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Case report

Primary diffuse large B-Cell lymphoma of the uterine cervix with severe lower urinary tract Symptoms: A rare case report and review of the literature

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ABSTRACT

Background: Diffuse large B-cell lymphoma (DLBCL) is a rare disease with a crude annual incidence rate of 3.8 cases per 100,000 people. Besides, primary cervical lymphoma is very rare, accounting for only 0.008% of cervical malignancies. (Sant et al., 2010) Although DLBCL patients often present with abnormal vaginal bleeding, it was not involved in this case. In this article, we present a rare case of primary cervical diffuse large B-cell lymphoma with urinary tract symptoms.

Case: A 71-year-old woman who had been suffering from dysuria for two months came to our hospital. A pelvic examination revealed a 10 cm cervical mass, while HPV and squamous cell carcinoma (SCC) antigen tests were negative. The bulky cervical mass invaded the posterior wall of the uterus, vagina, superior rectum, bladder, and bilateral lower ureters, resulting in dysuria and dilatation of the upper ureter. Histopathological and immunohistochemical examination confirmed DLBCL and PET-CT suggested that it was stage IV. After two cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), the large lesions were eliminated. Unfortunately, the patient suffered an untimely death unrelated to her disease before the fourth cycle of R-CHOP could begin.

Conclusions: DLBCL of the cervix is a rare, but potentially curable disease if the diagnosis is made accurately, and doing so requires a high index of suspicion for cervical masses with an atypical presentation in which traditional diagnostic methods are equivocal. Obtaining adequate multilayered lesion biopsies containing both cervical epithelium and mesenchyme helps to avoid misdiagnoses. Histopathological biopsy and immunohistochemistry are the gold standards for diagnosis, and R-CHOP chemotherapy is an effective treatment.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a rare disease with a crude annual incidence rate of 3.8 cases per 100,000 people. Primary diffuse large B-cell lymphoma of the cervix occurs primarily in older patients, with a peak incidence between 54 and 60 years old. (Nasioudis et al., 2017).

Premenopausal or postmenopausal abnormal vaginal bleeding is the most common presentation of DLBCL. Other symptoms include pelvic pain, vaginal discharge, and post-coital bleeding. Occasionally, DLBCL of the cervix is an incidental finding, and pelvic examinations often reveal a cervical mass or mass adjacent to the cervix.

Fox et al. (Fox et al., 1988) proposed the following criteria for diagnosing primary large B-cell lymphoma of the cervix: a) the lymphoma is confined to the cervix or adjunctive organs; b) full examinations fail to reveal evidence of lymphoma elsewhere; c) no abnormal cells are found in the peripheral blood or bone marrow; d) several months pass between the appearance of lesions in the genital tract and extragenital lesions; e) there is no prior history of lymphoma.

Histopathology and immunohistochemistry are recognized as the benchmarks for the diagnosis of DLBCL. Additionally, DLBCL is a chemotherapy-sensitive tumor, and R-CHOP chemotherapy (rituximab,

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cyclophosphamide, doxorubicin, vincristine, and prednisolone) is associated with favorable clinical outcomes.

In this study, we report on a very rare case of primary cervical diffuse large B-cell lymphoma with increased urinary frequency and dysuria. The patient was effectively treated with R-CHOP, but, Unfortunately, the patient suffered an untimely death unrelated to her disease before she completed her full course of treatment.

2. Case report

A 71-year-old patient was referred to our hospital complaining of increased urinary frequency for three months and dysuria for two months. She suffered weight loss but did not experience abnormal vaginal bleeding, abdominal pain, or distension. Also, she denied having a fever or night sweats and any underlying diseases such as pulmonary disease, cardiac disease, etc. before admission. She had undergone a thoracotomy 15 years previously, but there were no details of the surgery. Also, her family did not have a history of similar conditions.

