

## CASE REPORT

## Primary nodular lymphocyte-predominant Hodgkin lymphoma of uterine cervix mimicking leiomyoma

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### Funding Information

No sources of funding were declared for this study.

Received: 13 November 2014; Revised: 18 December 2014; Accepted: 20 February 2015

*Clinical Case Reports* 2015; 3(6): 349–352

doi: 10.1002/ccr3.246

### Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon subtype of Hodgkin lymphoma (HL) and the majority of cases arise from lymph nodes [1]. Primary NLPHL of extranodal origin is rare and may pose a diagnostic problem if its existence is not considered [2]. Here, we reported a case of primary NLPHL arising in uterine cervix. In this report, we reviewed the literature and discussed the relevant clinicopathologic features of NLPHL in uterine cervix.

### Clinical Summary

A 43-year-old G0P0A0 female had severe mental retardation and delayed general development from birth. She had had irregular menstrual cycle since adolescence. At 42 years, hypermenorrhea was noted. In December 2012, she suffered from massive vaginal bleeding with shortness of breath and dizziness. Anemia (Hb: 4.0 g/dL) was found and abdominal sonography showed a 5.3 × 3.9 cm mass in the uterine cervix (Fig. 1A). A cervical leiomyoma was

### Key Clinical Message

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) accounts for about 5% of all Hodgkin lymphomas and predominantly involves peripheral lymph nodes. Primary NLPHL of uterine cervix is very rare. Here, we report cervical NLPHL with CD21 expression in a 43-year-old woman, who presented with abnormal vaginal bleeding for 1 year.

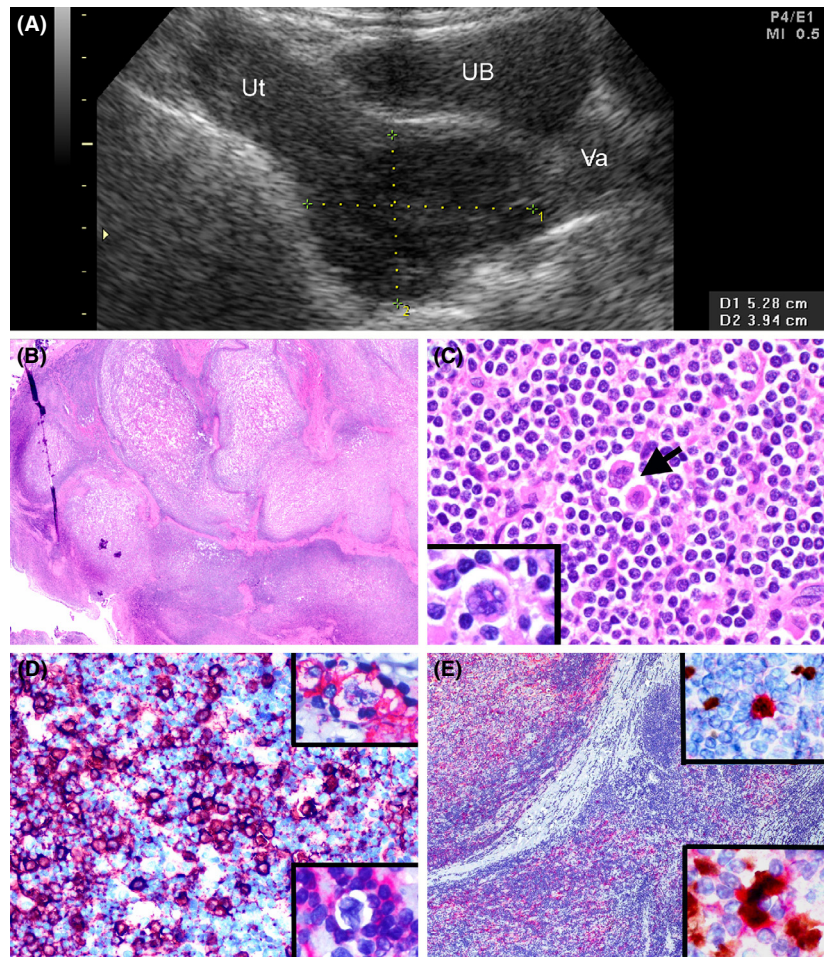
### Keywords

Hodgkin lymphoma, nodular lymphocyte-predominant type, primary, uterine cervix.

suspected and laparoscopy-assisted vaginal hysterectomy was performed. However, the pathologic diagnosis was NLPHL. The postoperative positron emission tomography-computed tomography (PET/CT) revealed a residual tumor in the vaginal stump. Lymph nodes on either side of the site were found to contain no cancer cells. Staging work-up including a bone marrow biopsy revealed an Ann Arbor stage IE disease. She received chemotherapy with an ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen. The therapeutic course was uneventful during a 12-month-period of follow-up and the impact of therapy on the mental state of the patient noted upon follow-up was negligible.

