



Case report

Two cases of spindle cell variant diffuse large B-cell lymphoma of the uterine cervix

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ABSTRACT

Lymphoma with prominent spindle cell features is a morphological variant of diffuse large B-cell lymphoma (DLBCL) and is categorized as a rare variant by the WHO classification. Most cases arise from the skin, with only two cases reported in the uterine cervix to date. Here, we report two cases of spindle cell variant DLBCL of the uterine cervix. Although these cases might be rare, we believe that, as gynecologists and pathologists increase their knowledge of this variant type, more cases will be diagnosed properly.

1. Introduction

Primary malignant lymphoma of the uterine cervix is a rare disease, accounting for 0.6% of extra-nodal lymphomas (Chan et al., 2005). The most common presenting symptoms are abnormal vaginal bleeding, and the classic appearance is a diffuse, circumferential enlargement of the cervix (i.e., a “barrel-shaped” cervix). Although diffuse large B-cell lymphoma (DLBCL) is the most common type, accounting for 70% of cases of malignant lymphoma, spindle cell is a morphological variant of DLBCL and categorized as a rare variant by the WHO classification. Since the tumor grows rapidly, prompt diagnosis is critically important. However, because of the rarity of the disease and the difficulty of tissue biopsy, it is quite difficult to diagnose it accurately. Here, we report two cases of spindle cell variant DLBCL of the uterine cervix. In both cases, bulky tumors in the uterine cervix were confirmed visually, but the previous physicians did not obtain proper tissue samples of the tumors. These patients were referred to our hospital with cervical cancer.

We propose that deep needle biopsy and knowledge about spindle cell variant DLBCL of the uterine cervix are essential for accurate diagnosis.

2. Cases

Case 1

The patient was a 50-year-old woman (gravida 4, para 3) with a history of deep vein thrombosis in the puerperal period, ovarian cystectomy at 21 years of age, and complications of hypertension.

The patient visited a clinic to take a screening for cervical cancer. She had no subjective symptoms, such as genital bleeding. She had undergone cervical cancer screening one year before at the same clinic, and no abnormality was detected at that time. This time, a bulky cervical tumor invading the vagina was identified, which tumor was extremely hard. Cervical cytology was negative, and only necrotic tissues were obtained in the biopsied tissue. She was suspected to have a cervical cancer and was referred to our hospital for further examination and treatment. Magnetic resonance imaging (MRI) of the pelvis showed a bulky tumor with a diameter of 5 cm in the uterine cervix. Vaginal invasion of the tumor reached the upper half of the vaginal wall (Fig. 1A). Computed tomography (CT) revealed invasion of the tumor into the left parametrium, with no space between the tumor and the left pelvic wall. The left urinary tract was involved in the tumor, which caused hydronephrosis of the left kidney (Fig. 1B). There was no elevation in tumor markers (SCC (squamous cell carcinoma-related antigen) 1.0 U/mL, CA19-9 5 U/mL, CA125 14 U/mL). Spindle cells