Physical examination: No significant abnormalities were detected in the superficial lymph nodes. A pelvic examination revealed a 10 cm cystic solid mass with poor mobility at the 12o'clock position of the cervix. The cervix and partial vagina were obscured by the bulky mass. There was no significant thickening of the parametrial and sacral ligaments and no blood staining in the rectal mucosa.

Laboratory test: The tests for hepatitis, AIDS, and HPV were all negative. Blood test results suggested anemia and hypoalbuminemia (hemoglobin level was 71 g/L; serum albumin level was 23.9 g/L). Tumor markers indicated low SCC and CA125 levels (SCC: 0.590 ng/mL; CA125: 5.92 ng/mL). A cervical cytology test revealed atypical squamous cells of undetermined significance (ASCUS).

Imaging examination: A contrast-enhanced CT of the pelvic revealed that: a) a thickening cervix with a mass of 9.3 × 10.1 cm invaded the posterior wall of the uterus and the vagina; b) the cervical mass was poorly demarcated from the superior rectum and protruded into the bladder; c) enlarged lymph nodes were found bilaterally next to the iliac vessels, and the largest one was about 3.4 × 2.5 cm; d) the tumor invaded the bilateral lower ureter, resulting in dilatation of the upper ureter, with the right ureter being the most prominent (Fig. 1).

A PET-CT scan indicated that: a) there was a bulky soft mass in the cervix and soft tissue nodules in the bilateral adnexa, compressing the rectum and invading into the area of the bladder triangle. Both were considered malignant with a high likelihood of lymphoma; b) the retroperitoneal and presacral lymph nodes were metastasized (Fig. 3).

Pathological findings (Fig. 2): A histopathological biopsy of the cervical mass revealed a non-germinal center B-cell-like (non-GCB) DLBCL. An immunohistochemical analysis revealed the following: CD20 (diffuse +), Ki-67 (+90%), CyclinD1 (diffuse +), BCL-2 (+), BCL-6 (+), MUM-1 (+), CD5 (T lymphocyte +), C-MYC (+50%), CD10 (-), CD30 (-), CD23 (-), P16 (-), EBER (-). Fluorescence in situ hybridization (FISH) assay results did not reveal segregated rearrangements of the MYC, BCL2, and BCL6 genes. Besides, immunohistochemistry of the bone marrow biopsy did not indicate significant lymphocytosis, and a bone marrow smear showed a proliferative active bone marrow image with an increased percentage of granulocytes. B lymphoma cells were not detected by immunophenotyping of bone marrow flow cytology.

Based on these observations, we ultimately diagnosed primary cervical lymphoma, non-Hodgkin lymphoma, and diffuse large B-cell lymphoma with stage IVB. The IPI score was 4, indicating a high-risk type.

3. Treatment

The patient was treated with R-CHOP chemotherapy once every three weeks for six cycles (rituximab 0.6 g d0, cyclophosphamide 1.1 g d1, doxorubicin liposome 60 mg d1, vincristine 4 mg d1, prednisone acetate 95 mg d1-d5).

Before R-CHOP treatment, the patient underwent ultrasound-guided right renal pelvic puncture and drainage. This significantly relieved severe right hydronephrosis with right ureteral dilatation because the tumor had invaded her bladder and bilateral lower ureters. She was also treated for hypoalbuminemia and anemia.

For efficient prediction of patient response to R-CHOP, we repeated the PET-CT procedure after two cycles of R-CHOP. Reexamination of the PET-CT results revealed that the former large soft tissue mass in the cervix and the soft tissue nodes in the bilateral adnexa had disappeared. Additionally, the hypermetabolic lymph nodes in the retroperitoneal and presacral regions were not observed (Fig. 3). Thus, the patient achieved effective remission.

Five days before the fourth cycle of R-CHOP chemotherapy was due to start, the patient was admitted to the emergency department of our hospital due to a drowning accident. She had choked on seawater and become unconscious. Arterial blood gas analysis suggested type I respiratory failure. Unfortunately, the patient's family abandoned the treatment and the patient died.

