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Is Uterine Cervix Lymphoma Missed Most of the Time? A Rare Case of Primary Cervical Lymphoma

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ABSTRACT

Background & Objective: Primary lymphoma of the cervix is rare and can be misdiagnosed most of the time. On the other hand, there is no consensus on the best treatment and follow-up strategy for this type of cervical malignancy. The present study aimed to present a misdiagnosed primary cervical lymphoma due to its confusing presentation and rarity.

Case Report: A 41-year-old woman presented with abnormal vaginal discharge and dyspareunia complaints. Unfortunately, the patient was not examined, and cervicitis was reported on biopsy. Therefore, the patient was treated for vaginitis for a long time. Due to a lack of response to antibiotic therapy, an ultrasound was performed, which showed a huge mass in the cervix. Patient was referred to the oncology department of obstetrics and gynecology center, Beheshti Hospital, Isphahan, Iran, in July 2013. Diffuse large B-cell lymphomas was diagnosed on a CT-guided biopsy of the presacral mass. Fortunately, despite the delay in diagnosis, 5 years after the last R-CHOP chemotherapic session (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), the patient has good quality of life with no sign of recurrences.

Conclusion: Due to the rarity of uterine cervix lymphoma, the diagnosis of genital lymphoma could be missed if the clinician does not consider this malignancy. High suspicion, rapid diagnosis and proper communication between clinician and pathologist lead to an excellent prognosis.

Keywords: B-Cell lymphoma, Cervix uteri, Extra-nodal lymphoma, Non-Hodgkin's lymphoma, Vaginal bleeding

Introduction

The diagnosis of primary genital lymphoma is rare, and its estimated incidence is 0. 5% of all Non-Hodgkin lymphoma **(1, 2)**. As the primary neoplasm of the uterine cervix, lymphoma may be presented with pelvic pain, abnormal vaginal bleeding, and prolonged malodor vaginal discharge **(3)**. Cervical lymphoma is missed in most cases because of subepithelial lymphomatous growth and intact superficial epithelium, leading to cervical sampling for accurate diagnosis **(1)**. Several studies report a high probability of diagnostic error by superficial sampling, so deep cervical biopsy or even excisional biopsy under anesthesia is recommended **(4)**.

On the other hand, it is challenging to differentiate benign lesions like chronic cervicitis from low-grade lymphoma. If there is high suspicion for a more vital diagnosis, immunohistochemistry staining could be helpful in such cases **(1)**. Imaging is used for determining malignancy dissemination, not a primary diagnosis, although it could be helpful in confirming the suspicious pelvic examination findings. For assessment of local extension or distant metastsis, PET/CT scan is a valuable technique **(5)**.

As cervical lymphoma is very rare, different treatment protocols have been suggested. Nowadays, conservative therapy with combined chemotherapy with or without radiotherapy is recommended, resulting in fertility preservation in reproductive age patients and good long-term results **(1, 4)**.

This study aims to report a primary uterine cervix lymphoma that was correctly diagnosed by pelvic examination and resampling that was successfully treated with combination chemotherapy.

Case Presentation

A 41-year-old gravida 3 para 2 abort 1 woman presented with complaints of pelvic discomfort, abnormal vaginal discharge, and dyspareunia in July of 2013, during the past three months. The patient had no additional point in her medical history. CO-test was

performed due to persistent complaints. The Pap smear result indicated bacterial vaginosis infection and severe inflammation with no response to antibiotic therapy. Then pelvic ultrasonography was requested, which showed a huge 7 × 5 cm heterogenic mass of the cervix and proximal part of the vagina. The patient was referred to a gyneco-oncologist who performed a bimanual pelvic examination for the first time. The bulky and firm cervix with posterior and lateral fornix adhesion was identified (parametrial involvement). Still, there was no specific finding via colposcopic examination, so a random cervical punch biopsy was done. The inflammatory changes were reported. Considering high suspicion of malignancy, a pelvic MRI with contrast was performed, which showed extensive tumoral involvement of the cervix.

