Gynecologic Oncology Reports 22 (2017) 78–81

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Primary, non-germinal center, double-expressor diffuse large B cell lymphoma confined to a uterine leiomyoma: A case report

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ARTICLE INFO

Keywords:
Diffuse large B cell lymphoma
Uterine leiomyoma
Double-expressor lymphoma

1. Introduction

Approximately two thirds of cases of non-Hodgkin's lymphoma (NHL) are nodal (arising from lymph nodes, spleen or bone marrow), while 1/3 arises from extranodal sites, with the most common being the GI tract, skin, bone and brain (Barbara Vannata, 2015). Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype among extranodal lymphomas, accounting for about 50% according to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (Barbara Vannata, 2015).

Though the female genital tract is commonly involved in disseminated lymphoma, primary lymphomas of the female genital tract are rare, accounting for 0.2–1.1% of extranodal lymphomas (Dimitrios Nasioudis et al., 2017). A SEER database study identified 697 cases reported from 1988 to 2012, with the ovary being the most common primary site (36%) and only 75 (12.8%) reported cases of DLBCL of the uterus (Dimitrios Nasioudis et al., 2017). Primary uterine lymphomas most often develop in the endometrial stroma (Mari Kasai et al., 2015) or involve the cervix (Vincenzo Dario Mandato et al., 2014). We present a unique case of a primary, non-germinal center, double-expressor diffuse large B cell lymphoma confined to a leiomyoma of the uterus.

2. Case report

A 69-year-old white female was referred to gynecologic oncology for an incidental finding of a complex ovarian mass on CT scan for follow-up of pulmonary nodules. It was described as a complex right adnexal cyst measuring 6.8 cm with cystic and fatty components consistent with a dermoid cyst without evidence of lymphadenopathy. Uterine fibroids were noted (Fig. 1). Her past medical history was significant for type II diabetes mellitus and intermittent atrial fibrillation, controlled on Glimepiride and Metoprolol, respectively. She had a small bowel resection with primary reanastomosis for microperforation of small bowel mesentery 2 years previously. Pathology showed small bowel necrosis and abscess consistent with perforation. Three lymph nodes were benign with no evidence of lymphoma.

On presentation, she was without complaint. She denied abdominopelvic pain or bloating, postmenopausal bleeding, early satiety, unintentional weight loss and changes in bowel or bladder habits. On exam, she was afebrile and her BMI was 24.8 kg/m^2. Her abdomen was non-tender. On bimanual exam, her uterus was 9 cm with irregular contour and a mobile, non-tender 8 cm mass was noted in the right adnexa. Her Ca-125 was 33 U/mL. Complete blood count (CBC) and comprehensive metabolic panel (CMP) were normal. Pap smear was negative for intraepithelial lesion. The differential diagnoses, including benign verses malignant ovarian neoplasm and uterine fibroids with remote chance of malignancy, and options for surgical management including unilateral or bilateral adnexectomy with or without hysterectomy were discussed with the patient.

She opted for total robotic hysterectomy, bilateral salpingo-oophorectomy. Surgical findings included a smooth, 8 cm right ovarian mass, normal left adnexa, and a fibroid uterus with one large, smooth anterior pedunculated uterine mass. Grossly, the uterine mass was a 136-gram, 10.0 × 8.0 × 5.8 cm, white-tan whorled nodule. Sectioning revealed a 2.5 cm focal area of degeneration. Frozen section showed benign uterine fibroid with myxoid changes.

3. Pathologic findings

Final pathology showed multiple benign uterine fibroids and a right ovarian serous cystadenoma. Cervix, bilateral fallopian tubes, and left ovary were without significant pathology. Final histology of the

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http://dx.doi.org/10.1016/j.gore.2017.10.003
Received 27 July 2017; Received in revised form 14 October 2017; Accepted 16 October 2017
Available online 18 October 2017

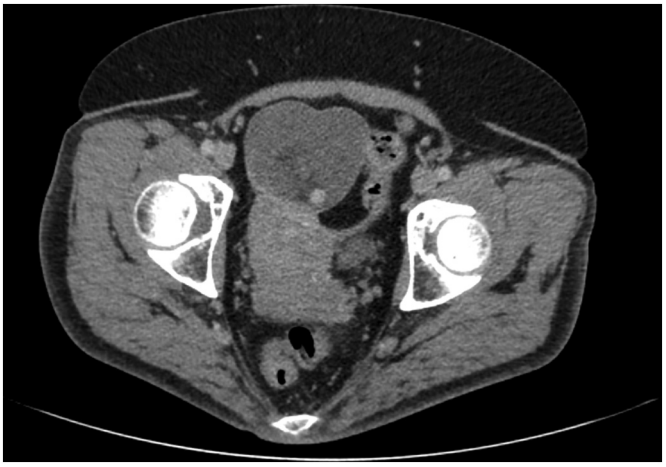

Fig. 1. Preoperative CT scan showing 6.8 cm mass anterior to the uterus.

