Two cases of uterine malignant lymphoma diagnosed by needle biopsy

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Abstract

The incidence of primary malignant lymphoma arising in the female genital tract is extremely rare and constitutes approximately 0.05% of malignant tumors. Uterine malignant lymphoma develops in the endometrial stroma, causing minimal necrosis. It is therefore difficult to diagnose malignant lymphoma, as it does not involve genital bleeding or epithelial defects. We have performed transcervical needle biopsies from deep in the myometrium, with the purpose of diagnosing uterine muscle layer lesions, such as leiomyosarcoma, but this is an unusual method. In this report, we suggest that transcervical needle biopsy is useful in the diagnosis of uterine malignant lymphoma.

Key words: diagnosis, malignant lymphoma, primary, transcervical needle biopsy, uterine body.

Introduction

Uterine malignant lymphoma (ML) is a rare disease, accounting for approximately 0.05% of malignant tumors of the uterus.1-3 Diagnosis by cervical smear and normal cervical biopsy is difficult because ML tumor cells develop in the endometrial stroma and cause minimal necrosis.4 The surgery for diagnosis and treatment often leads to major bleeding.5,6 The transcervical uterine biopsies described in this report are prevalently performed for the purpose of diagnosing tumors in myometrial lesions,7,8 but this is an unusual method. In this report, we suggest that transcervical needle biopsy is suitable for the diagnosis of uterine ML.

Case Report

Transvaginal biopsy of uterine body tumor

We carried out transcervical needle biopsy, which has been previously described,7,8 to differentiate between leiomyoma and other malignant tumors of the myometrium.

Biopsies were performed easily using a pro-Mag 2.2 biopsy system with an automatic cutting needle (25 cm long, 16-gauge, 17-mm notch) and 20-cm-long straight stainless-steel guide pipe with an external diameter of 4 mm and an internal diameter of 3 mm. Before biopsy, we confirmed the location of the target tumor, and the detection and distance from the uterine cavity using T2-weighted magnetic resonance imaging (MRI).

The patient was placed in the lithotomy position, using no anesthesia but only a painkiller suppository. The guide pipe was manipulated to the targeted tumor, and the biopsy needle was inserted into the target tumor through the guide pipe and ganned under transabdominal ultrasound guidance. To prevent sampling error, three or more biopsy cores per patient were obtained.

We have performed 885 transcervical needle biopsies since 1994.7,8 Almost all patients undergo the biopsy with minimal pain, using diclofenac sodium (25 mg suppository). The mean blood loss during the procedure was 11 g (1–115 g); there have been three cases in which the blood loss was >50 g. No major complications, such as infection, intraperitoneal hemorrhage, and injury of adjacent structures requiring surgery, have occurred.
Case 1
A 67-year-old woman, gravida 4, para 3, presented at another clinic with lower abdominal pain. During this consultation, she was diagnosed with uterine swelling and hydronephrosis of the right kidney, and was subsequently referred to our hospital.

MRI revealed that the tumor was located in the anterior wall of the uterine body and expanded toward the lower part of the bladder and the anterior wall of the uterine cervix. The tumor was 10 × 5 cm in diameter with an undefined edge, exhibited the same intensity signal of the myometrium on T1 weighted image (WI) and was uniformly high signal intensity on T2WI (Fig. 1a). Swelling was also observed in the lymph nodes (LN) around the left common iliac artery and vein, the left side obturator LN and both external iliac LN. No abnormalities on either side of the adnexa were observed. A cervical smear taken upon the first visit revealed atypical glandular cells (AGC); however, no neoplastic lesions were detected by endometrial or cervical biopsies. During the first visit, the patient’s serum lactate dehydrogenase levels were significantly higher than normal (1356 IU/mL compared with a normal range of 119–229 IU/mL). Based on the MRI results and significantly elevated soluble interleukin-2 receptor (s-IL2R) levels (13 314 IU/mL compared with a normal range of 135–483 IU/mL), we investigated the possibility of ML of the uterine corpus.

A transcervical needle biopsy was performed to obtain a tumor tissue specimen deep within the tumor. Hematoxylin–eosin (HE) staining of the needle biopsy specimen revealed that the tumor cells were relative small, and had round nuclei in which the nucleolus grew solid. Some mitotic figures were found; however, necrosis was not observed. Immunohistochemical staining revealed positive staining for CD79a and CD20, and negative staining for CD3, AE1/AE3, vimentin and S-100 (Fig. 2). On the basis of these immunohistochemical analyses, the patient was diagnosed with diffuse large B-cell lymphoma (DLBCL). Bone marrow biopsy was performed, but DLBCL cells were not found. The metastatic lesions were depicted in pelvic and para-aortic LN by computed tomography (CT). Uterine DLBCL was diagnosed with an Ann Arbor classification of stage IV. The patient underwent six cycles of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) therapy in the Hematology Department of our hospital. She has been followed up for 3 years and 10 months, during which time there has been no evidence of recurrence.

Case 2
A 77-year-old woman, gravida 3, para 2, visited another clinic for lower abdominal pain. During this consultation, she was diagnosed with uterine swelling and right hydronephrosis, and was subsequently referred to our hospital.

