

CASE REPORT

Primary extranodal diffuse large B-cell lymphoma of the uterine cervix

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Abstract

Extranodal non-Hodgkin lymphoma (NHL) of the female genital tract is a rare disease; with the primary disease of the cervix accounting for 0.2%–0.6% of NHL cases. Patients usually present with nonspecific signs and symptoms common to other more frequently encountered gynecological malignancies. The diffuse large B-cell lymphoma is the most prevalent subtype with distinctive pathological features, variable histopathological mimickers, unstandardised treatment protocols, and poor prognosis. We present a case of primary cervical diffuse large B-cell lymphoma in a 54-year-old woman with a prior history of subtotal hysterectomy and bilateral salpingo-oophorectomy. The patient was treated with radical surgery, chemotherapy, and radiation and remains disease-free at 24 months of follow-up.

Keywords: Cervix; diffuse large B-cell lymphoma; extranodal non-Hodgkin lymphoma.

INTRODUCTION

Primary extranodal non-Hodgkin lymphoma (NHL) of the female genital tract is rare and accounts for 0.2%–1.1% of all cases of extranodal NHL.¹ The most commonly affected sites are the adnexa (56%), the uterine corpus (15%), and the cervix (11%).² Primary NHL of the cervix is an exceptionally rare disease, representing <0.01% of all cervical tumours.³ Diffuse large B-cell lymphoma (DLBCL) is the most prevalent histopathological type and accounts for 30% of all primary cervical NHL cases.⁴ Patients usually present in the fourth decade with non-specific symptoms and in the absence of the common B symptoms of lymphoma.⁵ Due to the rarity of this tumor, the imprecise clinical and radiological presentation as well as numerous histopathological mimickers, diagnosis, and staging are often difficult. Moreover, the treatment protocols of primary cervical DLBCL have never been standardised.⁵ We present a case of primary DLBCL of the uterine cervix in a 54-year-old female who was successfully treated with surgery, chemotherapy, and radiation. We

also discuss the clinicopathological features and therapeutic options for this rare tumour.

CASE REPORT

A 54-year-old female, gravida 7 para 6+1, presented to the Emergency Department with a one-month history of abnormal vaginal bleeding and pelvic pain. She had no history of weight loss, fever, night sweats, or fatigue. Her surgical history included 2 caesarean sections and an abdominal subtotal hysterectomy with bilateral salpingo-oophorectomy for a large ovarian fibroma 9 months prior to her presentation. The patient had stable vital signs but looked pale. Her abdomen was soft lax with no palpable masses. No lymphadenopathy was detected. Pelvic examination showed a hypervascular cervix with a large bulging mass, measuring 7x5 cm. The patient's last Pap smear, performed a few months prior to her presentation, was negative. The patient's Eastern Cooperative Oncology Group (ECOG) performance status was 1 and all her haematological and biochemical laboratory investigations including tumour

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markers were within normal limits. Magnetic resonance imaging (MRI) of the pelvis showed a large (9 x 8 x 8 cm) lesion abutting the vaginal stump and compressing the right ureter with proximal moderate hydroureter. The lesion showed intermediate to low signal intensity on T1-weighted and T2-weighted images and enhanced on delayed images with diffusion restriction (Figure 1). Cervical punch biopsies were taken; however, the patient started to bleed massively, and she was rushed to surgery prior to the release of the histopathological results. She underwent an abdominal radical trachelectomy with complete surgical debulking. The surgery was complicated by massive blood loss requiring blood transfusion and an injury to the posterior bladder wall due to extensive adhesions requiring repair, ureteric reimplantation, and insertion of bilateral ureteric double-J stents.