pedunculated uterine mass showed a uterine leiomyoma with an abnormal localized nodule of lymphocytic infiltrate consisting of large atypical lymphocytes with large nuclei, pleomorphic forms, prominent nucleoli, brisk mitotic activity, and increased apoptosis (Fig. 2).

The tumor immunophenotype (Table 1) (Bancroft, 2008) supports the diagnosis of non-germinal center diffuse large B-cell lymphoma, according to National Comprehensive Cancer Network (NCCN) guidelines (Guidelines®) NCPGiON, 2017) and the Hans algorithm (Christine et al., 2004). In-situ hybridization for Epstein-Barr virus was negative. Forty-percent of cells were positive for c-MYC immunoreactivity, making it a double-expressor, with overexpression of BCL2 and c-MYC (Fig. 3).

4. Follow-up

Fluoro-deoxyglucose Positron Emission Tomography (F18-FDG-PET) skull base to mid thigh with CT for attenuation correction was performed 2 weeks post-operatively with no hypermetabolic activity seen to suggest residual or recurrent disease, giving her the final diagnosis of stage IE (Ann Arbor) primary non-germinal center, double-expressor DLBCL in a uterine leiomyoma. Given the aggressive nature of this neoplasm, she was referred to medical oncology with plans for 3 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). She is currently undergoing treatment and tolerating it well.

5. Discussion

Primary lymphoma of the female genital tract is rare, accounting for 1% of extranodal lymphomas (Dimitrios Nasioudis et al., 2017). DLBCL is the most common histologic subtype (Dimitrios Nasioudis et al., 2017). The most common sites of occurrence are the ovary (Dimitrios Nasioudis et al., 2017) and cervix (Vincenzo Dario Mandato et al., 2014). Primary DLBCL of the uterine corpus is exceedingly rare with only 75 cases identified by the SEER database in a 24-year period (Dimitrios Nasioudis et al., 2017).

Primary uterine lymphoma is difficult to diagnose preoperatively. Clinically, it often presents with abdominopelvic pain, distention, vaginal bleeding or discharge, urinary or GI symptoms (Dimitrios Nasioudis et al., 2017; Mari Kasai et al., 2015; Vincenzo Dario Mandato et al., 2014). Constitutional, “B” symptoms classically associated with NHL such as fever, night sweats and weight loss are less commonly associated with extranodal disease. As in our patient, it is asymptomatic in up to 11% of cases (Asima Kaleem Ahmad et al., 2014). There are no characteristic imaging patterns that can aid in distinguishing lymphomas from more common gynecologic malignancies (Dimitrios Nasioudis et al., 2017). However, some reports suggest contrast MRI can show a hypovascular hypointense mass on T-1 weighted imaging and moderate signal intensity on T-2 images with preservation of underlying zonal architecture (Asima Kaleem Ahmad et al., 2014).

It is difficult to distinguish a primary uterine neoplasm from uterine involvement of advanced stage disease (Lianhua Zhao et al., 2016). Methods have been created for assessing primacy of a particular lymphoma. This case meets the four diagnostic criteria for primary uterine lymphoma as set forth by Fox, et al.: 1) the disease process was clinically confined to the uterus at the time of initial diagnosis; 2) full investigation failed to reveal any evidence of disease elsewhere in the body; 3) the blood count showed no evidence of leukemia; and 4) if further lymphomatous deposits occurred at sites removed from the genital tract then a time interval of at least several months should have elapsed between the appearance of primary and secondary tumors (Fox & JRSM, 1965).

There are no guidelines regarding treatment of primary uterine lymphoma. Though surgery is not recommended, most cases are diagnosed following surgery for presumed gynecologic malignancy, which is likely due to the rarity of the disease and difficulty in making the diagnosis (Dimitrios Nasioudis et al., 2017). A standard chemotherapy regimen, such as R-CHOP, is typically administered with mean overall survival of 45.9 months in one review (Vincenzo Dario Mandato et al., 2014).