### Pathologic Findings

Pathologic examination revealed an ill-defined soft mass, 4.0 × 4.0 × 2.0 cm, at the left posterior lip of cervix with involvement of cervical wall and parametrium. The cut surface of the tumor was yellow white without necrosis or hemorrhage. Microscopically, the uterine cervix showed dense infiltration of lymphoid and histiocytic cells



**Figure 1.** Clinicopathologic features of cervical nodular lymphocyte-predominant Hodgkin lymphoma. (A) Sagittal view of sonography shows a large cervical mass (5.3 × 3.9 cm) involving cervical wall and parametrium (UB, urinary bladder; Ut, uterus; Va, vagina). (B) The cervical tumor shows dense infiltration of lymphoid cells in a large nodular pattern (4×, H&E). (C) Large atypical cells possess scant cytoplasm, multilobated popcorn-like nuclei and small basophilic nucleoli (arrow and inset, 400×, H&E). (D) The tumor cells in B-cell-rich nodules are immunoreactive for CD20 in the intensity stronger than background small B cells (200×, CD20) and the multilobated nuclei of L&H cells are highlighted in upper inset (400×, CD20). CD3-positive T-cell rosette surrounding L&H cells is indicated in lower inset (400×, CD3). (E) CD21 highlights the meshwork of follicular dendritic cells in the nodules (40×, CD21) and also stains the tumor cells by double staining of CD21 (red) and PAX5 (brown, insets, 400×).

in a vaguely nodular pattern (Fig. 1B). Among the infiltrate were large atypical cells with scant to moderate amount of cytoplasm, multilobated nuclei, and small nucleoli (Fig. 1C, arrow and inset). The background cells were composed predominantly of small lymphocytes and some histiocytes (Fig. 1C). The small lymphocytes were not atypical morphologically. Plasma cells, neutrophils, and eosinophils were negligible. The differential diagnosis included follicular lymphoma, NLPHL, lymphocyte-rich classical Hodgkin lymphoma, and T-cell/histiocyte-rich large B-cell lymphoma. Immunohistochemically, the B-cell-rich nodular pattern was highlighted by CD20, PAX5, and OCT-2, which also stained large atypical cells

(Fig. 1D, upper inset). CD3-positive T-cell rosettes surrounding L&H cells were noted (Fig. 1D, lower inset). These T cells were also stained by PD-1. EMA was focally and weakly positive for tumor cells. CD21 highlighted the meshwork of follicular dendritic cells in nodules (Fig. 1E) and also stained about 40% of L&H cells by CD21/PAX5 double staining (Fig. 1E, insets). The tumor cells and background B cells were negative for CD10, bcl-6, CD30, CD15, CD68, S-100, and ALK or in situ hybridization for Epstein–Barr virus-encoded RNAs (EBER). PCR for B-cell clonality was also negative. No microorganism was found on special stains. The diagnosis of NLPHL was established.

## Discussion

Primary lymphomas of the uterine cervix usually affect premenopausal women and most are non-Hodgkin lymphomas [2]. Primary HL of uterine cervix is extremely rare [2, 3]. Including our case, only seven HL cases of uterine cervix have been reported since 1960 (Table 1) [4–9]. The mean age is 45 years with a range of 39 to 54. The patients with diseases limited in uterine cervix are younger than those with lymph node involvement (mean age: 42.5 vs. 48.7 years). The more common symptoms are vaginal bleeding ( $n = 4$ ) and a mass lesion ( $n = 3$ ). In patients with stage I diseases, there is usually no mass (3/4, 75%) on pelvic examination or colposcopy. By contrast, a cervical mass (2/3, 67%) is the most common finding in patients with stage II/III tumors. Pap smear usually yields a negative result because the lymphoma cells may just infiltrate into the cervical stroma without involvement of overlying epithelium. Therefore, it is difficult to diagnose HL in early stage without biopsy. Five patients are classical HL and two are NLPHL. Five patients have surgical excision and three of them have adjuvant radiotherapy and one has adjuvant chemotherapy. Two patients underwent radiation alone. During the 18-month follow-up period, five patients were alive with

no evidence of the disease (NED), and two were alive with the disease (AWD, Table 1). The overall prognosis was excellent.