4. Discussion

Primary cervical lymphoma is extremely uncommon and makes up only 0.008% of cervical malignancies. (Sant et al., 2010) Additionally, diffuse large B-cell non-Hodgkin's lymphoma is the most common subtype. It occurs in perimenopausal or postmenopausal women and its clinical presentation is similar to other gynecological malignancies. It is mostly presented as abnormal vaginal bleeding with a large mass situated at the cervix. R-CHOP chemotherapy has a good prognosis overall, even in stage IV cases (Table 1). However, our case involved a 71-year-old patient with increased urinary frequency and dysuria but without the usual abnormal vaginal bleeding. According to a CT scan and enhanced pelvic and PET-CT scans, the tumor had invaded her bladder and bilateral lower ureters, resulting in urination problems and dilatation of the upper ureter. Thus, this is an example of a very rare case of

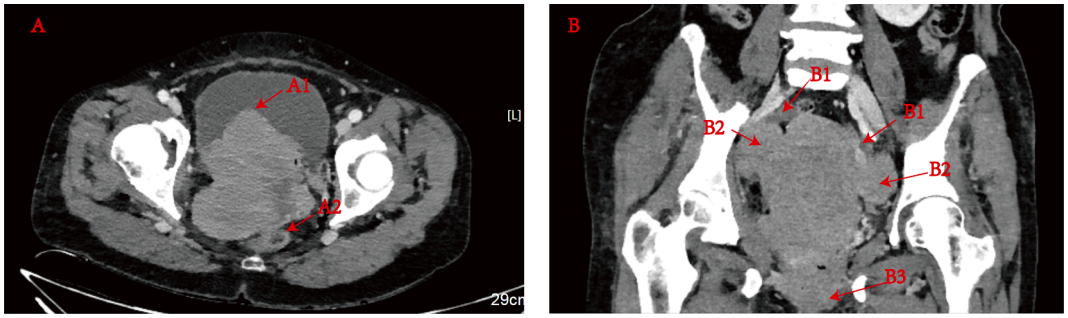

Fig. 1. Pelvic imaging. A pelvic CT detected a thickening cervix with a bulky mass invading the posterior wall of the uterus and the vagina (B3). The cervical mass was poorly demarcated from the superior rectum (A2) and protruded into the bladder (A1). Enlarged lymph nodes were found bilaterally next to the iliac vessels (B1). The tumor invaded the bilateral lower ureter, resulting in dilatation of the upper ureter, with the right side being the most prominent (B1).