Histopathological sections from the biopsies and resection specimen showed a diffuse infiltrate of the cervical stroma by atypical discohesive cells. The cells were pleomorphic medium to large with pale to eosinophilic cytoplasm, large irregular nuclei, prominent nucleoli, and frequent mitoses (Figure 2A). The overlying and adjacent cervical epithelium were benign-looking. No intercellular bridges, keratin formation, or

glandular structures were noted. No squamous or glandular intraepithelial lesions were seen. No intra- or extra-cytoplasmic pigment was seen. The tumour cells were CD45 and CD20 positive (Figure 2B), thus confirming their lymphoid lineage. They were also positive to BCL2, BCL6, and MUM1 immunohistochemical stains (Figures 2C-2E). C-Myc stain showed focal weak positivity in <20% of tumour cells (Figure 2F). Ki-67 index was high and reached up to 80% (Figure 2G). The tumour cells were negative to CD3, CD10, CD30, CD5, CD123, CD138, Cyclin-D1, and ALK-1 stains. They were also negative to epithelial, melanocytic, and mesenchymal markers including pan-CK, CK7, EMA, Vimentin, SMA, Desmin, S100, CD31, CD34, and HMB-45. The diagnosis of diffuse large B-cell lymphoma, activated B-cell subtype, was made. Staging computed tomography (CT) scans of the head and neck, chest, abdomen, and pelvis showed no lymphadenopathy or metastases. A bone marrow biopsy was obtained and it was negative. The patient fulfilled the criteria for a primary cervical DLBCL and she was staged as Ann Arbor stage IE.

The patient received 6 cycles of R-CHOP chemotherapy followed by multiple sessions of radiotherapy with a total dose of 20 Gy. CT

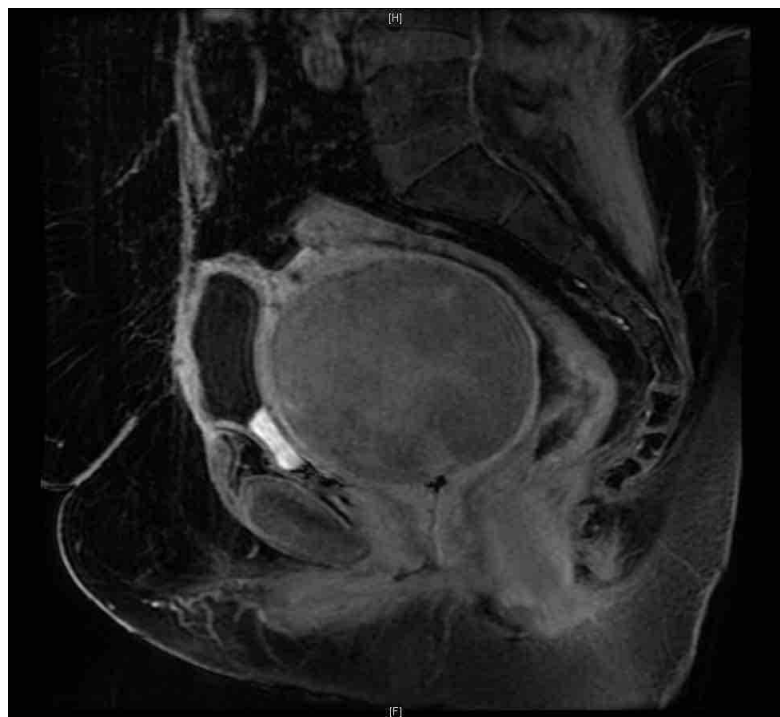


FIG. 1: A sagittal MRI T2-weighted image showing a mass arising proximal to the vaginal stump, with pressure effect on the adjacent rectum and bladder without direct invasion.

