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Case report

Spindle cell variant of diffuse large B-cell lymphoma of the uterine cervix; a case report of a rare entity and a potential pitfall

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Abstract

Introduction: Primary lymphomas involving the uterine cervix are rare. The spindle cell variant of diffuse large B-cell lymphoma (sDLBCL) occurring in the uterine cervix is extremely rare.

Case report: This is a 57-year-old woman, who presented with acute retention of urine. Clinical examination revealed a lesion obliterating the external os of the cervix. The ultrasound scan (USS) and contrast enhanced computerised tomography (CE-CT) confirmed the presence of a cervical mass with parametrial invasion. The cervical biopsy revealed an invasive tumour with a spindle cell morphology. Positive staining of tumour cells with immunohistochemical markers LCA and CD20 and a Ki-67 proliferation index of >90% was compatible with the sDLBCL. BCL6 positivity along with negative CD10 and IRF4/MUM1 was compatible with the germinal centre B-cell subtype. The bone marrow biopsy showed a tumour with similar immunomorphological features. The lymphoma was stage IV according to the Ann Arbor lymphoma staging system.

Discussion and conclusion: Owing to its rarity and histomorphology, the sDLBCL is often misdiagnosed as carcinosarcoma, melanoma or sarcoma on routine haematoxylin and eosin (H&E) stained sections. Therefore, appropriate immunohistochemical analysis is mandatory to distinguish sDLBCL from tumours with similar histomorphology. The prognosis of this rare tumour is not well- documented. Eight months after the initial presentation, the patient has completed six cycles of R-CHOP and is awaiting radiotherapy.

Keywords: diffuse large B-cell lymphoma, spindle cell variant, sarcomatoid, rare variants, cervix

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Introduction

Primary lymphomas of the uterine cervix are rare, accounting for 0.6% of all extranodal lymphomas and less than 1% of all cervical malignancies. Diffuse large B cell lymphoma (DLBCL) is the commonest type accounting for 70% of cases (1,2). Spindle cell variant of diffuse large B-cell lymphoma (sDLBCL) is a rare morphological variant categorized in the latest edition of World Health Organization (WHO) classification of tumours of haemopoietic and lymphoid tissue. It mostly arises in extranodal sites, the skin being the predominant site (2,3,4). To the best of our knowledge, only five cases of sDLBCL of the uterine cervix have been reported in the literature to-date (1,2,4,5,6).

Case report

A 57-year-old woman presented with acute retention of urine. She had diabetes mellitus and hypertension as comorbid factors. She denied any associated constitutional symptoms, such as weight loss, night sweats or fever. On admission, her renal function tests, full blood count, including a haemoglobin level of 13g/dL, and C-reactive protein level were within normal limits. Clinical examination revealed a bulky, fragile cervix with circumferential enlargement and obliteration of the external cervical os. There was no peripheral lymphadenopathy or hepatosplenomegaly. The ultrasound scan (USS) showed an irregular mass in the uterine cervix with extra cervical infiltration. The contrast enhanced computerised tomography (CE-CT) revealed a uterine cervical mass with parametrial invasion and evidence of obstruction of the right ureter. There was no evidence of distant metastasis or para-aortic or mediastinal lymphadenopathy.

The cervical biopsy revealed a diffuse infiltrate of spindle cells with oval to elongated hyperchromatic nuclei and minimum cytoplasm in a slerosed stroma (Figure 1). A storiform pattern was observed focally. The squamous epithelium of the cervix was not infiltrated by the tumour. The initial differential diagnoses included tumours with spindle cell histomorphology; carcinosarcoma, sarcoma, melanoma and reactive spindle cell lesions.

