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Diffuse large B cell lymphoma of the cervix with rectal involvement

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1. Introduction

Primary non-Hodgkin lymphoma (NHL) of the genital tract is a rare finding accounting for less than 1% of all extra-nodal disease, with that of the cervix accounting for 0.2–0.6% (Chan et al., 2005). Most patients present at a mean age of 46 with vaginal bleeding, a large, bulky cervix on exam, and without the common B symptoms of lymphoma. Cervical cytology is not always helpful as the disease originates from the cervical stroma (Chan et al., 2005). Approximately 70% are diagnosed at Ann Arbor stage I, 22% at stage II, and 8% stage III and above. To date, approximately 120 cases of primary extra-nodal cervical lymphoma have been reported. Diffuse large B-cell lymphoma (DLBCL) subtype is most commonly found at a rate of 30% (Anagnostopoulos et al., 2013). We describe an interesting case by virtue of the unique presentation of this disease and the extent of pelvic organ involvement.

2. Case

A 22 year old G1P1 Hispanic female presented with complaints of left lower extremity edema and rapidly increased abdominal girth with pelvic pain over the past two months. She reported a history of normal menses, except for the most recent which was prolonged. She had no history of abnormal pap smears. Obstetrical history noted a single spontaneous vaginal delivery at term in 2012. Her medical and surgical history was significant for the report of two negative lymph node biopsies (inguinal and cervical neck) performed in Puerto Rico for a reason unknown to the patient.

Physical exam revealed the left lower extremity with +1 pedal and ankle edema, and trace lower leg edema. Right leg was normal, with no calf tenderness bilaterally. Pelvic exam revealed a firm cervix with no gross lesions, upper one third of vagina was firm, indurated nearly circumferentially. Left parametria was firm and 12 cm uterus fixed to left sidewall. Her initial work up was negative for lower extremity deep venous thrombosis. Presenting laboratory values showed a white blood count $9.7 \times 10^3/\text{mm}^3$, hemoglobin 10.5 g/dL, platelets $232 \times 10^3/\text{mm}^3$, and a creatinine of 5.26 mg/dL.

A pelvic CT scan without contrast revealed marked thickening of the cervix and lower uterine segment, bilateral obstructive hydronephrosis and hydroureter, with circumferential thickening of the bladder and inflammatory changes in the left inguinal and femoral region of the left upper thigh. Nuclear renal scan revealed complete absence of left kidney function.

A percutaneous nephrostomy tube was placed in the right kidney to treat the obstruction. An endometrial biopsy and pap smear were also performed and noted secretory endometrium and atypical squamous cells of undetermined significance, human papilloma virus negative, respectively. Colposcopy revealed no lesions and two biopsies of the transformation zone and ECC displayed no evidence of malignancy.

Once her creatinine normalized an MRI with contrast was obtained, revealing a large mass involving the posterior portion of the cervix extending upward toward the body of the uterus for a distance of 6.1 cm and measured 4.1 cm in transverse dimension demonstrating a slight increase in T2 signal with minimal enhancement. The mass extended laterally to the pelvic sidewall, posteriorly into the presacral space and inferiorly making it contiguous with the left lateral wall of the rectum. Bulky left internal iliac adenopathy was also present (Fig. 1).

An exam under anesthesia with loop electrosurgical excisional procedure and vaginal biopsies was performed. Histology revealed diffuse infiltration by large neoplastic lymphocytes. Immunostaining was diffusely positive for pan B-cell markers CD20 and PAX5 with lymphoma cells showing an activated B-cell immunophenotype (CD10 negative; BCL6 and MUM1 positive) using the Hans algorithm. The proliferation index as determined by Ki67 staining was estimated to be 70–80% (Figs. 2, 3). These findings led to the diagnosis of DLBCL.