Presacral space, bilateral parametrium, ischiorectal fat pads, and medial portion of piriformis muscle were involvedand. Multiple bilateral parailiac lympha-denopathies were also seen (Figure 1). The patient was referred to Beheshti Hospital, Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences. A CT-guided biopsy of the presacral mass was performed; two cylindrical tissues measured 1.2 and 1 cm in length, and 0. 1 cm in diameter were identified. Core biopsy revealed infiltration of large mononuclear cells between striated muscles fibers. In the first step, immunostaining for CK, LCA, and vimentin were requested by an expert pathologist. Only LCA immunolabeling was positive. The second immunohistochemical panel was done and the

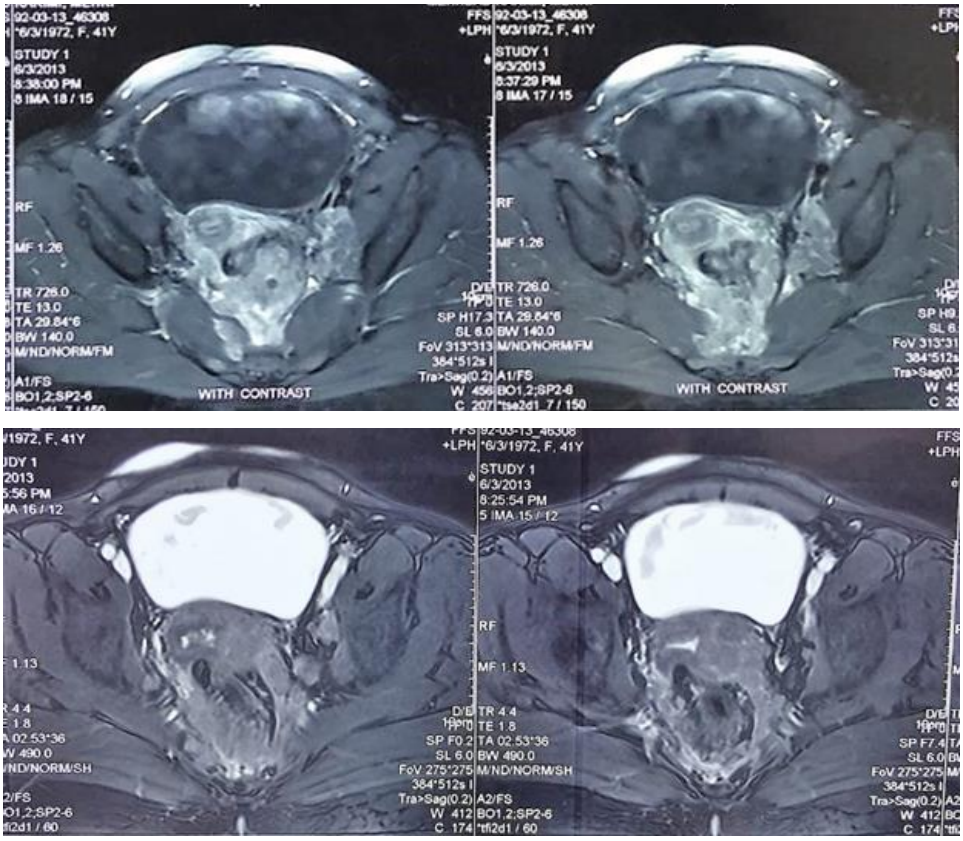

Figure 1. Pelvic MRI showed (with/without contrast) an infiltrative mass in favor of tumor involvement in the cervix with presacral and piriformis muscle infiltration and metastatic lymphadenopathy around internal iliac artery without any other organ involvement which confirmed stage IE for the patient

Following results were obtained

CD20: positive, CD3: negative, CD30: negative, ki-67 idex: more than 95%. According to morphological and immunohistochemical findings, Diffuse large B-Cell lymphoma of the cervix was diagnosed (Figure 2).

Whole-body CT scan and bone marrow aspiration demonstrated no distant metastasis. Based on the Arbor staging system, the stage of disease was determined as stage IE.

According to multidisciplinary consultation, the patient underwent six sessions of R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) every three weeks. Close surveillance was planned following a favorable response to chemotherapy (Figure 3). Now, 5 years after the last chemotherapic session, the patient has good quality of life with no sign of recurrences.

