*[12] reported lymphoid malignancies in 0.008% of the cervical tumours. In a series of 2733 extranodal NHLs at the M.D. Anderson Cancer Center, there were only 18 cases with uterine or cervical origin.[13] The median age of the patient with cervical lymphoma is 44 years, ranging from 27 to 80 years.[14] Our patient was an 80 postmenopausal woman. The clinical symptoms are non-specific and frequently mimic other benign or malignant diseases, such as cervical or endometrial carcinoma, uterine fibroids, adenomyosis and endometriosis. The most common presenting symptom is abnormal uterine bleeding[15] but other patients' complaints include abdominal or pelvic pain, dyspareunia, low-back pain or vaginal discharge.[16] B symptoms are not usually seen.[17] This case had abnormal uterine bleeding without evidence of B symptoms. It should be noted that CT scan is the study of choice for detection and evaluation of the extention of cervical lymphoma.[18] CT scan can provide information that can be used to plan an appropriate therapeutic regimen as well as follow response to treatment. In about our case, CT scan showed a diffuse, hypodense uterine cervical mass measuring 7×4 cm. No evidence of involvement of the uterine body, parametrium and the adjacent organs was seen. In cases of primary cervical lymphoma such as in our patient, pelvic lymphadenopathy is rarely present. At colposcopic examination diffuse cervical enlargement is the most common finding.[10 14] Cervical cytology is usually negative because these tumours arise from cervical stroma, and the overlying squamous epithelial is preserved, at least, initially.[17 19] Thus, negative cytological result cannot rule out the existence of cervical lymphoma. Andrews *et al*[20] showed that only 10–40% of cases of cervical lymphoma had positive cervical smear. As a result, a deep cervical biopsy is necessary for definitive diagnosis.[10] The majority of uterine cervix lymphomas are diffuse large B cell type. The presented case also was a DLBCL. Generally cervical NHL has a good prognosis.[21] Extention of the disease, size of tumour and histological subtype have significant prognostic effects, but because of its rarity, the standard uniform treatment has not been defined. Some authors suggested that local therapy alone would be sufficient to treat stage 1E lymphomas, but with bulky disease, neoadjuvant chemotherapy followed by radiotherapy has been recommended.[13] Heredia *et al* reported two cases of DLBCLs of the cervix treated with three courses of CHOP and involved field radiotherapy. Both patients were disease-free at 5 years and 15 months.[22] According to some reported studies, the anti-CD20 immunochemotherapy, the RCHOP regimen has been administered as the standard therapy.[13 23] Rituximab is the monoclonal antibody used for the treatment of B cell lymphoma, it has clinical effectiveness and little drug side effects.[13] Our patient received RCHOP. Thus, in view of the literary evidence, we chose to manage our patient with abbreviated CHOP-rituximab and achieved a relatively good response but her family refused consolidation radiotherapy and surgery and eventually she died due to myocardial infarction.

Learning points

- Primary malignant lymphoma of the female genital tract is an extremely rare clinical entity.
- The management of this disease is not well defined in the literature.
- The clinical symptoms are non-specific and frequently mimic other benign or malignant diseases.
- Cytological differential diagnosis can be difficult and as a result a deep cervical biopsy is necessary.

Competing interests None.

Patient consent Obtained.

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