NLPHL constitutes around 5% of all HLs and 1.5% of all lymphomas [1]. Patients with NLPHL are predominantly male and most are in the fourth to fifth decades. It usually involves peripheral lymph nodes, while about 15% of the cases developed in extranodal sites, such as liver, bone, lung, salivary gland, skin, and soft tissue [10]. Primary NLPHL of uterine cervix is very rare. It may lead to delayed diagnosis and treatment if its existence is not considered. Only recently have Jastaniyah et al. [9] reported the first case in a 54-year-old woman presenting with vaginal bleeding. Our case is the second one, who also presented with vaginal bleeding. Interestingly, our case showed expression of CD21 in 40% of LP cells, a phenomenon not reported so far. Expression of follicular dendritic cell markers has been noted in 7% of classical HL cases and is a favorable prognostic factor [11], but has not been described in NLPHL [12]. CD21, the complement C3d receptor, plays a role in B-cell activation and maturation [13]. CD21 is expressed on subsets of B cells, particularly mantle cells. CD21-expressing B cells can capture and process antigen-immune complexes efficiently and subsequently display a germinal center phenotype [13], consistent with the phenotype of

**Table 1.** Summary of primary Hodgkin lymphoma (HL) of uterine cervix reported in the literature.

Case	Age	Clinical presentation	Pap smear	Diagnosis Procedure	Diagnosis	Involved site	Stage	Treatment	Outcome	Follow-up (months)	Reference
1	48	Bleeding	Negative	Conization	Classical HL	Cervix	I	Radiation	NED	2	Retikas [4]
2	39	Bleeding	Suspicious	Biopsy	Classical HL	Cervix	I	Radiation, then hysterectomy & salpingo-oophorectomy	NED	8	Nasiell [5]
3	40	Mass	Negative	Hysterectomy	Classical HL	Cervix	I	Radiation	NED	12	Anderson [6]
4	42	Amenorrhea	Dysplasia	Conization	Classical HL	Cervix, neck lymph node	III	Radiation and mono-chemotherapy (endoxan), then hysterectomy	AWD	18	Knobel and Gage [7]
5	50	Necrotic mass	Squamous cell carcinoma	Cervix and lymph node biopsy	NLPHL and adenosquamous carcinoma	Cervix, uterus, left ovary, right paratubal soft tissue, iliac lymph nodes	II	Radical hysterectomy	NED	8	Lovell and Valente [8]
6	54	Mass with bleeding	Negative	Biopsy	NLPHL	Cervix, left inguinal and bilateral iliac lymph nodes	II	Radiation	NED	18	Jastaniyah et al. [9]
7	43	Bleeding	Not done	Hysterectomy	NLPHL	Cervix	I	Chemotherapy (ABVD)	AWD	12	Our case

NED, alive with no evidence of disease; AWD, alive with disease; NLPHL, Nodular lymphocyte-predominant Hodgkin lymphoma.

NLPHL precursor cells. The acquisition of CD21 in NLPHL cells may suggest the development of tumor in an inflammation-prone milieu [14].

NLPHL progresses slowly, with fairly frequent relapses. The prognosis of patients with early stage (I/II) is excellent and the 10-year overall survival rate is over 80% [15]. Transformation to large B-cell lymphoma has been reported in 3–20% of patients [16]. The NCCN (National Comprehensive Cancer Network) guidelines suggest radiotherapy for the limited-stage disease [17]. Multidrug chemotherapy plus radiotherapy is indicated for the patients with advanced-stage diseases. Given that NLPHL cells express CD20 antigen, rituximab, an anti-CD20 antibody, may be useful in combination with chemotherapy [18]. Our patient initially received hysterectomy and the follow-up imaging showed residual tumor in the vaginal stump, which warranted further treatment. Considering that our patient had mental retardation and would be unamenable to the radiotherapy procedure, adjuvant chemotherapy was given and the therapeutic course was uneventful.

In summary, we reported a rare case of primary cervical NLPHL in a 43-year-old woman with vaginal bleeding. This entity has a relatively good prognosis, although multiple relapses and transformation to diffuse large B-cell lymphoma may occur. The guidelines suggest radiotherapy for limited diseases and chemotherapy for advanced diseases. Rituximab immunotherapy may be useful in selected patients.

## Conflict of Interest

None declared.

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