

Case Report

Primary natural killer/T-cell lymphoma of the cervix: a case report and literature review

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Abstract: Background: Non-Hodgkin lymphoma (NHL) involvement of the uterus is rare. Histologically, the majority of previously reported cases of NHL involving the female genital tract have been aggressive B-cell lymphomas, while natural killer (NK)/T-cell lymphoma involving the uterus is extremely rare. Case presentation: We report a case of primary cervical extranasal NK/T-cell lymphoma in a 36-year-old Chinese woman who complained of irregular vaginal bleeding. A computerized tomographic (CT) scan of the pelvis revealed a mass about 5 cm in size in the cervix with evidence of pelvic lymph node enlargement. Microscopic examinations showed prominent necrosis, angiocentric growth and diffuse infiltration by medium- to large-sized atypical lymphoid cells. The neoplastic cells were negative for CD20 and positive for cytoplasmic CD3, CD56, and granzyme B. In-situ hybridization showed that the tumor cells were positive for Epstein-Barr virus (EBV)-encoded small RNAs (EBERs). Based on these findings, the diagnosis of primary cervical extranasal natural killer (NK)/T-cell lymphoma was made. Four months after the chemotherapy and local radiation therapy, a mass lesion of the right orbit was observed by follow-up magnetic resonance imaging (MRI). In spite of intensive chemotherapy, the patient died of disease dissemination with an overall survival of 15 months. Conclusions: Due to its rarity and nonspecific clinical signs, uterine cervical lymphoma is sometimes a diagnostic challenge. The case described here may be of value in elucidating the biological behavior and natural history of NK/T-cell lymphoma.

Keywords: Non-Hodgkin lymphoma, natural killer (NK)/T-cell lymphoma, uterus, diagnosis

Introduction

Non-Hodgkin lymphoma (NHL) involvement of the female genital tract is uncommon, with a frequency of only 0.002% in all patients with extranodal lymphomas [1], and most often presents as a manifestation of systemic involvement. The ovary is the most common site of disease [2] and uterine involvement is uncommon except in disseminated disease [2-5]. A study of extranodal lymphoma over a 14-year period indicated that NHL of the uterus was present in only three out of 12,447 Caucasian patients [4]. Another study of NHL involving the female genital tract showed that the uterus was involved in only five patients with disseminated aggressive disease out of 902 patients over a 15-year period [3]. According to

statistics, primary lymphomas of the uterus were reported at a frequency of only 2% of all extranodal lymphomas in women. Histologically, most previously reported cases of NHL involving the female genital tract have been aggressive B-cell lymphomas [2, 3, 5], while NK/T-cell lymphoma involving the uterus is extremely rare, with only a few cases reported in the English-language literature to date [6-15].

Case presentation

A 36-year-old Chinese woman (gravida 3, para 3, abortion 0), without relevant previous medical history, was admitted to the hospital in May 2009 complaining of irregular vaginal bleeding for about four months. Physical examination revealed a friable, necrotic uterine

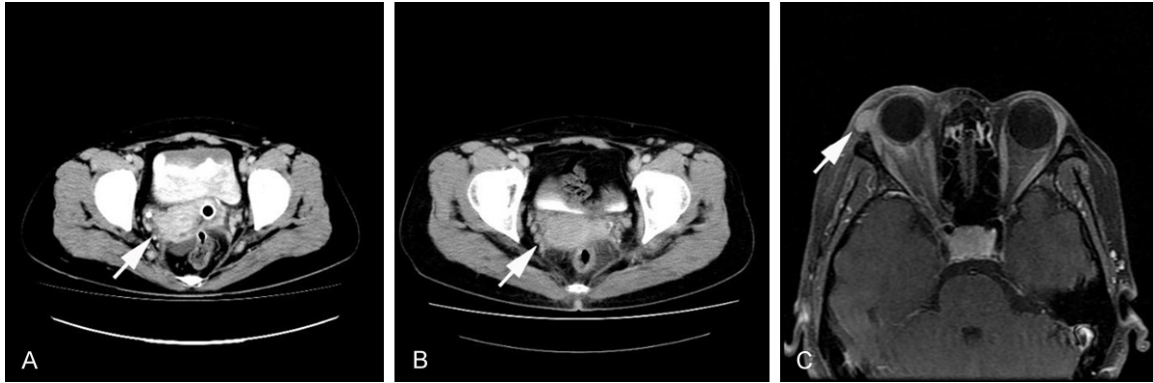


Figure 1. A computerized tomographic (CT) scan of the pelvis showed a bulky cervix (arrow) with evidence of lymphadenopathy (A). The cervical tumor showed regression by CT scan after two courses of chemotherapy (B). Four months after local radiation therapy, a mass lesion (arrow) of the right orbit was noted by magnetic resonance imaging (MRI) (C).