MRI depicted one mass (8 × 6 cm diameter) in the corpus uteri, and a second mass (5 × 3 cm diameter) with a poorly defined edge and low signal intensity on T1WI and hyperintense on T2WI in the uterine cervix, replacing the normal muscle layer (Fig. 1b). Swelling was observed in the lymph nodes surrounding the para-aortic artery. A cervical smear performed at first visit was negative for intraepithelial lesion and malignancy and no neoplastic lesions were detected by endometrial biopsy. Levels of serum lactate dehydrogenase at the first visit

Figure 1 T2-weighted sagittal magnetic resonance imaging. (a) Case 1. A 10 × 5-cm-diameter mass with poorly defined edges was located inside, and was uniformly hyperintense. (b) Case 2. An 8 × 6-cm-diameter mass was in the corpus uteri, and a hyperintense 5 × 3-cm-diameter mass with a poorly defined edge was in the uterine cervix, replacing the normal muscle layer.
were significantly higher than normal levels (2497 IU/mL vs 119–229 IU/mL, respectively); however, s-IL2R was not detected. While no neoplastic lesions were observed by endometrial curettage, it was suspected that the tumor may be growing in the muscle layer lesion. Based on this, we performed a transcervical needle biopsy. HE staining of the biopsy specimen revealed cord-like circular tumor cells and the presence of mitotic figures. Immunohistochemical analyses revealed positive staining for CD20 and leukocyte common antigen (LCA) and negative staining for CD3 and AE1/AE3 (Fig. 3). CT depicted pelvic and para-aorta LN swelling and positron emission tomography identified the hot lesion in the liver, mesentery membrane and left inguinal LN. A bone marrow biopsy was not performed. Based on this, the patient was diagnosed with DLBCL with an Ann Arbor classification of stage IV. The patient received six cycles of R-CHOP therapy and has been followed up for 9 months with no evidence of recurrence.

Discussion

The incidence of primary ML arising in the uterus is rare. Previous reports indicate that the cervical site is
predominantly involved, with 75% of primary ML occurring in the female genital tract; however, cervical ML is rare and represents <0.01% of all cervical tumors.\textsuperscript{4,10,11}

The two cases described in this report involved DLBCL arising in the uterus. The tumor was observed in the corpus and cervix of the uterus, therefore it was difficult to determine the exact origin of the tumor. Although examination of the bone marrow was not performed, we considered both cases to be ML arising in the uterus, as both cases met the diagnostic criteria of uterine ML proposed by Fox et al.: (i) the disease process was clinically confined to the uterus at the time of initial diagnosis; (ii) full investigation failed to reveal any evidence of disease elsewhere in the body; (iii) the blood count showed no evidence of leukemia; and (iv) if further lymphomatous deposits occurred at sites removed from the genital tract, then a time interval of at least several months should have elapsed between the appearance of primary and secondary tumors.\textsuperscript{12} We considered that the pelvic and para-aortic LN were regional LN. In case 2, bone marrow biopsy was not performed and the tumor origin was not revealed.

The major complaint of both patients was lower abdominal pain, and both patients also presented with hydronephrosis. Previous studies have reported that uterine ML leads to secondary hydronephrosis in many cases.\textsuperscript{9,13}

Uterine ML develops in the endometrial stroma and causes less necrosis, therefore the rate of detection by cervical or endometrial cytology is 20–50% lower than that of epithelial tumors.\textsuperscript{4,14} If genital bleeding is observed when the tumor grows from the stroma to the epithelium, and make an ulcer, it is possible to obtain the tumor cells and identify lymphoma earlier by uterine cervical or endometrial cytology from the missing epithelial part.

In the two patients described above, genital bleeding symptoms were not observed, therefore it was difficult to diagnose by cytology, cervical biopsy and endometrial curettage. We were able to obtain ML tissue in the deep endometrial stroma and diagnose patients using transcervical needle biopsy. Importantly, complications associated with this procedure were not observed. It was more suitable than the surgery for the diagnosis and treatment because a large amount of bleeding was reported when the debulking was carried out.\textsuperscript{5,6}

The diagnostic accuracy of this examination is problematic, as it is based on examination of small samples. For example, if the specimens obtained contain many necrotic areas, the number of specimens available for pathological diagnosis is reduced and accurate diagnosis is more difficult. However, this method may also facilitate the diagnosis of uterine ML, as we can investigate the immune phenotype of tumor cells by immunohistochemical staining. MRI is an important tool in the detection of ML, with the ability to identify tumors with low signal intensity on T1WI and uniformly hyperintense on T2WI.\textsuperscript{15} We suspected uterine ML in one patient in this study on the basis of MRI analyses and sIL-2R levels. In some cases, the MRI of uterine ML are similar to those observed in cervical cancer and histopathological examination using biopsy specimens is essential to confirm diagnosis.

Hysterectomy is not involved in the prognosis of this condition and a large amount of bleeding during hysterectomy has been reported.\textsuperscript{5,6,9}

The standard treatment for uterine ML has not been established; however, chemotherapy is administered in many cases of systemic disease. R-CHOP therapy, the combination of CHOP therapy, which until now has been the standard treatment, and rituximab, a chimeric anti-CD20 monoclonal immunoglobulin G antibody, has been successfully used to treat CD20-positive B-cell non-Hodgkin’s lymphoma.\textsuperscript{16,17} This treatment protocol was selected for our two patients, and we observed tumor regression in one patient and eradication of the tumor in the other patient.

We recommend needle biopsy as a suitable method for diagnosing uterine ML because it avoids the diagnostic surgery.

Disclosure

None of the authors has anything to disclose.

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