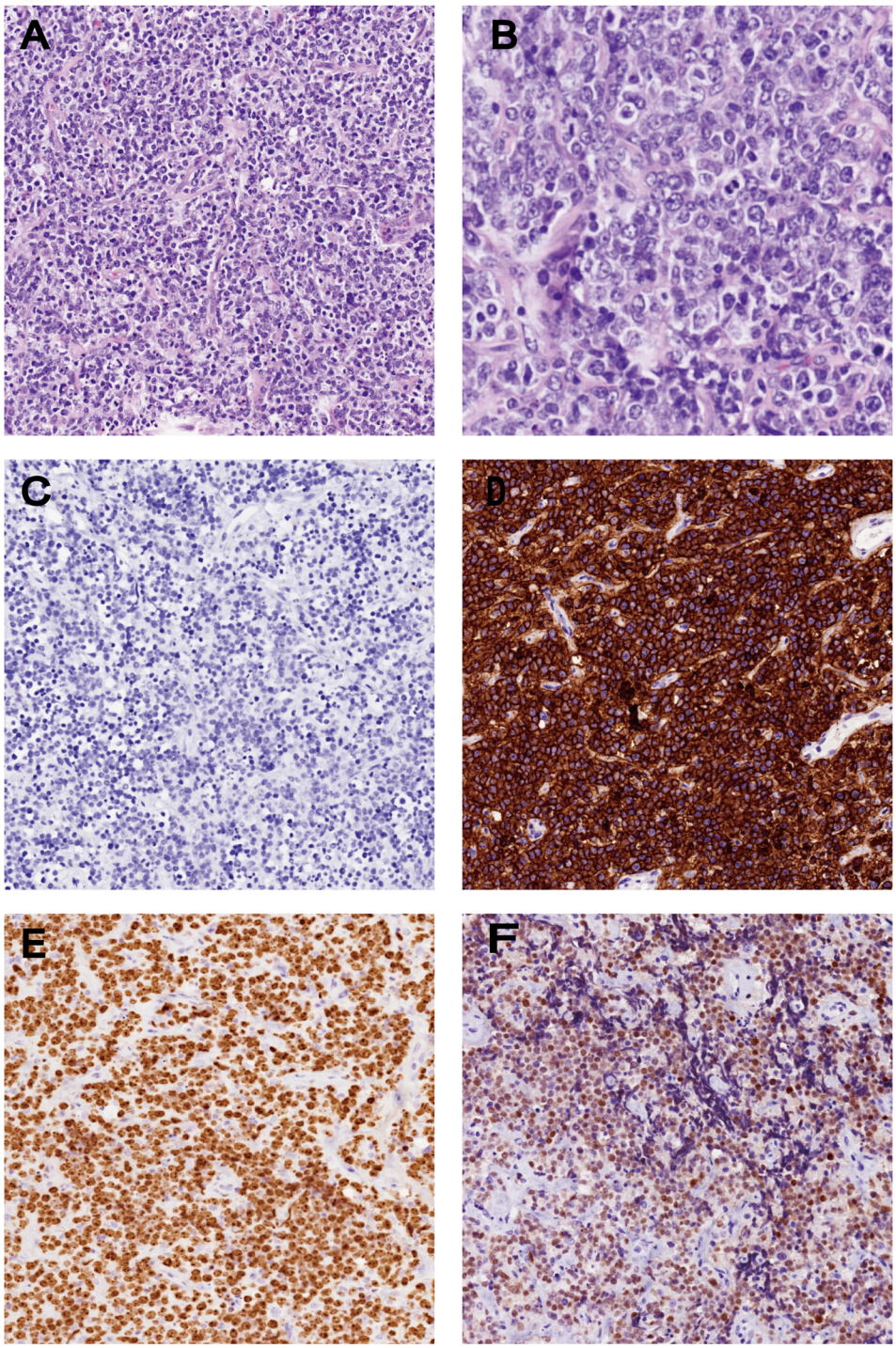

Fig. 2. Pathological findings. A and B illustrate the histological appearance of the cervical mass. There were localized proliferative lesions of lymphoid tissue with diffuse distribution of deeply stained cells**.** No normal lymphoid structures were observed. A: HE 20×; B: HE 40×; C to F display the immunohistochemical images. C: CD10 (-); D: CD20 (diffuse +); E: Ki-67 (+90%); F: MUM-1 (+).

primary cervical DLBCL with urinary tract symptoms.

DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-cell; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP chemotherapy treatment = doxorubicin, vincristine, cyclophosphamide, and dexamethasone; ISRT = involved site radiotherapy; IFRT = involved field radiotherapy; CR = complete remission; R-THP-COP = pirarubicin, cyclophosphamide, vincristine, and prednisone.