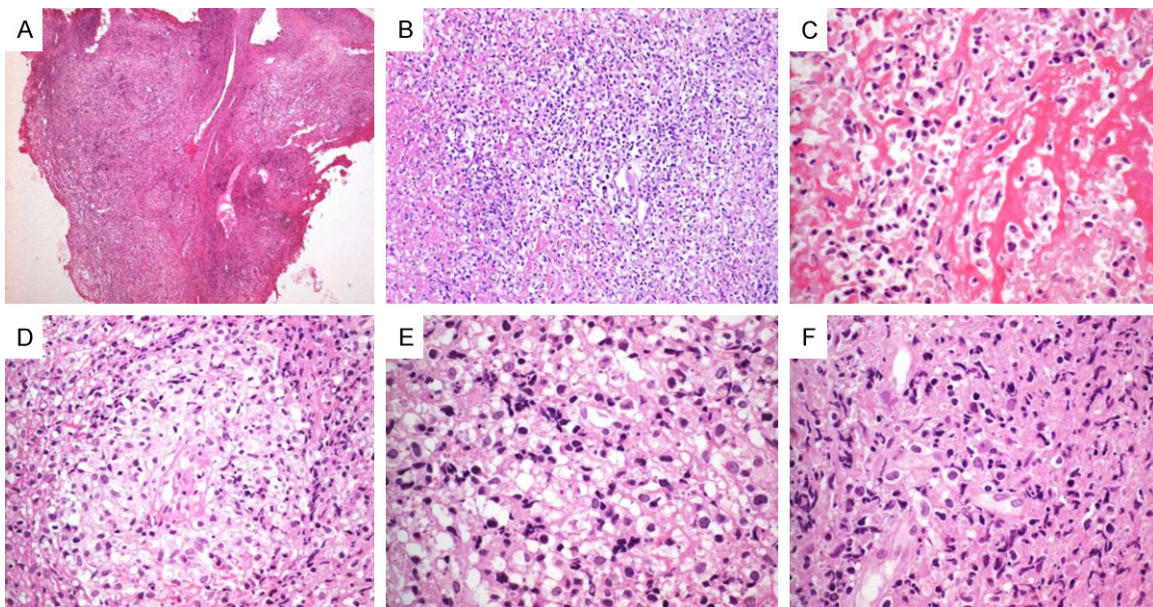


Figure 2. Low power view showing prominent necrosis and ulceration (A), diffuse infiltration by medium- to large-sized atypical lymphoid cells (B). High power view showing extensive necrosis (C), angiocentric growth (D), and medium- to large-sized lymphoid cells with irregular nuclear membranes and coarse chromatin (E, F).

cervix without a well-defined mass. Cervical cancer was suspected. A complete blood count showed a hemoglobin level of 10^5 g/L (normal range [NR]: 110-150 g/L) and leukocyte count of 4.3×10^9 /L (NR: $4-10 \times 10^9$ /L) with a normal differential and platelet count 138×10^9 /L (NR: $100-300 \times 10^9$ /L). The lactate dehydrogenase (LDH) level was 360 IU/L (NR: 80-190 IU/L). A computerized tomographic (CT) scan of the pelvis revealed a mass about 5 cm in size in the cervix with evidence of pelvic lymph node enlargement but absence of involvement of the adjacent organs (**Figure 1A**).

A biopsy of the cervix was performed. Microscopic examination showed prominent necrosis, ulceration of the squamous epithelium, and the presence of acute inflammatory cells (**Figure 2A, 2C**). The cervical stroma was diffusely infiltrated by medium- to large-sized atypical lymphoid cells with irregular nuclear membranes, coarse chromatin, scant to moderate cytoplasm, vesicular nuclei, and brisk mitotic activity (**Figure 2B-F**). Several areas showed angiocentric and angio-invasive growth, in which neoplastic lymphoid cells preferentially invaded and destroyed blood vessel walls (**Figure**