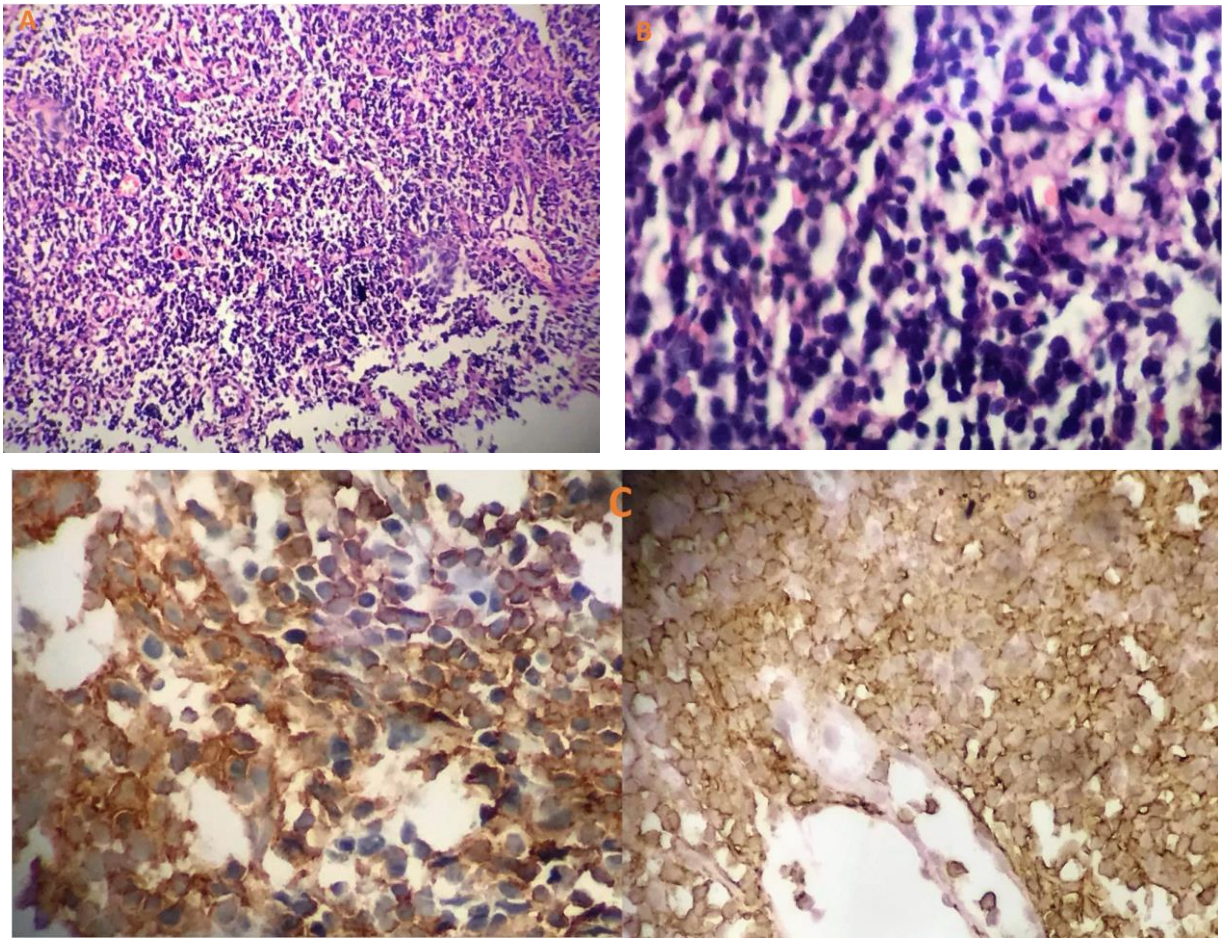

Figure 2. **The microscopic evaluation of the specimen showed neoplastic proliferation of small and uniform lymphoid cells in diffuse and infiltrative pattern between striated muscles fiber (A). Mitotic figure is scant (B). The IHC evaluation revealed: CK, CD99: negative, vimentin: negative & LCA: positive (C), CD20: positive, CD3: few stained for mature lymphocytes, CD30: negative, KI67: more than 95%; that confirmed high grade B-cell lymphoma**