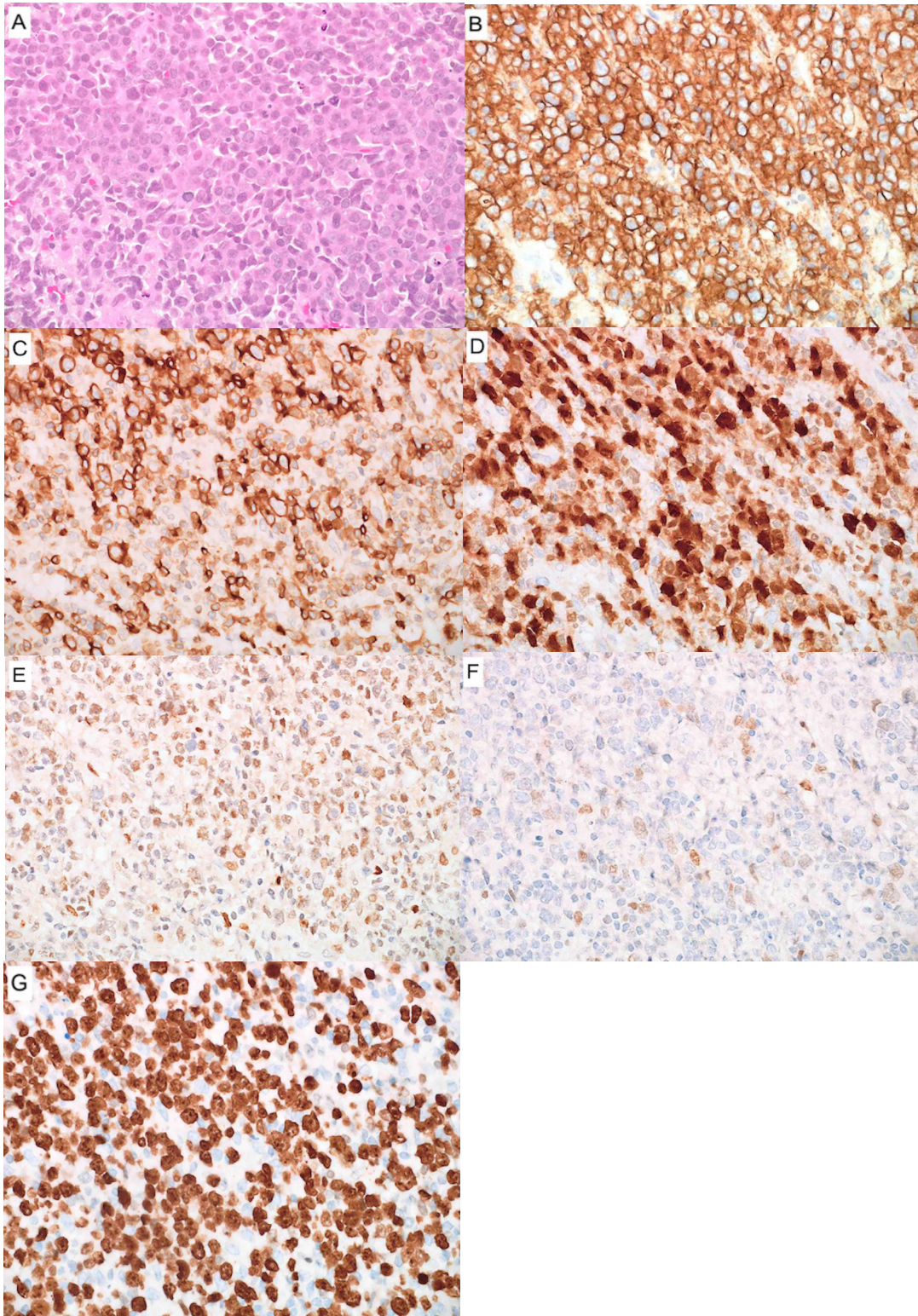


FIG. 2: (A) A photomicrograph showing solid sheets of medium to large atypical lymphocytes. The cells are positive to (B) CD20, (C) BCL2, (D) MUM1 and (E) BCL 6. (F) c-Myc stain shows weak positivity in <20% of cells. (G) Ki-67 index is around 80% (H&E and immunohistochemical stains, magnification x400).

scans showed no evidence of disease and the patient is alive and disease-free after 24 months of follow-up.