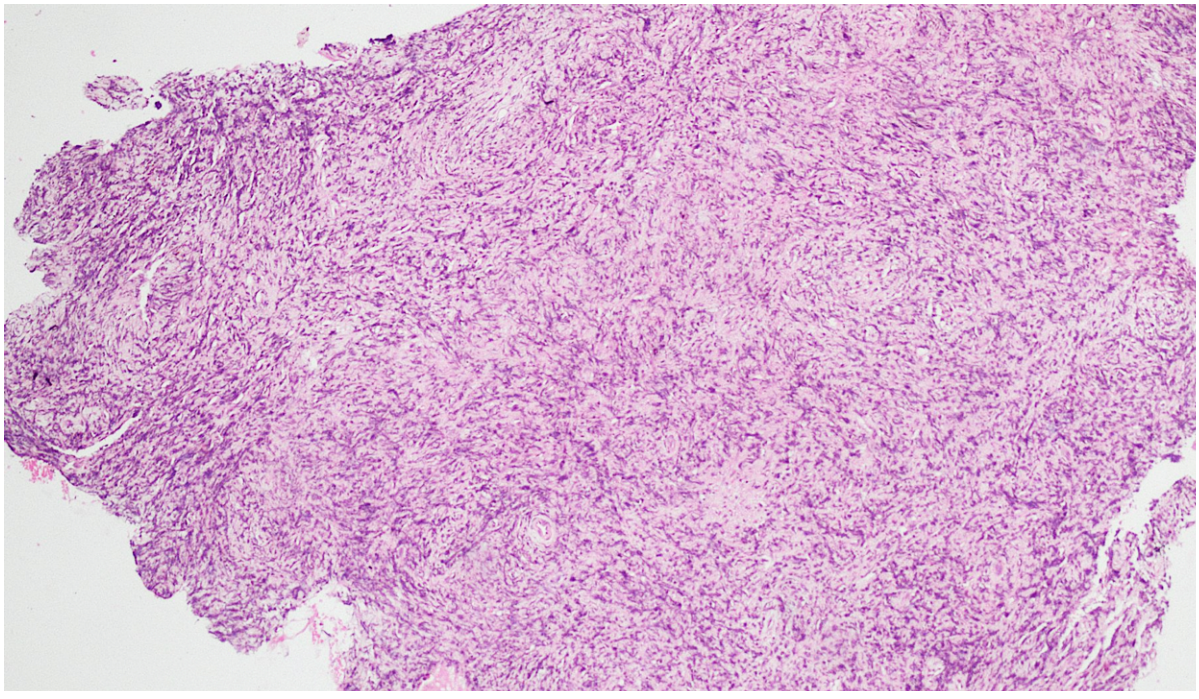

Figure 1. Cervical biopsy showing an infiltrating spindle cell tumour (H&E x100)

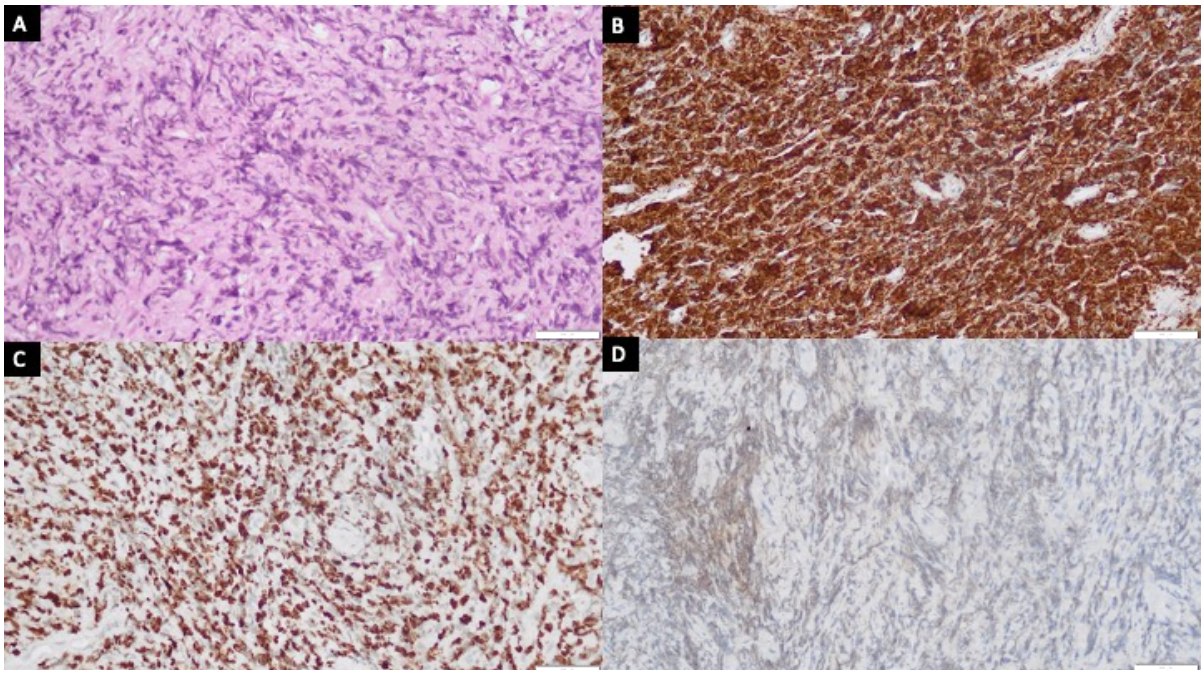

Figure 2. **A.** Cervical biopsy showing a lesion with spindle shaped cells (H&E x400), **B.** with positivity for CD20 (IHC x400), **C.** high Ki-67 proliferative index (IHC x400) and **D.** BCL-6 staining (IHC x400)