PET scan displayed FDG activity in the known pelvic mass as well as posterior direct extension into the adjacent rectal wall. Nodal masses were noted lateral to the left side of uterine body and right internal iliac. Bone marrow biopsy was performed, but specimen was insufficient for accurate evaluation, staging her lymphoma at IIE. The patient started chemotherapy within a few weeks of diagnosis. Treatment consisted of

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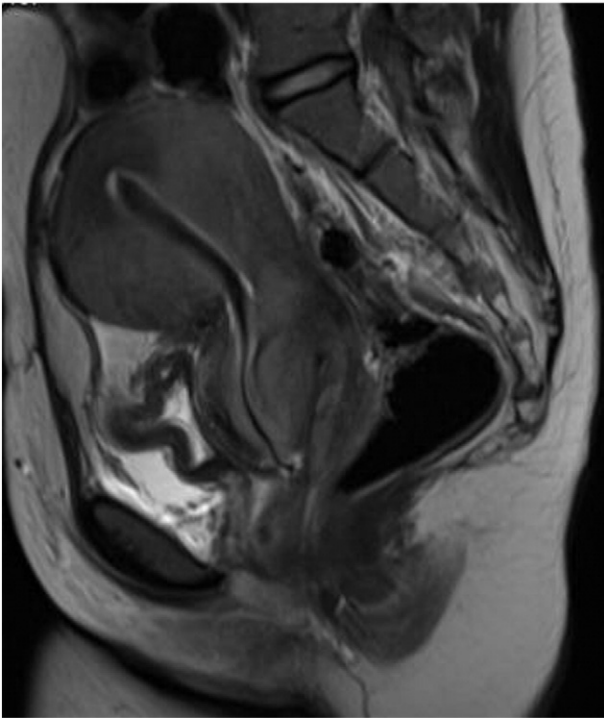E-mail address: elenaigwe@gmail.com (E. Igwe).

Fig. 1. MRI image of large bulky cervix with posterior mass contiguous with wall of rectum.

rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin and prednisone (R-CHOP).

Due to the concern of rectal involvement a gastroenterology workup was initiated. A lower endoscopic ultrasound revealed a hypoechoic mass in the anterior perirectal space. Sonographic evidence suggested invasion into the muscularis propria between 12 and 18 cm from the anal verge. Diagnostic laparoscopy was performed with the intent of performing a diverting colostomy, but due to difficulty mobilizing the descending colon secondary to dense adhesions, a loop ileostomy was performed in order to provide prophylaxis against possible bowel perforation at chemotherapy induction.

Our patient is still undergoing chemotherapy, but has had significant delays in timing of treatments due to numerous hospital admissions for neutropenic fever, pain, and urinary infections. A CT scan during a hospitalization, approximately 3 months after her diagnosis and third cycle of R-CHOP showed significant response as judged by the size and homogeneity of the uterus and cervix. To date she has received 5 of 6 total cycles of R-CHOP. PET/CT after cycle 5 showed no evidence of residual metabolically active tumor in the abdomen or pelvis and no sites of FDG activity to suggest recurrence of nodal or extranodal lymphoma. There is no current plan for radiation treatment.

3. Discussion

This case is very unique and challenging due to its rarity, metastatic location and patient age. Only one case of DLBCL of the cervix presenting with bilateral hydronephrosis in an 82 year old exists in the literature and with no mention of direct rectal invasion (Novotny et al., 2011). This patient is the youngest documented to be affected by the disease (Anagnostopoulos et al., 2013).