DISCUSSION

Primary extranodal NHL of the female genital tract comprises a very rare group of tumours with that of the cervix accounting for 0.2%–0.6% of all NHL.⁶ Most cases are aggressive DLBCL and usually pose a diagnostic challenge when not suspected.⁴ In a review by Mandato *et al.*, the mean age of patients with primary cervical DLBCL was 49.6 years (range = 20–82 years).⁵ Patients may be asymptomatic (12.84%); however, most present with signs and symptoms similar to other gynecological malignancies e.g. abnormal vaginal bleeding (64.22%–70%), perineal discomfort (40%), persistent vaginal discharge (20%), pain (4.59%) or with multiple symptoms (14.68%) and they often lack the “B” symptoms associated with systemic lymphomas (e.g. fever, fatigue, weight loss, and night sweats).^{2,4}

Clinically, primary cervical DLBCL can be polypoid, sessile, or exophytic with or without invasion to the parametria, vagina, or pelvic wall.⁷ Pap smears taken during clinical examinations have limited values as the disease is derived from the cervical stroma with preservation of the lining epithelium especially during the early stages of the disease.⁶ Earlier publications reported that 30–40% of cervical DLBCL patients have a positive Pap smear^{8,9}; however, more recent studies showed that Pap smears are rarely diagnostic (1.39% of all cases) and only in the presence of surface ulceration.^{3,10} When detected in a Pap smear, malignant lymphoma cells are usually seen as large scattered cells (3–4 times the size of a mature lymphocyte), with a round to oval nuclei, a central eosinophilic nucleolus, and scant cytoplasm.¹¹ Scant multinucleated cells mimicking Reed-Sternberg cells were also reported in a case report by Bellevicine *et al.*¹¹

The differential diagnosis of primary cervical DLBCL includes small cell carcinoma, poorly differentiated carcinoma, melanoma, sarcoma, and chronic cervicitis. The assessment of the microscopic features, immunohistochemistry, and flow cytometry can limit the differential diagnosis and exclude most entities; however, one histopathological mimicker proves to be problematic and that is the lymphoma-like lesions of the cervix. First described in 1985, lymphoma-like lesion (LLL) is a term that describes a benign nonspecific florid lymphoid

proliferation that can closely mimic lymphoma.¹² Important diagnostic clues that can differentiate these lesions from primary cervical DLBCL are their superficial distribution and the absence of a gross mass or ulceration.¹² LLL usually has a polymorphous appearance with plasma cells and neutrophils.¹² The mitotic activity is variable both in neoplastic and inflammatory lesions. Unfortunately, light chain restriction and clonal IgH rearrangement do not exclude the diagnosis of LLL. The immunohistochemical evaluation of light chain expression is usually difficult and shows a monotypic pattern in DLBCL and a polytypic pattern in LLL; however, the latter can occasionally present with a monotypic pattern.¹³ Geyer *et al.* identified monoclonal IgH gene rearrangements, *via* polymerase chain reaction, in four (44%) of nine cases of cervical LLL.¹⁴ These results were due to the presence of occasional bands of clonal appearance attributed to clinically irrelevant lymphocytic populations.¹⁴ Thus, the interpretation of these studies should be done with caution and in correlation with the histopathological features and clinical presentation.

The rarity of patients presenting with primary cervical DLBCL lymphoma contributes to the lack of consensus regarding treatment. In one of the largest reviews, Anagnostopoulos *et al.* showed that among 118 patients, 16.8% were treated by chemotherapy, 10.9% had radiation, 9.2% had only surgery and the remaining patients had multiple modalities of treatment. Rituximab was used in 11.7% of patients with no evidence of recurrence in 85.2% of cases (mean follow-up of 40.5 months).⁴ R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) is one of the most commonly used regimens with 70% to 80% of patients obtaining complete remission after completing 6 cycles in Ann Arbor stages I and II.¹⁵ Radiotherapy is usually considered for residual lesions, lesions with incomplete response to chemotherapy, or large tumours (>10 cm).^{5,16} Radical surgery is usually avoided.^{5,16} Infertility is the main concern for patients treated with pelvic radiotherapy and chemotherapy; however, successful pregnancies, within 20- and 72-months following treatment with CHOP, CHOP, and cold knife cone or R-CHOP, have been reported.^{17,18}

The most reproducible prognostic factor for primary cervical DLBCL is the revised international prognostic index; which includes the Ann Arbor stage, number of involved

nodal sites, haemoglobin level, and serum LDH level. Although most cases of primary cervical DLBCL present at stages I or II, bone marrow involvement and central nervous system metastasis have been reported in 20-30% and 5-10% of patients, respectively.^{16,19}

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