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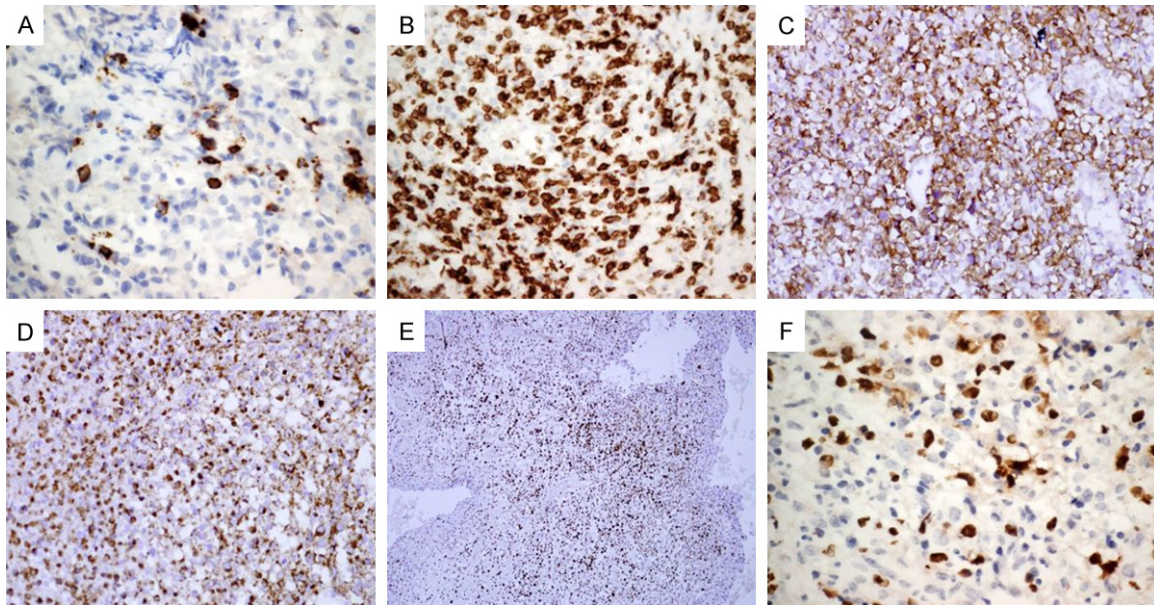


Figure 3. Immunohistochemical staining shows that the neoplastic cells were negative for CD20 (A) and positive for cytoplasmic CD3 (B), CD56 (C), granzyme B (D), and Ki-67 (E). In-situ hybridization shows that the tumor cells were positive for Epstein-Barr virus (EBV)-encoded small RNAs (EBERs) (F).

2D). The neoplastic lymphoid cells were shown to be CD20-, PAX-5-, CD2+, cytoplasmic CD3+, surface CD3-, CD5-, CD7+, CD4-, CD8-, CD56+, TIA-1+, GrB+ and Ki-67 index 80% by immunohistochemical studies on paraffin sections (**Figure 3A-E**). In-situ hybridization for Epstein-Barr virus (EBV)-encoded small RNAs (EBERs) was positive in the tumor cells (**Figure 3F**). Polymerase chain reaction studies showed no evidence of monoclonal T-cell receptor gene or immunoglobulin gene rearrangements. On the basis of morphological, immune-phenotypical, and molecular characteristics, the diagnosis of primary cervical extranasal natural killer (NK)/T-cell lymphoma was made. A chest radiograph and head, neck, thoracic, and abdominal CT scans were unremarkable. Bone marrow trephine biopsy revealed no evidence of lymphoma infiltration. The patient was staged as IIB.

The patient's treatments included chemotherapy combined with radiotherapy. Follow-up CT scans showed that the cervical NK/T-cell lymphoma had improved after two courses of chemotherapy using gemcitabine, dexamethasone and cisplatin (GDP) (**Figure 1B**). Partial remission was achieved after four courses of GDP and involved-field radiotherapy. Four months after the local radiation therapy, the patient was admitted to the hospital as a result of swelling and pain in the right eye. A mass le-

sion of the right orbit was observed by magnetic resonance imaging (MRI) (**Figure 1C**). The chemotherapy regimen was immediately changed, and the patient underwent salvage chemotherapy with etoposide, ifosfamide, and cisplatin (VP16+IFO+DDP) followed by radiation therapy at a dose of 40 Gy. In spite of intensive chemotherapy, the patient died of disease dissemination after five months in July 2010, with an overall survival of 15 months. Autopsy was not performed.

