Primary endometrial B-Cell lymphoma: Rare etiology of abnormal uterine bleeding and potential nonsurgical therapy

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We present a case of primary endometrial B-cell lymphoma, pathologically confirmed. The patient is a 68-year-old female with postmenopausal bleeding. Ultrasound revealed endometrial thickening and was followed up with endometrial biopsy. F18-FDG PET, performed for staging, demonstrated abnormally increased radiotracer uptake isolated to the endometrium. The patient was treated with chemotherapy (R-CHOP) and external-beam radiation. Endometrial activity was resolved on post-treatment followup F18-FDG PET. Primary endometrial lymphoid neoplasms are extremely rare (approximately 2% of extranodal lymphoid neoplasms); even rarer is primary B-cell lymphoma. To our knowledge, this is the first reported case of a successful treatment of endometrial lymphoma using external-beam radiation and chemotherapy in a patient who did not receive hysterectomy.

Case report

Our patient, a 68-year-old Caucasian female, had a 4-to-6-week history of postmenopausal vaginal bleeding requiring more than 2 pads per day. Pelvic ultrasound demonstrated uterine prominence (8.6 cm x 6.1 cm x 4.9 cm) with thickening of the endometrial complex (1.2 cm), as well as uterine fibroids (Fig. 1). An endometrial biopsy demonstrated diffuse large B-cell lymphoma, CD-20 positive (Fig. 2). FDG-18 PET/CT of the skull to mid-thigh, performed for staging, demonstrated moderate FDG uptake within the uterine endometrium with an SUV max of 4.0 (Fig. 3). No other FDG-avid foci were evident. Bone-marrow biopsy was morphologically and immunophenotypically negative for involvement by large B-cell lymphoma.

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Figure 1. A. Sagittal endovaginal grayscale sonographic image demonstrates endometrial thickening of 1.16 cm. B. Sagittal endovaginal color Doppler image does not demonstrate increased vascular flow.
The patient underwent three cycles of systemic chemotherapy with combination Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone (R-CHOP), followed by external-beam radiation therapy totaling 40Gy, delivered in 20 fractions.

A followup FDG-18 PET-CT scan 5 months after treatment was negative (Fig. 4). As of nine months post therapy, the patient remains asymptomatic and without signs of recurrence.

Discussion

Primary, aggressive Non-Hodgkin’s lymphoma (NHL) of the uterus is an exceedingly rare cause of postmenopausal bleeding, and there are few studies evaluating its management. Past literature has suggested the use of radical hysterectomy as a curative option for uterine NHL, but there remains limited data on the success of nonsurgical methods (1-2). With respect to nonuterine NHL, chemotherapy with adjunctive external beam radiation has been proven effective, and is the standard of treatment (3-5). Our patient demonstrates the potential for a nonsurgical, chemotherapy- and radiation-based approach to curative uterine NHL treatment.

The differential diagnosis for a patient with postmenopausal bleeding includes endometrial atrophy (the most common cause), endometrial polyps, submucosal fibroids, endometrial hyperplasia, endometrial carcinoma, and estrogen withdrawal (6). At present, the American College of Obstetrics and Gynecology (ACOG) states that any patient with postmenopausal bleeding should receive malignancy workup with either endometrial biopsy or pelvic ultrasound (7). Reports comparing sonographic endometrial thickness to biopsy results in postmenopausal patients have demonstrated that an endometrium of less than 4-5mm has a negative predictive value for malignancy of greater than 99% (4, 5, 8).

Figure 2. A. H&E-stained biopsy photomicrograph with cellular atypia. B. Endometrial biopsy photomicrograph with CD-20 specific stain.

Figure 3. A. Sagittal fusion 18FDG PET/CT demonstrating focal increased activity within the endometrium. Incidental note is made of benign excreted FDG tracer in the bladder to the right of the uterus. B. Coronal fusion 18FDG PET/CT demonstrates focal increased activity within the endometrium.

Levine et al evaluated endometrial thickness and its changes in postmenopausal patients using hormone replacement therapy (HRT) over a three-year period. They evaluated those patients on unopposed estrogen therapy, combined continuous estrogen and progesterone therapy, and sequential estrogen and progesterone therapy (estrogen is taken for days 1-25 and progesterone is taken on days 10-25), and then compared these groups to a control group of patients not on HRT. The mean endometrial thicknesses were 5mm (+/- 2.9mm) in the control group, 6.6mm (+/- 4mm) in the continuous unopposed estrogen group, 6.2mm...
(+/−2.4) in the dual therapy group, and 8.3mm (+/−3.9mm) in the sequential therapy group. Additionally, they recorded thickness changes during the study: 1-4mm (mean 2mm) in the control group, 0-6mm (mean 2mm) in the continuous estrogen group, 1-9mm (mean 3mm) in the continuous combined therapy group, and 0-13mm (mean 4mm) in the sequential therapy group (9).