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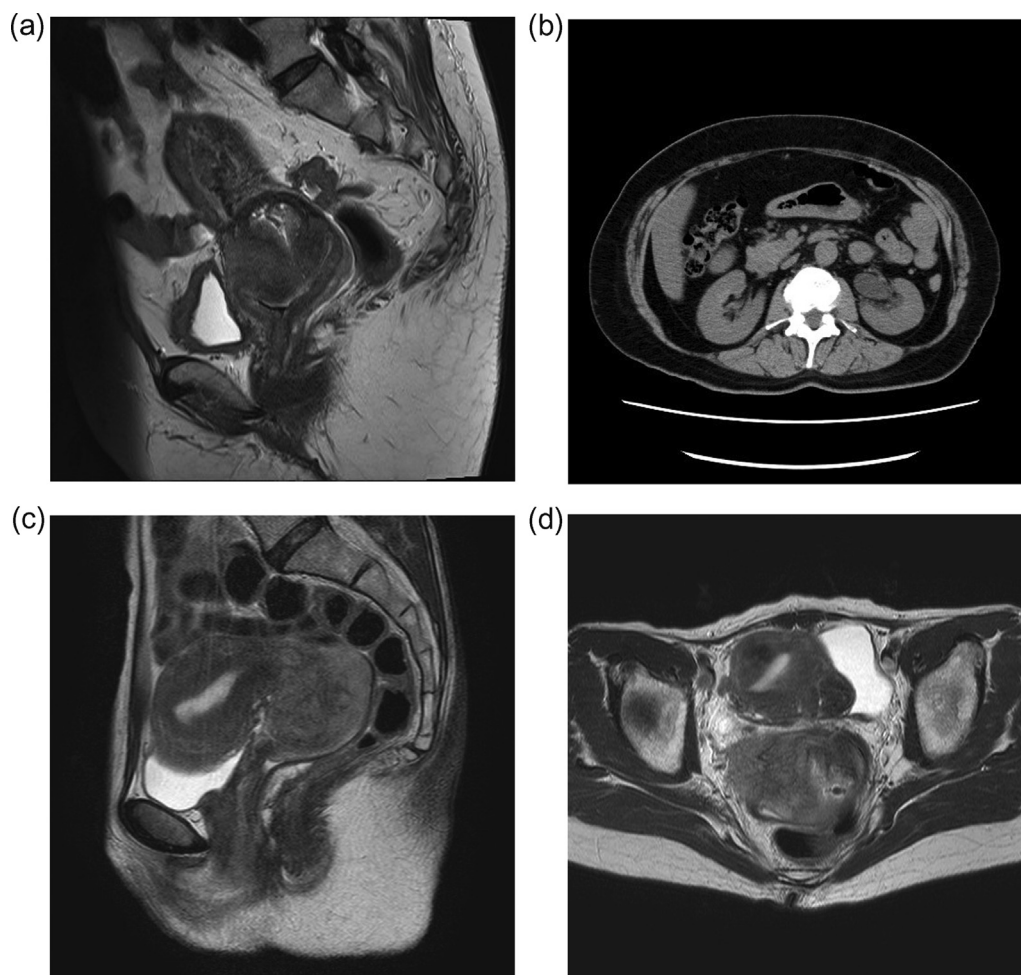


Fig. 1. MRI and CT scan of Case 1 & 2. In Case1, MRI (T2WI) of the pelvis showed a bulky tumor with a diameter of 5 cm in the uterine cervix. Vaginal invasion of the tumor reached the upper half of the vaginal wall (A). CT revealed invasion of the tumor into the left parametrium. The left urinary tract was involved in the tumor, which caused hydronephrosis of the left kidney (B). In Case2, MRI (T2WI) of the pelvis showed a bulky tumor with a diameter of 6.5 cm in the uterine cervix(C). CT revealed invasion of the tumor into the right parametrium (D).

backed with collagen fiber were observed in the tissues taken by 14Fr core-needle biopsy which were performed in clinic without anesthesia (Fig. 2A). Chronic cervicitis, soft-tissue sarcoma, and spindle cell carcinoma were considered as differential diagnoses, but immunohistochemical staining excluded these diagnoses. On the other hand, leucocyte common antigen (LCA) was diffusely positive (Fig. 2B), and cluster of differentiation 20 (CD20) was diffusely strong positive (Fig. 2C). We considered malignant B-cell lymphoma as a diagnosis, but tissue morphology, stained by hematoxylin and eosin, did not show the typical large cell proliferation of DLBCL, and the immunoglobulin heavy chain (IGH) gene rearrangement was very weak. Therefore, we could not make a diagnosis of malignant B-cell lymphoma. We first thought that the multitude of spindle cells in the tumor came from the destruction of the cells caused by the needle biopsy, but we then realized that the tumor was a spindle cell variant of DLBCL and not a typical B-cell malignant lymphoma. More tissues were obtained by additional needle biopsies, and IGH gene rearrangement was confirmed, leading to the diagnosis of a spindle cell variant DLBCL of the uterine cervix. F-fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) showed high accumulation of FDG (SUV max = 9.9) in the tumor extended from uterine cervix to upper vagina, and no abnormal accumulation in the other parts including lymph nodes, bone marrow and spleen. She was diagnosed with primary uterine lymphoma and clinical Ann-Arbor stage IV.