The diagnostic challenge is revealed by the similar presentation to squamous cell carcinoma of the cervix with vaginal bleeding, fixed, enlarged uterus and cervix as well as possible parametrial infiltration (Durson et al., 2005). It is very important to differentiate the etiology of the tumor as treatment options are very different between squamous cell/adenocarcinoma of the cervix versus B cell lymphoma, as surgery and
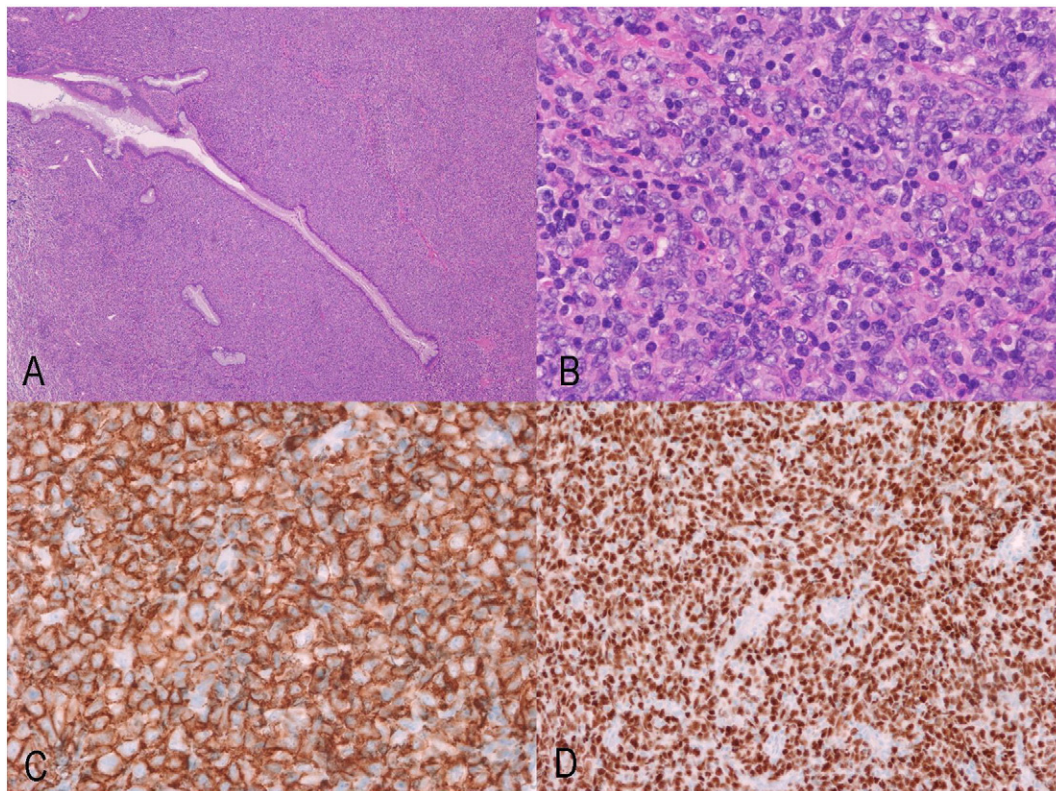

Fig. 2. Diffuse large B-cell lymphoma of the cervix. A. Diffuse infiltration by the tumor cells (H&E, 40×). B. Tumor cells with large vesicular nuclei (H&E, 400×). C. Diffuse membranous staining for CD20 (H&E, 400×). D. Strongly positive PAX5 staining (H&E, 200×).
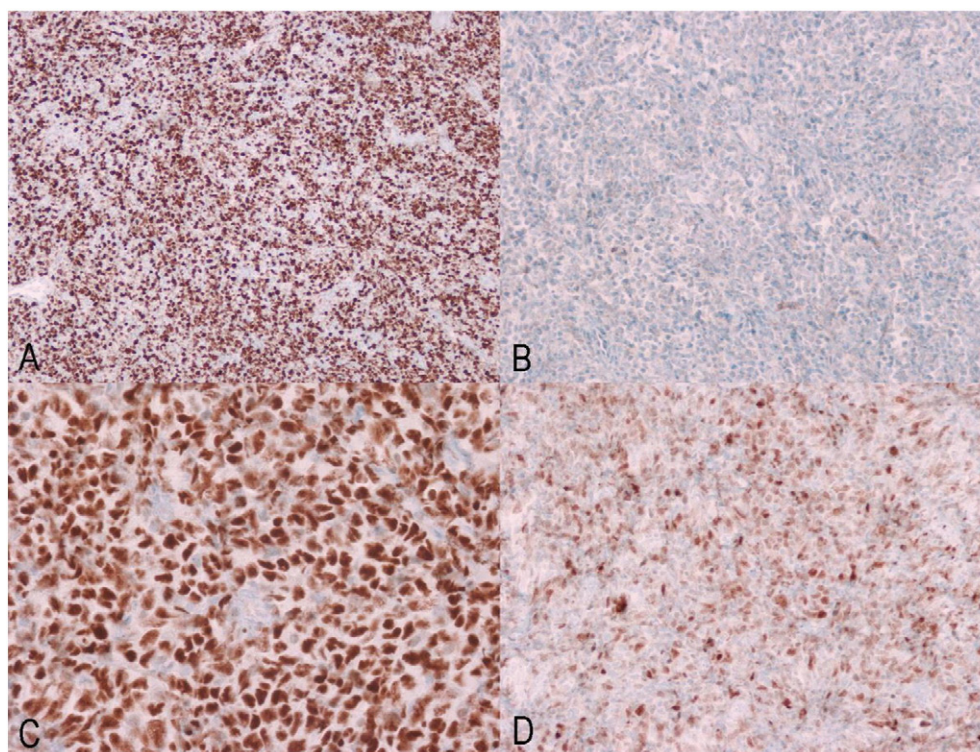
Fig. 3. Diffuse large B-cell lymphoma. A. Proliferation index of 70–80% (H&E, 200×). B. Negative CD10 staining (H&E, 200×). C. Positive BCL6 staining (H&E, 400×). D. Positive MUM1 staining sssH&E, 200×).