Discussion

Extranodal NK/T-cell lymphoma is an uncommon tumor that occurs with a higher prevalence in East Asia, Mexico, and Central and South America, accounting for approximately 6% of all NHLs in these populations [16]. Among mature T-cell and NK-cell lymphomas, extranodal NK/T-cell lymphoma constitutes 22.4% of cases in Asia (up to 44%, excluding Japan), compared with 4.3% to 5.1% in North America and Europe. Extranodal NK/T-cell lymphomas are a group of heterogeneous lymphomas that are divided into two subtypes according to the clinical features: nasal NK/T-cell lymphoma and extranasal NK/T-cell lymphoma. Nasal NK/T-cell lymphomas arise in the nasal cavity, nasopharynx, or upper aerodigestive tract, and frequently spread to the adjacent anatomic

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Table 1. Summary of the clinical and pathological features of NK/T-cell lymphoma arising in the corpus uteri and cervix reported previously in the literature

Authors	Age	Location	Past history	Immunohistochemistry	EBER	TCR rearrangement	Treatment	Clinical outcome
Chim <i>et al</i> [6]	47	Corpus uteri	NHL of nasopharynx	CD3ε+, CD5-, CD2+, CD56+	+	NA	Hysterectomy + CHOP + APSCT	Alive 5 M
Mhaweche <i>et al</i> [7]	30	Corpus uteri	None	CD3+, CD56+, TIA-1+, LMP1-	-	-	Hysterectomy	NA
Mhaweche <i>et al</i> [7]	45	Cervix	Blastoid NK-cell lymphoma/leukemia	CD3+, CD56+, TIA-1-	-	-	Hysterectomy + bilateral	NA
Nakamura <i>et al</i> [8]	44	Corpus uteri	None	CD3ε+, CD5+, CD2+, CD56-	-	-	Hysterectomy + CHOP	Alive 39 M
Nakamura <i>et al</i> [8]	21	Corpus uteri	None	CD3ε+, CD5-, CD56+	+	-	CHOP	Died after 16 M
Nakamura <i>et al</i> [8]	36	Corpus uteri	None	CD3ε+, CD5-, CD56+	+	-	Hysterectomy + CHOP	Died after 9 M
Murase <i>et al</i> [9]	51	Corpus uteri	NKTCL of the right nasal cavity	CD3ε+, CD5-, CD2+ CD56+	+	-	CHOP	Died after 2 M
Briese <i>et al</i> [10]	73	Corpus uteri	None	CD3ε+, CD56+, TIA-1+	-	-	NA	NA
Wei <i>et al</i> [11]	36	Corpus uteri	None	CD3ε+, CD56+	+	+	CHOP	Died after 76 D
Méhes <i>et al</i> [12]	48	Corpus uteri	None	CD3ε+, CD56+, TIA-1+	+	-	Hysterectomy+ CHOP	Died after 5 M
Fang <i>et al</i> [13]	41	Corpus uteri	None	CD3ε+, CD56+, TIA-1+	+	NA	Hysterectomy + CHOP	Died after 54 D
Wang <i>et al</i> [14]	54	Cervix	None	CD3ε+, CD56+, TIA-1+	+	+	Hysterectomy + bilateral adnexectomy	NA
Omori <i>et al</i> [15]	65	Cervix	None	CD3ε+, CD56+, TIA-1+	+	NA	CHOP	Died after 4 M
Present case	36	Cervix	None	CD3ε+, CD56+, TIA-1+	+	-	GDP + radiotherapy	Died after 15 M

Non-Hodgkin lymphoma: NHL; Natural killer cell: NK-cell; NK/T-cell lymphoma: NKTCL; Not available: NA; Autologous peripheralstem cell transplantation: APSCT; Cyclophosphamide, doxorubicin, vincristine and prednisolone: CHOP.

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structures such as the paranasal sinus, orbit, and oral cavity. Extranasal NK/T-cell lymphoma is less common than the nasal type. The most frequently involved sites are the skin, gastrointestinal tract, testis, lung, eye, soft tissues, and spleen; these are the same sites to which nasal NK/T-cell lymphoma tends to disseminate during the course of the disease. Other sites also may be involved. However, uterine involvement is extremely rare and only a few cases have been reported in the literature [6-15]. **Table 1** summarizes the clinical and pathological features of NK/T cell lymphoma arising in the uterus that have been reported previously in the literature. Most reports have described involvement of the corpus uteri by systemic NK-cell lymphoma, and only three cases of NK/T-cell lymphoma arising in the cervix have been reported to date [7, 14, 15].

The most common symptoms of lymphoma in the cervix are irregular vaginal bleeding, discharge, and cervical tumor. The presenting symptoms are not characteristic of cervical lymphoma, because they can also occur in other diseases. The unusual location and non characteristic symptoms may confuse clinicians and pathologists. Correct distinction of this tumor from chronic cervicitis, carcinoma, and other hematopoietic lesions such as peripheral T-cell lymphoma and other types of NHL is important.