The patient was treated with six courses of rituximab,

cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy and achieved a complete response (CR). Half a year has passed since the treatment, and she is free of recurrence based on PET-CT scans.

We reviewed cases diagnosed as malignant lymphoma of the uterine cervix over the past 20 years in our hospital, and only another two cases were detected. Histological morphology of one case revealed typical DLBCL that was diagnosed by needle biopsy without difficulty.

The other case was similar to the first. It was diagnosed as malignant B-cell lymphoma with unknown histological type, because of atypical tissue morphology. We reviewed this case as Case 2.

Case 2

The patient was a 46-year-old woman (gravida 2, para 2) with no medical history or reported complications. She visited a hospital with a chief complaint of abnormal genital bleeding. Pap smear was negative for intraepithelial lesion or malignancy. Because of the presence of a large cervical tumor and tumor invasion to the right parametrium, she was suspected to have cervical cancer. MRI of the pelvis showed bulky tumor with a diameter of 6.5 cm in the uterine cervix (Fig. 1C). CT revealed invasion of the tumor in to the right parametrium (Fig. 1D). The patient was diagnosed with cervical cancer of at least stage IIB by her previous physician. She was referred to our hospital for further examination and treatment. Her CA19-9 level was scarcely elevated (43 U/mL), but other markers were within normal limits (i.e., SCC 0.8 U/mL, CA125 28 U/mL). Pap smear revealed atypical glandular cells, not