There are 2 subtypes of DLBCL, which correspond to the tumor's cell of origin and play a significant role in prognostication. Germinal center DLBCL has a gene expression profile that fits closely with a normal germinal center-derived B cell and portends a better prognosis than non-germinal center DLBCL, where gene expression profiling is closer to a normal activated B cell (Sonali & Smith, 2017). The Hans algorithm allows for prediction of the cell of origin and thus, survival via immunohistochemistry (Christine et al., 2004).

The t(8;14) translocation in which MYC is rearranged is classically associated with Burkitt lymphoma, but can also be seen in DLBCL. The t(14;18) translocation involving rearrangement in BCL2 is associated with drug resistance and a poorer prognosis (Sonali & Smith, 2017).

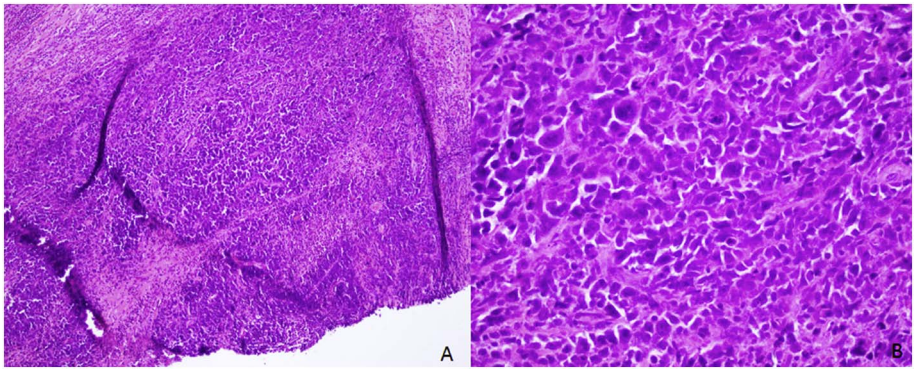

Fig. 2. Histologic features of tumor. A) Low-powered view of neoplastic cells. B) Higher-powered view showing large, atypical lymphocytic infiltrate with large nuclei, pleomorphic forms, prominent nucleoli and brisk mitotic activity.

Table 1
Description of immunohistochemical studies performed and their significance.

Marker	Description	Status in our patient	Significance
CD45	Pan-leukocyte antigen	+	Indicates lymphocytic origin
CD20	Pan-B-cell antigen	+	Indicates B-cell origin
CD19	B-cell antigen	+	Indicates B-cell origin
CD30	Tumor necrosis factor receptor; lymphocyte activation antigen	−	Used in diagnosis of Hodgkin's lymphoma
BCL6	Germinal center marker	+	May be positive in T-cell, Burkitt, DLBCL, Follicular, and Hodgkin's lymphomas
BCL2	Proto-oncogene; prevents cells from undergoing apoptosis	+	May be positive in Follicular, Burkitt, DLBCL, Hodgkin's, Mantle Cell, and Marginal Zone lymphomas
Multiple Myeloma 1 (MUM1)	Intra- and post-germinal center B-cell marker	+	Helps distinguish between germinal center and non-germinal center DLBCL
CD10	Cell membrane metallopeptidase; germinal center marker	−	May be positive in germinal center DLBCL, Burkitt, Follicular, Hairy cell lymphomas. Occasionally expressed in uterine smooth muscle tumors
Ki-67	Labile, non-histone nuclear protein. Marker of cell proliferation	+ (90%)	Higher nuclear staining indicates more aggressive tumor
CD3	pan-T-cell antigen	−	Indicates T cell origin of lymphocytes
Smooth muscle actin (SMA)	Expressed by smooth muscle cells	−	Indicates smooth muscle origin
Desmin	Expressed by smooth muscle cells	−	Indicates smooth muscle origin
Murine Double Minute 2 (MDM2)	Protein that inhibits p53	−	Amplified in liposarcoma
S100	Cytoplasmic EF-hand Ca2 + -binding protein	−	Marker of neural tissue and melanocytic differentiation
Cytokeratin AE1/AE3	Keratin marker	−	Used to identify epithelial tissue

According to the revised World Health Organization (WHO) classification of lymphoid neoplasms published in 2016, the concurrent overexpression of the MYC and BCL2 proteins is termed a “double-expressor” lymphoma, occurs in 20–35% of cases, and has been associated with worse outcomes (Swerdlow et al., 2016). However, overexpression of oncogenic proteins alone does not cause DLBCL and t(8;14) has been observed in healthy individuals, suggesting other mechanisms, such as environmental exposures associated with lymphogenesis (Qingqing Cai et al., 2015). Though family members of patients with NHL have a 1.7-fold increased risk of developing NHL (James & Cerhan, 2015), gene expression profiles are heterogeneous and a heritable pattern has not been clarified (Wang et al., 2007). Providers may consider a genetics referral, but surveillance of family members is not recommended (James & Cerhan, 2015).