Nasal and extranasal NK/T-cell lymphomas have similar morphologic features, which are characterized by prominent ulceration and necrosis, angiocentric and angio-invasive growth, and neoplastic cells that are variable in appearance and often admixed with apoptotic bodies and inflammatory cells. However, there also exist some site-specific morphologic features. The neoplastic cells are positive for CD56, CD2, and cytoplasmic CD3, but negative for surface CD3 and B-cell antigens. Occasional cases may show minor deviations, such as lack of cytoplasmic CD3 or CD56 expression. Other T-cell-associated antigens such as CD4, CD5, CD8, TCR $\alpha\beta$, and TCR $\gamma\delta$ are usually negative. Cytotoxic molecules such as TIA-1, granzyme B, and perforin are usually positive. Most nasal NK/T-cell lymphomas are EBV-positive, but some extranasal NK/T-cell lymphomas (in non nasal sites) are EBV-negative [7, 8, 10]. The majority of cases do not show evidence of T-cell receptor or immuno-

globulin gene rearrangements, as expected in tumors that arise from NK cells.

The characteristic histologic and immune-phenotypic features, presence of EBV infection in the tumor cells, and clinical history of our patient were interpreted to support the diagnosis of extranasal NK/T-cell lymphoma arising in the cervix. Primary cervical NHL is rare, and there have been few large case series reports to date from any single institution. Most patients with extranasal NK/T-cell lymphomas have a nasal lesion or disseminated disease, and pure extranasal disease is uncommon. To diagnose primary cervical NHL, it must fulfill all the following criteria proposed by Fox and More [17], such as that the lesion must be confined to the cervix at the time of diagnosis, and usually there is no evidence of NHL in other sites for at least several months following diagnosis. Therefore, it is appropriate for the patient in our case to be diagnosed with primary cervical extranasal NK/T-cell lymphoma. Primary cervical extranasal NK/T-cell lymphoma is extremely rare. To the best of our knowledge, prior to the current report, only three cases of primary cervical extranasal NK/T-cell lymphoma have been reported in the literature [7, 14, 15].

Most patients with nasal NK/T-cell lymphoma have early-stage disease (about 70% stage I or II) at presentation and experience good outcomes. However, extranasal NK/T-cell lymphoma often presents at an advanced stage (about 80% stage III or IV), accompanied by the presence of B symptoms such as fever, malaise, and weight loss; elevated serum LDH; and poor European Cooperative Oncology Group (ECOG) scores. Extranasal presentation has been shown to impact disease-free survival. A study of 84 cases of extranodal NK/T-cell lymphoma from India [18] showed that among 11 patients with extranasal disease, eight were found on follow-up to have a nasal mass and four had disseminated disease. Survival curves showed inferior overall survival in patients with extranasal presentation as compared to those with nasal disease. It was reported that extranodal NK/T-cell lymphomas have a median survival of only 0.28 years [19]. For comparison, the patient described here had better prognosis, with an overall survival of 15 months. At present, treatment experience has mostly been limited to cases of upper aerodigestive tract

disease. Extranodal NK/T-cell lymphomas in other sites are extremely rare, and very limited data regarding optimal treatment strategies is currently available. Treatment of NK/T-cell lymphomas of the cervix includes surgery, radiotherapy, and chemotherapy alone, or a combination of these therapies. The optimal therapy is still unknown. Therefore, more effective therapeutic regimens should be actively sought.

In conclusion, the authors report a case of primary cervical extranasal NK/T-cell lymphoma. Due to its rarity and nonspecific clinical signs, the diagnosis of uterine cervical lymphoma is sometimes challenging. Extranodal NK/T-cell lymphoma of the cervix is highly aggressive; therefore, early diagnosis and appropriate therapies are essential. This case may be of value in elucidating the biological behavior and natural history of NK/T-cell lymphoma.

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Disclosure of conflict of interest

None.

Authors' contribution

YPC contributed to the concept and design of the report and writing the article. JPL, LL, WFZ, TMH, HMM, CWX and GC performed surgery and took care of the patient. HMM arranged and performed adjuvant therapies. WFZ and JPL carried out autopsy and histological investigations. All authors read and approved the final manuscript.

Abbreviations

NHL, Non-Hodgkin lymphoma; CT, Computerized tomographic; EBV, Epstein-Barr virus; ECOG, European Cooperative Oncology Group; MRI, Magnetic resonance imaging.

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