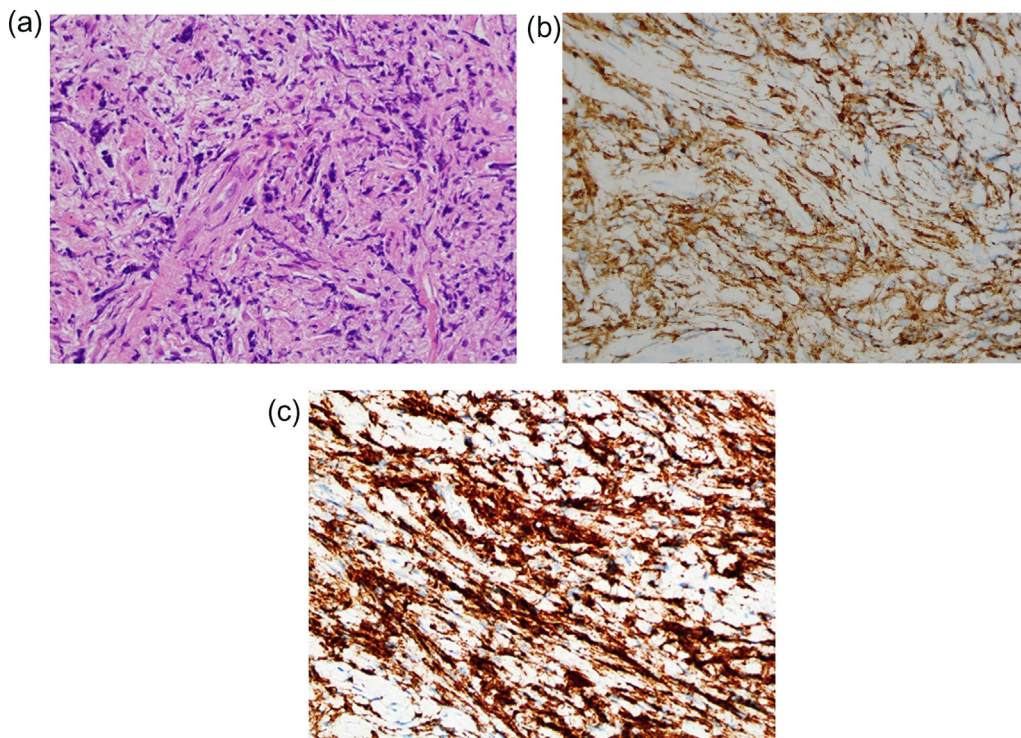


Fig. 2. Hematoxylin and eosin staining and immunohistochemical staining in Case 1 Proliferated spindle cells showed a vague storiform pattern with hyalinized fibrosis in the background (A) (400 \times , hematoxylin and eosin stain). Atypical spindle cells showed diffuse strong immunochemical stains for LCA (B) and CD20 (C) (400 \times , immunohistochemical stain).

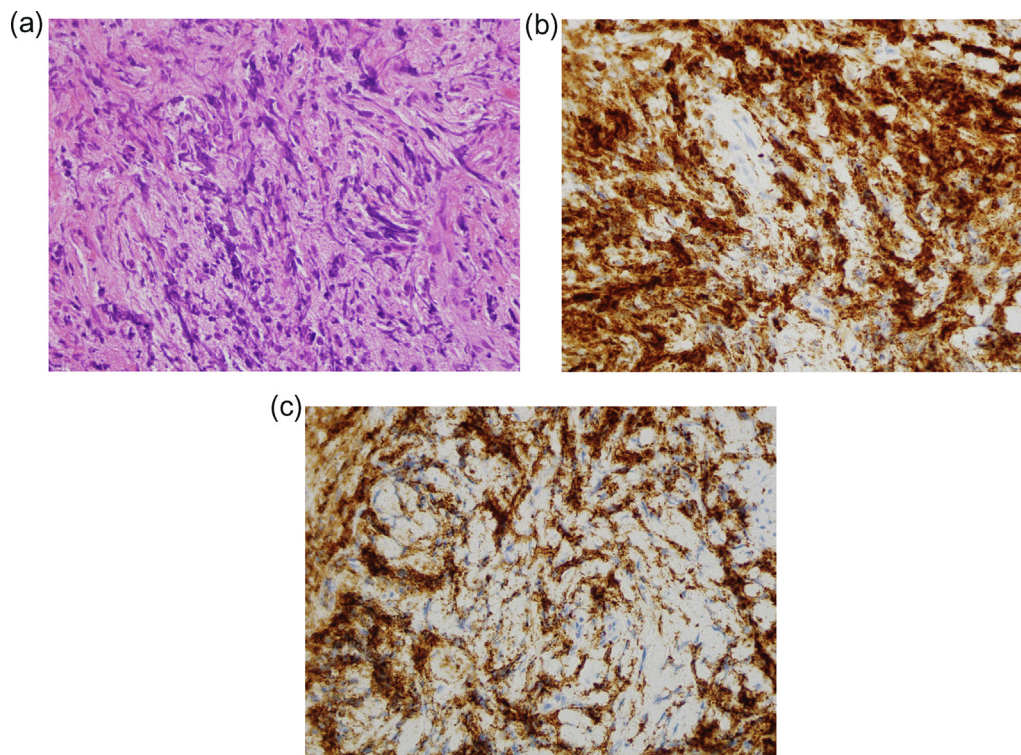


Fig. 3. Hematoxylin and eosin staining and immunohistochemical staining in Case 2 Proliferation of spindle cells were seen (A) (400 \times , hematoxylin and eosin stain). Spindle cells showed diffuse strong immunochemical stains for LCA (B) and CD20 (C) (400 \times , immunohistochemical stain).

otherwise specific. Spindle cells with proliferation of lymphocytes were observed in the tissues obtained by needle biopsy (Fig. 3A). Immunohistochemical staining of the tissues was positive for LCA (Fig. 3B) and CD20 (Fig. 3C), and the IGH gene rearrangement was positive. The case was diagnosed as malignant B-cell lymphoma. However, the histological type was unknown, as detailed observation of cell morphology was difficult because of the cell destruction caused by needle biopsy.