Most cases of primary uterine DLBCL originate in the endometrial stroma (Mari Kasai et al., 2015). The finding of a DLBCL within a uterine leiomyoma has only been reported once previously. Zhao, et al. described a 73-year-old woman with a 17 cm uterine mass who underwent hysterectomy, bilateral adnexectomy and received a diagnosis of stage IE (Ann Arbor) primary DLBCL arising from a uterine leiomyoma with tumor extending into the adjacent myometrium, including an intravascular tumor thrombus. Though a complete CT or PET scan was not available to confirm lack of disease elsewhere, the patient did not progress within a follow-up period of greater than 1 year, despite having no adjuvant therapy (Lianhua Zhao et al., 2016). As with our case, this tumor expressed BCL2, CD20, MUM1, and displayed a high proliferative index with 50% staining of Ki-67 (Lianhua Zhao et al., 2016). However, immunohistochemical studies of the tumor in our case

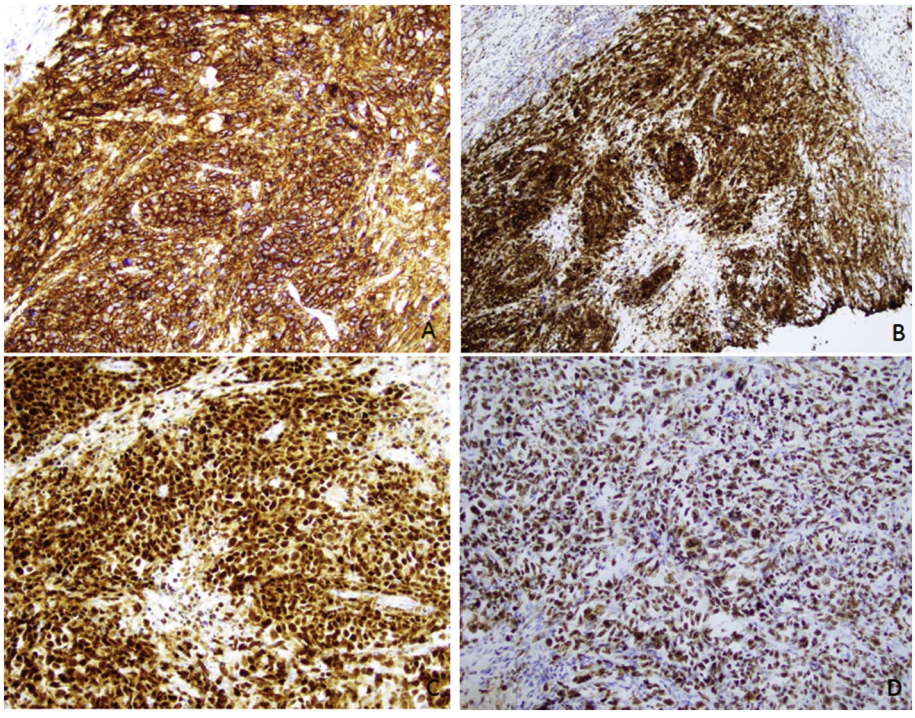

Fig. 3. Immunohistochemical features. Neoplastic cells positive for A) CD20, B) BCL2, C) MUM1, mD) Ki-67.

also revealed a higher proliferative index, BCL2, BCL6 and c-MYC positivity, making it a double-expressor lymphoma.

To our knowledge, this is the second report of a primary DLBCL in a leiomyoma and the first of a double expressor non-germinal center DLBCL confined to a uterine leiomyoma.

This diagnosis should be considered when forming a differential for other gynecologic pathology. Our aim is to increase provider awareness of this rare disease, highlight the need for better diagnostic techniques allowing for a more timely diagnosis, formulation of an appropriate treatment plan, and avoidance of unnecessary surgery.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors declare no conflicts of interest.

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