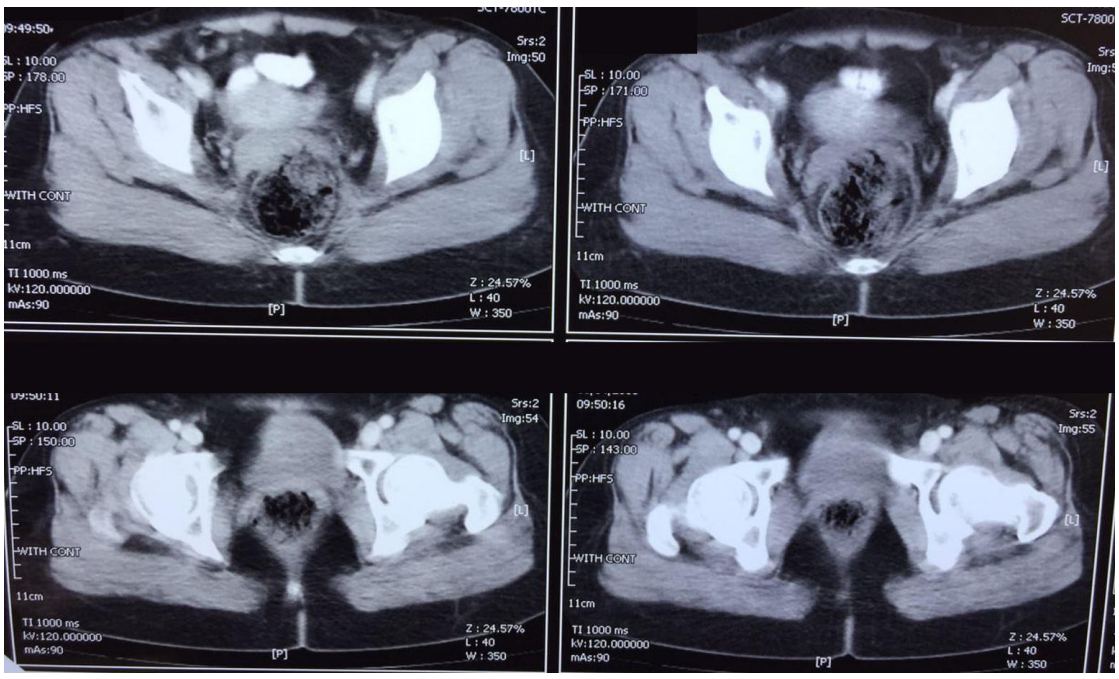

Figure 3. **The pelvic MRI showed (with/without contrast) dramatic response after chemotherapy**

Table 1. Comparative study of cases of primary cervical lymphoma reported in early stages: patient characteristics, treatment, prognosis

Author	Presented history	Diagnostic method	Stage of disease*	Treatment	Prognosis
Chan *et al.* (3)	62 Y vaginal bleeding previous subtotal hysterectomy	P: (-) BX: (+)	IE	Trachelectomy and LND.	Delay in chemotherapy administration due to surgical complication So the disease was disseminated and metastasis but chemotherapy BACOD++ Regimen lead excellent response with no recurrences even after 6 years
Garavaglia *et al.* (4)	76 Y Vaginal bleeding	BX: (+) P: ASCUS	IE	TAH-BSO-LAD+ pelvic RT	No recurrences after 1 years
	38 Y Incidental bulky cervix on examination	BX: (+) P: ASCUS	IIE	TAH-BSO at the end. + MACOP-B#	No recurrences after 7 years
	35Y Vaginal bleeding Bulky cervix on examination	BX: (+) BME: (-)	IIE	R-CHOP **+ TAH-BSO at the end.	No recurrences after 6 years
Yang *et al.* (9)	69 Y Urinary frequency cervical huge mass in imaging	P: (-) BX-IHC: (+) In the second evaluation session BME: (-)	IE	R-CHOP	-
Mouhajir *et al.* (10)	49 Y Vaginal bleeding Bulky cervix on examination	BX-IHC: (+) BME: (-)	IEA	CHOP + pelvic RT	No recurrences after 16 years
Shan Li *et al.* (11)	43 Y Vaginal bleeding bulky cervix on examination (the patient was underwent hysterectomy prior to pathology documentation)	BX-IHC: (+) In the evaluation of hysterectomy sampling BME: (-) Pet scan: vaginal cuff involvement	IE	≠ ABVD	No recurrences after 1 years