Currently, accurately diagnosing DLBCL is extremely challenging. Cervical lymphoma has no specific presentation in terms of symptoms, physical examination results, ultrasound, or CT scans. It is similar to other common gynecological neoplastic diseases such as cervical squamous cell carcinoma. However, unlike squamous cell carcinoma, DLBCL lesions originate in the cervical stroma and the superficial squamous epithelium is not usually affected. Thus, routine cervical cytology smears or superficial tissue biopsy results may be prone to generating false negatives or missing the lesion in deeper sites. (Del et al., 2020; Chan et al., 2005) In this case, cervical cytology revealed atypical

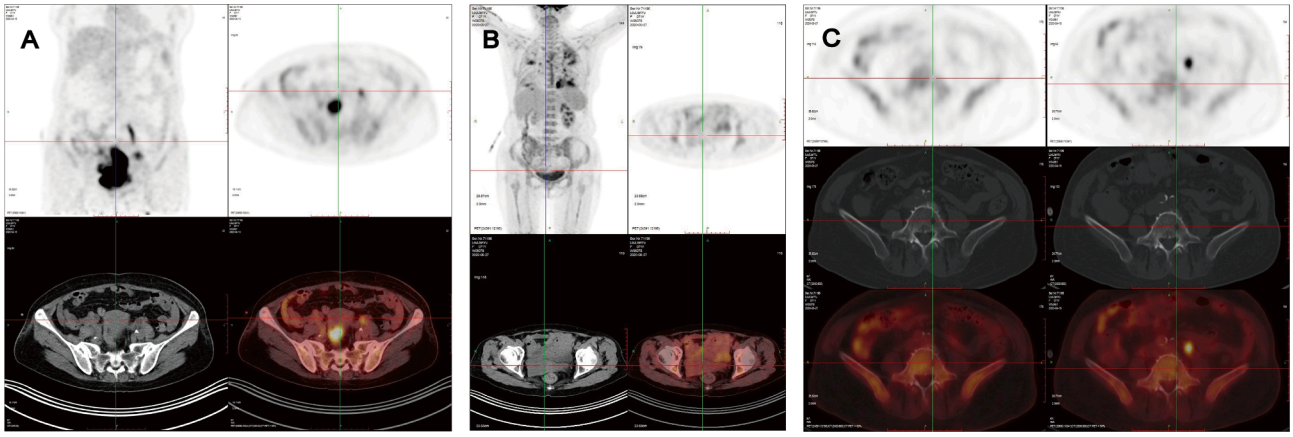

Fig. 3. PET-CT imaging. A: Image before treatment. There is a soft bulky mass in the cervix and soft tissue nodules in the bilateral adnexa, compressing the rectum and invading the bladder (triangle). Both are considered malignant with a high likelihood of lymphoma. The retroperitoneal and presacral lymph nodes are involved or metastasized. B and C: Imaging after 2 × R-CHOP. The large soft tissue mass in the cervix and the bilateral soft tissue nodes in the bilateral adnexa have disappeared. Additionally, the hypermetabolic lymph nodes in the retroperitoneal and presacral regions were not detected.

Table 1
Primary cervical lymphoma cases between 2013 and 2022.