Levine et al. did not establish guidelines regarding when to biopsy the presumably thickened endometrium. Instead, the biopsy decision was left to the discretion of the managing physician and patient. Levine et al. concluded that follow-up pelvic ultrasound should be performed before biopsy in patients without atypical uterine bleeding and in patients on sequential hormones because of the normal physiologic endometrial changes. If the repeated exam still demonstrated thickness >8mm, then biopsy would be indicated. In patients on other hormone regimens, an endometrial thickness >8mm should be viewed as atypical, with biopsy indicated. Abnormal uterine bleeding with an endometrial thickness of 5-8mm should call for biopsy as well. In the absence of uterine bleeding, an endometrium of 5-8mm is considered probably normal (9).

The role of PET/CT in the initial evaluation of a primary endometrial malignancy is limited, as staging of endometrial cancer is primarily performed surgically: endometrial biopsy, total abdominal hysterectomy, salpingooopherectomy, pelvic and para-aortic lymph-node dissection, and peritoneal cytology (10). FDG PET is primarily used to evaluate for the extent of disease. Use of CT and MRI for assessment of lymph-node involvement is unreliable (10). Grisby et al were able to detect pelvic and para-aortic lymph-node metastasis with a sensitivity of 60% and a specificity of 98% in patients with uterine corpus malignancy (10). Saga et al evaluated the use of FDG PET in postoperative patients with endometrial cancer for recurrence of disease or response to therapy and showed that, when coupled with anatomic information from CT or MRI, the sensitivity of FDG PET was 100% and the specificity was 88%. Additionally, FDG PET had a high negative predictive value for exclusion of recurrence (11).

Since primary endometrial lymphoma is rare, a clinical dilemma one will likely encounter when interpreting FDG PET is nonspecific endometrial activity. Lerman et al. evaluated 285 pre- and postmenopausal patients to determine normal and abnormal endometrial and ovarian uptake of F-18 FDG. They found that in premenopausal patients, SUV were 5+/−3.2 (SD) and 3.7+/−0.9 during menstruation and ovulating phases, respectively. The proliferative and secretory phases were 2.6+/−1.1 and 2.5+/−1.1 SUV, respectively. The mean SUV in postmenopausal patients was 1.7+/−0.7. Therefore, increased endometrial activity in postmenopausal patients should be viewed as suspicious for malignancy (12).

Kitajima et al. reviewed FDG PET/CT findings in benign and malignant tumors (uterine cervical cancer, endometrial cancer, leiomyosarcoma, and other sarcomas such as endometrial stromal and uterine carcinosarcoma). Benign tumors generally show mild FDG uptake, for which the authors gave an example of faint FDG activity with an SUV of 2. Activity in leiomyomas was seen in 10.4% of premenopausal patients and in only 1.2% of postmenopausal patients. Factors causing increased leiomyoma activity include those affecting normal endometrial activity in the premenopausal patient, as well as vascularity, cellularity, and inflammation. Adenomyosis is most affected during menstruation and ovulation. Additionally, endometrial hyperplasia can also demonstrate mildly increased activity. In general, malignant tumors demonstrate increased FDG activity. Exceptions to this include small tumors, beyond the spatial resolution of PET imaging, and those of low cellularity. High FDG activity can be seen in cervical cancers (squamous cell) with a mean SUV of 11.4, endometrial cancer with a mean SUV of 11.2+/−5.9, leiomyosarcoma with a mean SUV 6.4+/−4.3, and other malignancies such as metastatic tumors, which also generally show intense FDG uptake. Because there is a potential overlap between leiomyosarcoma and leiomyoma, FDG PET cannot be used to differentiate between the two (13).

Conclusion

Primary, aggressive Non-Hodgkin’s lymphoma (NHL) of the uterus is a rare cause of postmenopausal bleeding and has imaging characteristics overlapping with other uterine malignancies. We report this case to broaden the differential diagnosis of abnormal endometrial thickening and to highlight a nonsurgical-based treatment for primary NHL of the endometrium.

References


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