PET-CT revealed a strong accumulation of FDG in her cervix and cancer invasion to the right parametrium and right urinary tract. The patient was assigned an Ann-Arbor clinical stage of IV. She was treated with seven courses of R-CHOP chemotherapy and achieved CR. In the 3.5 years since her treatment, the patient has been free of recurrence, as verified by PET-CT scan. We reviewed the tissues of case 2 obtained by needle biopsy and founded the tissue morphologies were very similar to

the case 1. Although, on the previous diagnosis, the prominent spindle cells in the tumor had been considered as destructed cells by the needle biopsy, we confirmed the tumor was a spindle cell variant of DLBCL.

3. Discussion

Malignant lymphoma of the uterine cervix is very rare. The overall incidence of malignant lymphomas of the cervix is less than 1% among all cervical malignancies (Calli et al., 2012). Usually, malignant lymphoma produces a bulky and hard tumor in the uterine cervix and the tumor grows rapidly. As histological classification, DLBCL is the most common type of primary uterine lymphoma accounting for about 70% of cases.

Lymphoma with prominent spindle cell features is an unusual morphological variant of DLBCL in the WHO classification. It was first reported as B-cell lymphoma with a pseudosarcomatous growth pattern in maxilla (Kluin et al., 1984). Several cases have been reported to date, with most sites including the skin (Cerroni et al., 2000; Goodlad, 2001; Ries et al., 2007; Wang et al., 2010), some maxilla sites (Kluin et al., 1984), and soft-tissue sites. With regard to the uterine cervix, only two cases have been reported so far (Kahlifa et al., 2003; Fratoni et al., 2016), and here, we report two additional cases of spindle cell variant DLBCL of the uterine cervix.

Cervical lymphoma typically originates from the cervical stroma, and the superficial squamous epithelium is often preserved (Chan et al., 2005). Therefore, deep needle biopsy is essential to obtain proper tissues. We performed tissue biopsy and needle biopsy in Case 1 at her first visit to our hospital, but only normal squamous epithelium was obtained by tissue biopsy. From the immunohistochemical staining of the specimen by a needle biopsy, we considered the case to be malignant B-cell lymphoma. However, we could not confirm the typical morphology of DLBCL and IGH gene rearrangement. We resected the tumor by loop electrosurgical excision procedure to obtain tumor tissue without destruction, but we failed to reach the tumor tissue. We conducted additional deep needle biopsies to obtain sufficient tissues. Ultimately, we were able to diagnose it as a spindle cell variant of DLBCL.

Although malignant lymphoma of the uterine cervix is rare and sometimes difficult for the pathological diagnosis, six to eight cycles of R-CHOP chemotherapy is effective for DLBCL, and the CR achievement rate is high (Pfreundschuh et al., 2011). We did not perform a hysterectomy and referred her to the Department of Hematology of our hospital for treatment. She was treated with six courses of R-CHOP chemotherapy and achieved a CR. Thus, accurate diagnosis of malignant lymphoma is essential to avoid unnecessary surgery or medical treatment.

Based on our experience with Case1, we reviewed the cases of malignant lymphoma of the uterine cervix in our hospital and were able to confirm a histological diagnosis of Case 2, who had been diagnosed as B-cell malignant lymphoma with histologically unknown.

It is essential for more gynecologists and pathologists to be knowledgeable about spindle cell variant DLBCL of the uterine cervix and to diagnose it rapidly and accurately.

4. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRedit authorship contribution statement

Hiroko Murata: Investigation. **Harumi Nakamura:** Supervision, Resources. **Yukinobu Ohta:** Resources. **Masanori Kitamura:** Supervision, Resources. **Shinichi Nakastuka:** Supervision, Resources. **Jun Ishikawa:** Supervision, Resources. **Shoji Kamiura:** Writing - review & editing, Supervision, Resources.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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