Author	Age	Presentation	Local examination	Pap smear	Pathology	Stage	Therapy	Follow-up
Capsa et al (Capsa et al., 2022)	75	Vaginal bleeding	A bleeding tumor occupying the entire vagina	–	DLBCL	IE	CHOP × 6 + local radiotherapy × 5 weeks	CR, 29 mo
Goda et al (Goda et al., 2020)	52	Vaginal bleeding	A large growth involving both lips of cervix(6 × 6 cm)	–	DLBCL (GCB)	IAE	R-CHOP × 6 + ISRT	CR,18 mo
	50	Vaginal bleeding	A cervical mass(3 × 3 cm)	–	DLBCL (GCB)	IE	R-CHOP × 6 + IFRT TO PELVIS	CR, 43 mo
	39	Foul smelling discharge	A lesion in the posterior lip of the cervix (8 × 7 cm)	–	DLBCL (non-GCB)	IAE	R-CHOP × 6 + ISRT to cervix + pelvic nodes	CR, 8 mo
	62	Vaginal bleeding	A soft mass in cervix (6 × 5 cm)	–	DLBCL (non-GCB)	IIAE	R-CEOP × 6 + IFRT to pelvis	CR, 10 mo
Zhou et al (Zhou et al., 2021)	52	Lower abdominal pain	The uterine rectum lacuna was like a hard nodule of about 3. 2 cm.	–	DLBCL (GCB)	IE	R-CEOP × 6	CR, 12 mo
Del et al (Koyanagi et al., 2018)	36	Vaginal bleeding, pelvic pain, dysuria	A firm and fixed cervical mass of 7 cm invading the right parametrium and the anterior vaginal wall	–	DLBCL (GCB)	IV	R-CHOP × 6	CR, 15 mo
Koyanagi et al (Regalo et al., 2016 2016.)	74	No clinical symptoms	A whitish hemorrhagic tumor occupying the anterior lip of the uterine cervix	Non-epithelial malignant tumor, including malignant lymphoma	DLBCL	IIEA	R-CHOP × 6	CR
Cubo et al (Cubo et al., 2017)	51	Vaginal bleeding	A cervix, with a large exophytic lesio (9 × 10 cm) , infiltrating the upper vagina and both parametria and extending to the pelvic wall	–	DLBCL (GCB)	IE	R-CHOP × 6	CR, 24 mo
Regalo et al (Sharma et al., 2016)	40	Swelling of the right lower extremity and vaginal bleeding	A bulky cervical mass (7.9 × 7.6 cm)	–	DLBCL	IIE	R-CHOPx1 + R-CVPx 8; Recurrence: 4 × R-CHOP + pelvic radiotherapy	CR, 45 mo (the first therapy) ; Asymptomatic, 3 mo(recurrence)
Sharma et al (Sugimoto et al., 2013)	61	Vaginal bleeding	A 7 × 6 cm mass in the cervix and extending to lower uterus and upper third of vagina	–	DLBCL	IVB	R-CHOP × 6 + pelvic radiotherapy × 5 weeks	CR
Sugimoto et al (Bull et al., 2013)	72	Abdominal fullness	A giant, mass that was about the size of a small child's head	ClassIIto Class III	DLBCL	–	R-THP-COP × 6	CR, 36 mo
Bull et al (Wang et al., 2019)	47	A malodorous discharge	An extremely purulent discharge with and a firm mass at the cervix.	–	DLBCL	IIEB	R-CHOP × 6	CR

DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-cell; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP chemotherapy treatment = doxorubicin, vincristine, cyclophosphamide, and dexamethasone; ISRT = involved site radiotherapy; IFRT = involved field radiotherapy; CR = complete remission; R-THP-COP = pirarubicin, cyclophosphamide, vincristine, and prednisone.

squamous cells of undetermined significance (ASCUS), while HPV and SCC tests were negative, suggesting abnormal lesions in the cervix. Due to the obvious lesion, biopsy samples were taken during gynecological examination. Two grey-brown lesions were extracted with biopsy forceps, both of which were at the brittle solid part of the tumor and were the obvious focal tissue. The size of the biopsy tissue was about 2 × 0.5 cm. Thus, we ultimately diagnosed DLBCL. Due to inconsistencies between cytological and histological results and the rarity of this case, it may be difficult to diagnose DLBCL. As a result, larger and deeper cervical biopsies may be required. Diagnosis can be made with biopsies conducted during the gynecological examination while the cervical tumor is bulky and sufficient tissue is present. Also, colposcopy and biopsy under colposcopy are helpful, such as deep needle biopsies and biopsies taken by biopsy forceps. (Cubo et al., 2017) When initial biopsies are noncontributory, repeated biopsies may be required and deep cervical incisions or loop cone biopsies may have to be performed. It is recommended that a surgical excision biopsy remains the best method of diagnosis and a fine-needle aspirate should not be used as the sole basis for diagnosis by European Society for Medical Oncology (ESMO) clinical guidelines. (Tilly et al., 2015).