RT: radiotherapy, LEEP: loop electrosurgical excisional procedure, AH: abdominal hysterectomy, LND: lymph node dissection.
*Lymphoma staging; according to Ann Arbor Staging System.
**R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone)
#MACOP-B (methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin)
++ BACOD(bleomycin, doxorubicin, cyclophosphamide, and vincristine)
≠ ABVD (doxorubicin, bleomycin, vinblastine, and Dacarbazine)
¥RCVP (rituximab, cyclophosphamide, vincristine, prednisolone)
(+): positive/ (-): negative
Y: year old/ BX: biopsy of cervix/P: Pap smear/ BME: Bone marrow examination/ IHC: immunohistochemistry staining /G: gravida

Discussion

Primary Non-Hodgkin's lymphoma is a rare genital tract neoplasm, and the incidence is about 1% of all cervical cancer **(2)**. According to the literature, this neoplasm is mostly seen in post-menopausal women, although our patient was of premenopausal age **(1)**. Most patients like this one present with a pelvic mass, vaginal bleeding, or abnormal discharge. Thus clinicians should consider the possibility of cervical malignancy **(1, 3, 6)**. As diagnosis is too complex and often delayed due to nonspecific symptoms or normal Pap tests, it is essential to do a pelvic examination for accurate diagnosis **(4, 7)**. In addition to physical examination, imaging could be helpful. On ultrasound, a large multi-lobulated mass with the vascular flow, like the presented patient, could be characteristic of lymphoma diagnosis. However, the PET/ CT scan is recommended for distant metastasis assessment **(5, 6)**. Diagnostic errors may occur by improper cervical sampling, and superficial sampling may be misinterpreted as benign lymphoid infiltration like what happened to our patient **(4, 5)**. The lymphoma-like lesion is the most crucial differential diagnosis composed of florid lymphoid infiltration. Mixed superficial infiltration with surface erosion, without evidence of mass formation, deep invasion, and prominent sclerosis are in favor of lymphoma-like lesions **(8)**.

Immunohistochemical staining is an ancillary method that could confirm the diagnosis; positive staining of B cell marker (CD20, PAX5), BCL 6, MUM1, BCL2 (variable), CD10 (variable) and negative staining of T cell marker as CD3, CD5, and high ki-67 index revealed the diagnosis of high-grade B cell lymphoma **(5, 6)**. So high clinical suspicion, proper and adequate sampling, and good communication between physicians and pathologists all help us in the proper diagnoses. The prognosis of non-Hodgkin's lymphoma depends on the age, tumor size, pathology subtype, and disease dissemination at the time of diagnosis. More than 70% of cases are identified in early-stage **(5, 6)**. The latest review article by Nasioudis *et al.* in 2016 reviewed 149 cases of primary and secondary uterine cervical lymphoma during the past 30 years, but they did not conclude due to the lack of standard chemotherapy regimen in the treatment of the cases **(5)**. Despite persistent debate on the standard management of early stage cervical B-cell lymphoma in literature (Table 1), the R-CHOP chemotherapy regimen without surgical treatment is the most acceptable approach **(2, 6)**. Our patient was treated with a six-cycle R-CHOP chemotherapy regimen and achieved a complete response, which was confirmed via pelvic examination, imaging, and cervical sampling and has had a good life.

Conclusion

Due to the rarity of uterine cervix lymphoma, the diagnosis of genital lymphoma could be missed if the clinician does not consider this malignancy. High suspicion, rapid diagnosis, and proper communication between clinician and pathologist lead to an excellent prognosis.

Acknowledgments

None.

Conflict of Interest

The authors declared no conflicts of interest.

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