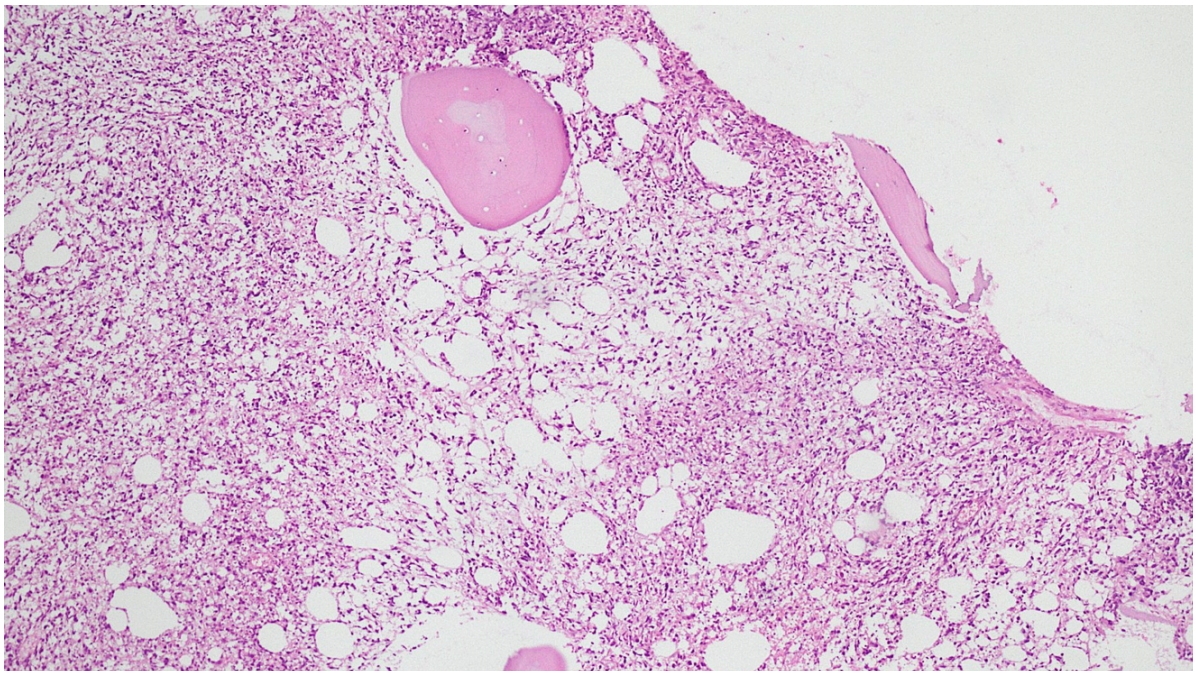

Figure 3. Bone marrow biopsy showing infiltration by spindle shaped cells (H&E x 400)

The tumour cells showed negative staining with the initial panel of immunohistochemical markers AE1/AE3, CK7, CK20, S100, desmin, SMA, synaptophysin and chromogranin. LCA and CD20 were performed as the second panel, and both showed diffuse strong staining of the spindle cells. The Ki-67 proliferation index was >90%. In addition, tumour cells showed positive staining with BCL6 (Figure 2). CD5, CD23, BCL2, CyclinD1, CD10 and IRF4/MUM1 showed negative staining. A diagnosis of primary cervical sDLBCL was made.

Subsequently, three months after the initial presentation, a bone marrow biopsy was

performed for staging, which showed involvement by a tumour with a similar histomorphological and immunohistochemical profile (Figure 3). The lymphoma was staged as stage IV according to the Ann Arbor lymphoma staging classification system.

The haemoglobin level of the patient dropped to 10.6 g/dl at the time of the bone marrow examination. Erythrocyte sedimentation rate (ESR) was 125 mm/1 hour, the serum lactate dehydrogenase (LDH) level was 396 U/L (135-214 U/L), serum tumour markers: carcinoembryonic antigen (CEA) (0.5 ng/ml), CA125 (7.7 U/ml) and alpha-feto protein (AFP) (2.9 ng/ml) were not elevated.

The patient was offered six cycles of R-CHOP (rituximab, cyclophosphamide, hydroxy-daunorubicin hydrochloride, vincristine and prednisolone) and radiotherapy, and will be followed up with rituximab as the maintenance therapy. Eight months after the initial presentation, the patient has completed six cycles of R-CHOP and she is awaiting local radiotherapy.

Discussion

sDLBCL was first reported in 1984 as a growth in the maxilla, which was diagnosed as B-cell lymphoma with a pseudosarcomatous growth pattern by Kluin et al.(2). Thereafter, it has been reported predominantly in extranodal sites, the skin being the commonest site (2). Cases have been reported in the female genital tract, the commonest site being the ovary followed by the cervix and vagina.