Histopathology and immunohistochemistry are recognized as the benchmark for the diagnosis of DLBCL. ESMO clinical guidelines recommend that the immunohistochemical panel for DLBCL should include CD20, CD79a, BCL6, CD10, MYC, BCL2, Ki67, IRF4, CyclinD1, CD5, and CD23. (Tilly et al., 2015) In our case, immunohistochemistry revealed that BCL6, BCL2, and C-MYC were positive. Dual immunohistochemical expression of MYC and BCL2 is generally associated with poor prognosis, (Tilly et al., 2015) so we further refined the MYC gene rearrangement assay (FISH). Subsequently, no segregated rearrangements of MYC, BCL2, and BCL6 genes were found, so we diagnosed diffuse large B-cell lymphoma of the cervix.

Table 2. Immunohistochemistry patterns of primary cervical lymphoma between 2013 and 2022.

It is necessary to differentially diagnose DLBCL from cervical squamous cell carcinoma and chronic inflammatory processes, especially cervical lymphoma-like lesions. While the symptoms of DLBCL can easily be confused with cervical squamous cell carcinoma, the SCC and HPV tests of cervical squamous cell carcinoma are often positive. Besides, according to histopathology and immunochemistry, in cervical squamous cell carcinoma cases, the squamous epithelial markers are positive. In our case, the SCC and HPV tests were negative and DLBCL was confirmed by histopathology and immunochemistry. Histologically, cervical lymphoma should be distinguished from the lymphoma-like lesion (LLL), which presents dense lymphoid infiltration. The histology of LLL is a pleomorphic polyclonal proliferation, such as polymorphonuclear leukocytes and plasma cells, with no monoclonal rearrangement of the IgH gene. In contrast, cervical lymphoma often exhibits a monomorphous lymphoid infiltrate with coarse chromatin, a preserved epithelium, and monoclonal rearrangement of the IgH gene. In histology and immunophenotyping, other lesions such as follicular lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma, and T-cell lymphoma should be considered in the differential diagnosis.

Currently, the staging of cervical lymphoma follows the Ann Arbor staging system. Fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) are recommended for staging patients with DLBCL according to the standards that were devised at the International Conference on Malignant Lymphoma (Lugano Classification) and ESMO. (Tilly et al., 2015; Cheson et al., 2014) Combined with the results of PET-CT, the case was staged as IVB. DLBCL of the cervix is a chemotherapy-sensitive tumor and patients treated with six to eight cycles of R-CHOP chemotherapy often achieve high rates of complete remission (Table 1). However, it is still unclear whether surgery, radiotherapy, or a combination of the two is preferred. A cohort study including 697 women with primary lymphoma of the genital tract revealed that surgery did not provide a reduction in mortality. (Nasioudis et al., 2017) Also, there are no studies that clearly show a significant survival benefit with radiotherapy. Patients treated with chemotherapy have slightly higher survival rates than those treated with radiotherapy, surgery, or a combination of radiotherapy and chemotherapy. (Awwad et al., 1994) Awwad et al. suggested that radiation-only therapy was unwise because occult distant foci may not be detected by imaging techniques, despite adequate local control, (Vang et al., 2000) and patients may eventually succumb to distant metastases. In contrast to surgery or radiotherapy, chemotherapy prevents and controls the occult or disseminated foci, which is beneficial for patients in advanced stages of the disease.

To avoid unnecessary treatment, the treatment strategy for DLBCL patients should be adjusted according to the patient's age, international prognostic index (IPI), and feasibility of dose-intensive methods.