radiation are the mainstays of the former and immuno/chemotherapy and at times radiation are of the latter. Cervical lymphoma is differentiated by its lack of involvement of squamous epithelium, therefore making cytology smears generally non-diagnostic. This malignancy arises from the cervical stroma (Anagnostopoulos et al., 2013), and generally requires a deep cervical biopsy for diagnosis. Histopathologic evaluation must be carried out for definitive diagnosis of specific cell type of lymphoma, as was done in our patient.

Given the rare nature of cervical lymphoma, there is no consensus regarding management and all therapies have been extrapolated from other types of non-gynecologic lymphoma. Successful treatments have been reported with the regimen of cyclophosphamide, hydroxydaunomycin, Oncovin and prednisone (CHOP), new immunotherapy rituximab in addition to CHOP (R-CHOP), radiation and surgery. Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen on B-cells, in addition to CHOP has shown, in numerous randomized control trials, to have better overall survival than CHOP alone for non-gynecologic DLBCL (Coiffier et al., 2002). Looking at treatment options specifically for cervical lymphoma, the largest review of cases to date, consisting of 118, showed that 9.2% had surgery only, 16.8% had chemotherapy only, 10.9% had radiotherapy only and the remaining had multi-modal treatment. Rituximab was utilized in 11.7% of cases. No evidence of recurrence was found in 85.2% of patients at a mean follow-up of 40.5 months, with 10 patients died from their disease within 40 months (Anagnostopoulos et al., 2013). Although there is no gold standard for treatment, most treatments involve chemotherapy and have led to acceptable survival data.

Another interesting challenge in our patient is her rectal involvement. The majority of colorectal NHL is secondary to metastasis, with the rectum being a common site (Ghimire et al., 2011). It was decided that our patient would benefit from bowel diversion due to the rare but possible risk of tumor necrosis causing intestinal perforation after chemotherapy induction (Vaidya et al., 2013). There is no consensus whether surgery is indicated in all cases. One investigator reported better outcomes with

surgical resection of lymphomas followed by chemotherapy. Important factors in the decision making process are the intestinal location, extent of disease and pace of disease progression (Zinzani et al., 1997). Our patient's invasive perirectal mass and tumor burden made laparoscopic mobilization of the descending colon at the time of colostomy difficult, so an ileostomy was performed to gain the benefit of diversion while remaining minimally invasive with less morbidity.

Since most cases of this disease are found at a mean age of 46, the consideration of future fertility in this 22 year old primipara was very important. There are few reports in current literature, but successful pregnancies have occurred after cervical lymphoma treatment with CHOP, R-CHOP or CHOP and cold knife cone. These women presented in their late twenties and became pregnant within 20 and 72 months, having uncomplicated full-term deliveries (Parva et al., 2011; Lorusso et al., 2007). With our patient's current treatment regimen of immuno/chemotherapy her fertility is preserved for possible future childbearing.

Although primary cervical lymphoma is a very rare diagnosis, it is important to be on the differential diagnosis as treatment generally leads to a better prognosis than other advanced gynecologic malignancies.

Conflict of interest statement

There are no conflicts of interest by any author.

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