The age range of the patients of the five previously reported cases of primary cervical sDLBCL was 32-54 years (1,2,4,5,6). The most common presenting symptom of uterine sDLBCL was vaginal bleeding, which was encountered in three out of five patients; one had difficulty in passing urine and defaecation (2,4,5). One patient was detected incidentally at the cervical cancer screening clinic and the other patient presented with a vulvo-vaginal growth (2, 6). A mass lesion was seen in three of the previously reported cases and presented as a bulky tumour with "barrel shaped" cervix in two patients (2,4,5,6).

The microscopic appearances of the sDLBCL described in the previously reported cases in the literature were similar to this case. The first line differential diagnosis included carcinosarcoma, sarcoma and melanoma. Negative immunohistochemical markers resulted in the exclusion of these differentials and also directed towards performing immunohistochemical markers for a lymphoma, as in this case.

The differential diagnoses of a CD20 positive mature B-cell lymphoma with high proliferation index, namely Burkitt lymphoma, follicular lymphoma-grade 3, transformed small cell lymphoma and extranodal marginal zone lymphoma and blastoid variant of mantle cell lymphoma, were excluded by immunohistochemistry.

Molecular subtyping of DLBCL, not otherwise specified (NOS), is based on the cell of origin. DLBCL, (NOS) is subtyped as germinal centre origin (germinal centre B-cell subtype) or post germinal centre origin (activated B-cell subtype). A minority, around 10-15 %, remain unclassified. This subtyping signifies different biology based on gene expression, chromosomal aberrations, and recurrent mutations (3). Owing to the survival differences noted following treatment in the initial clinical trials, the subtype of DLBCL, NOS is considered an important predictive factor. Subtyping is best done by molecular analysis, however, when these tests are not available, immunohistochemical markers are accepted as surrogate markers along with the immunohistochemical algorithms, such as Hans algorithm or Modified Hans algorithm (3).

Most cases of sDLBCL reported in the literature were of germinal centre B-cell subtype, showing a positive staining pattern with CD10 and/or BCL6. This is supported by an analysis

done by Carbone et al., using five cases of sDLBCL, three of which were from extranodal sites (7). Similarly, in the present case, BCL6 was positive along with negative CD10 and IRF4/MUM1, compatible with the germinal centre phenotype according to the Hans algorithm. Genotype analysis, including MYC rearrangement is the best practice, however, these technologies are currently not available in the local setting.

Molecular testing data of sDLBCL is limited. An analysis done by Carbone et al. showed the presence of BCL6 mutations and absence of t(14;18), which is indistinct from DLBCL, NOS (7). Li et al. performed molecular analysis of lower uterine segment sDLBCL and have reported that gene mutations were similar to that of DLBCL, NOS (4).

The cause of the spindled histomorphology of sDLBCL is thought to be related to the tumour microenvironment rather than genetic or epigenetic factors (7,9). Compared to DLBCL, NOS, sDLBCL is found to have increased T cells, macrophages and myofibroblasts, leading to a postulation that increased number of fibroblast growth factor 2 (FGF2) and transforming growth factor beta 1 (TGF-β1) positive stromal cells may contribute to the spindle cell morphology of the tumour cells (7).

Carbone et al. has reported that serum LDH levels of patients with sDLBCL were usually within the reference range (7), although a slightly higher value was observed in this patient. A study done by Endrizzi et al. reports that the serum LDH level can be considered as a useful predictor of response to therapy and of survival in patients with NHL (8). According to this study, three prognostic groups, level 1, 2 and 3, were formulated depending on the serum LDH values (8).This patient's value falls into the moderate prognostic group.

Clinical behaviour and prognosis of sDLBCL is not well-documented due to the scarcity of available staging and follow up data. However, according to the risk stratification of the International Prognostic Index (IPI) for DLBCL, this patient has a score of 02/05 (age<60 = 0, Ann Arbor stage III-IV = 1, Eastern Cooperative Oncology Group performance status = 0, Serum LDH level = 1, >1 Extranodal sites = 0) (10).

As for any other lymphoma, all reported cases were treated with chemotherapy, and none have been offered surgical therapy.

Conclusion

sDLBCL is a rare morphological variant of DLBCL. Therefore it should be considered in the differential diagnoses of spindle cell lesions to avoid unnecessary delay in diagnosis. Appropriate immunohistochemical analysis is mandatory to distinguish sDLBCL from tumours with similar histomorphology. Therefore, the histopathologist plays a key role in directing the multidisciplinary team in the correct pathway by providing the accurate diagnosis.

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