Our patient was a 71-year-old female with extensive lesions involving the posterior wall of the uterus, vagina, bladder, upper rectum, and bilateral lower ureters, as well as retroperitoneal and anterior sacral lymph node metastases. Besides, the patient was at an advanced stage (stage IVB), had a high-risk IPI score (IPI = 4), and had severe underlying conditions (anemia, hypoalbuminemia). This made her unsuitable for surgery, which is a risky treatment with many potential complications and a tremendous physical burden. Because the bladder, rectum, and bilateral lower ureters had been invaded, the patient was no longer suitable for radiotherapy. Thus, due to its effectiveness, R-CHOP chemotherapy was administered after treatment targeting the underlying disorders of hypoalbuminemia and anemia led to significant improvements in the patient's condition. For efficient prediction of patient response to R-CHOP, we repeated the PET-CT procedure after two cycles of R-CHOP. The second PET-CT scan revealed that the bulky lesions had disappeared, suggesting that R-CHOP was an effective treatment. More specifically, the large masses in the cervix and bilateral adnexal areas had been eliminated and the retroperitoneal and presacral hypermetabolic lymph nodes were not detected.

The prognosis of DLBCL is related to clinical stage, IPI, and

Table 2
Immunohistochemistry patterns of primary cervical lymphoma between 2013 and 2022.

Author	Age	CD5	CD10	CD20	BCL2	BCL6	MUM1	Ki-67(MIB-1) (%)	Cyclin D1
Capsa et al (Capsa et al., 2022)	75	–	NA	+	+	+	–	50% (+)	NA
Goda et al (Goda et al., 2020)	52	NA	+	+	NA	NA	–	70–80% (+)	NA
	50	NA	+	+	NA	NA	–	70–80% (+)	NA
	39	NA	–	+	NA	NA	–	50–60% (+)	NA
	62	NA	+	+	NA	NA	–	NA	NA
Zhou et al (Zhou et al., 2021)	52	NA	+	+	NA	+	–	70–80% (+)	NA
Del et al (Koyanagi et al., 2018)	36	–	–	+	+	+	–	60% (+)	–
Koyanagi et al (Regalo et al., 2016 2016.)	74	NA	–	+	–	NA	NA	NA	NA
Cubo et al (Cubo et al., 2017)	51	+	–		+	+	–	60% (+)	–
Regalo et al (Sharma et al., 2016)	40	–	+	+	+	+	NA	NA	–
Sharma et al[15]	61	NA	NA	+	NA	+	+	70–80% (+)	NA
Sugimoto et al (Bull et al., 2013)	72	NA	–	+	NA	NA	NA	low (+)	–
Bull et al (Wang et al., 2019)	47	NA	+	+	+	+	+	80% (+)	NA

pathological staging. The disease stage (Ann Arbor classification) is a crucial predictor of survival since late-stage patients have a poorer 5-year survival rate than those in the early stages. (Swerdlow et al., 2016) The IPI is based on age, tumor stage, serum lactate dehydrogenase concentration, performance status, and the number of extranodal disease sites. In predicting long-term survival, the IPI and the age-adjusted IPI are considered more accurate than the Ann Arbor classification. The IPI score of our patient was 4, which indicated high risk. The pathology of DLBCL can be divided into GCB (germinal center B cell-like) and non-GCB types. The overall survival rate of DLBCL patients with non-GCB subtypes is significantly lower than those with GCB subtypes. (Camicia et al. (2015)). Moreover, dual expression of immunohistochemical MYC and BCL2 is usually associated with a poor prognosis. (Tilly et al., 2015).

In conclusion, patients who present higher urinary frequency or dysuria, have a large cervical mass, suffer no vaginal bleeding, and have negative HPV and SCC tests may be suffering from primary cervical lymphoma. Obtaining adequate multilayered lesion biopsies containing both cervical epithelium and mesenchyme helps to avoid misdiagnosis. Histopathology and immunohistochemistry are the gold standards for diagnosis, along with genetic testing, if necessary. Also, while it is essential to make an individualized and effective treatment plan based on the patient's physical condition, R-CHOP chemotherapy is generally very effective.

5. Ethics and patient consent

The patient's families have provided written informed consent for the case details and images to be published. Institutional approval was not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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