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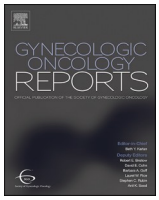

Case series

Primary gynecologic lymphoma when diagnosed by a gynecologist: A case series

Alexandra J. Lamacki [a], Caroline Montag [b], Elizabeth Kertowidjojo [c], S. Diane Yamada [d], Katherine C. Kurnit [d,*]

[a] University of Chicago Medical Center, Department of Obstetrics and Gynecology, Chicago, IL, USA
[b] University of Chicago, Pritzker School of Medicine, Chicago, IL, USA
[c] University of Chicago Medical Center, Department of Pathology, Chicago, IL, USA
[d] University of Chicago Medical Center, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Chicago, IL, USA

A B S T R A C T

Introduction: Primary lymphomas of the gynecologic tract are a rare pathology that may present with typical gynecologic symptoms. Unlike other gynecologic malignancies, surgical management is not considered an essential part of the treatment regimen for gynecologic lymphomas but may be required for diagnosis. The purpose of this series is to report on symptom presentation and management from the gynecologic specialist's perspective.
Methods: Records from an institutional pathology database identified patients diagnosed with primary gynecologic lymphoma between 1993 and 2023.
Results: Eight patients were identified for this series. Patients presented with pelvic pain, abnormal vaginal bleeding, and/or a mass on pelvic exam. The majority were diagnosed with lymphoma only after surgical resection. The most common pathology was diffuse large B-cell lymphoma (DLBCL). Seven of the eight patients received chemotherapy, which was administered by a medical oncologist.
Conclusions: Our series highlights the presentation, diagnostic workup, and management of gynecologic lymphomas with attention to the role of surgical management and intraoperative pathologic evaluation as well as medical treatment of these cancers after surgical debulking.

1. Introduction

Lymphomas of the female genital tract are a rare entity constituting less than 1 % of all non-Hodgkin lymphoma cases (Crump et al., 2017; Li et al., 2018). As surgical management is the standard of care for many gynecologic malignancies, gynecologic lymphomas are typically diagnosed on evaluation of resected specimens. However, surgical resection has limited utility in the management of most lymphomas (NCCN Clinical Practice Guidelines, 2024). Management more frequently includes multi-agent chemotherapy and possibly radiation, with surgical resection only indicated in clinical scenarios such as presence of certain gastric and splenic lymphomas (NCCN Clinical Practice Guidelines, 2024; Weledji and Orock, 2015). Therefore, gynecologic cancer treatment algorithms used for more common gynecologic malignancies typically do not apply.

In this series, we focus on the presentation, diagnosis, and treatment of primary gynecologic lymphomas specifically diagnosed by a gynecologic specialist to highlight the role that gynecologic specialists may play in the diagnosis and treatment of these rare tumors.

2. Methods

This is an IRB-approved case series (IRB23-0040), and the requirement for consent was waived. Patients with a lymphoma involving the female genital tract diagnosed between January 1, 1993 to December 31, 2023 were identified by the University of Chicago Medical Center Pathology Department. Patients who underwent assessment and workup by a gynecologic specialist that ultimately led to the diagnosis of a primary female genital tract lymphoma were included. The electronic medical record was reviewed to identify patient demographics, pathology results, and clinical course. Cases were then reviewed by a gynecologic pathologist (EK) to confirm the diagnosis. The World Health Organization (WHO) classification of lymphomas was used (Swerdlow et al., 2016).

3. Results

A total of 8 patients with primary gynecologic lymphomas who initially presented to a gynecologist for their workup were identified between 1993 and 2023. A summary of all cases is provided in Tables 1,

* Corresponding author at: University of Chicago, 5841 S. Maryland Ave., MC205, Chicago, IL 60637, USA.
E-mail address: kkurnit@bsd.uchicago.edu (K.C. Kurnit).

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2, and 3. Age at presentation ranged from 38 to 73 years old (median 45 years, interquartile ratio 19.5 years). Time between last treatment and most recent follow up ranges from 1-20 years (median = 2 years).

On presentation, most patients presented with pelvic pain (B, C, D, E, H) and/or abnormal vaginal bleeding (B, C, G). Two patients were managed for presumed fibroids (C, F), and one was managed for an abnormal pap smear (A). Three patients (C, E, F) had a mass on bimanual exam while Patient B had a cervical mass on exam. Two patients (B, G) underwent biopsies which led to a diagnosis of diffuse large B cell lymphoma (DLBCL) of the cervix (B) and uterus (based on endometrial sampling (G). The remainder of patients were diagnosed after surgical resection and debulking procedures. A LEEP specimen for Patient A raised concern for lymphoma, but further tissue from surgical resection was required to confirm the diagnosis.

Of the seven patients who were managed surgically (including patient G who had persistent vaginal bleeding symptoms after systemic treatment for lymphoma), six had hysterectomies and bilateral salpingo-oophorectomies (BSO), one of which was done minimally invasively (A). Patient H had an open oophorectomy and pelvic wall mass resection without hysterectomy. Patients C and F were undergoing surgery for management of presumed fibroids, but then underwent more extensive procedures given intraoperative concern for malignancy due to appearance of invasive disease intraoperatively. Four patients had lymph node dissection (A, C, E, and F), and one required a bowel resection (C). Intraoperative frozen pathology was performed for two patients (C and D) and was reported as malignant epithelioid neoplasm and blue cell tumor, respectively.

Table 1
Initial presentation and imaging findings of patients with gynecologic lymphoma.

Case	Age at diagnosis (years)	Presenting symptoms	Imaging modality	Imaging findings
A	65	Abnormal pap smear	PET	Hypermetabolic cervical lesion and a pelvic lesion
B	44	Pain, bleeding, mass on exam	CT, MRI	9 cm cervical mass involving upper third of vagina, pelvic and inguinal lymphadenopathy, bilateral hydronephrosis, parametrical involvement and possible invasion into bladder and rectosigmoid
C	42	Pain, bleeding, mass on exam – presumed fibroids	TVUS	Globular uterus of average size
D	73	Pain	CT	Large, heterogenous pelvic mass, abdominal lymphadenopathy, and encasement of mesenteric vessels
E	46	Mass on exam, pain	TVUS, CT	13 cm heterogenous pelvic mass involving right adnexa, aortocaval lymphadenopathy
F	40	Mass on exam – presumed fibroids	TVUS	No specific findings in available records
G	56	Bleeding	TVUS, PET	Small pulmonary nodules, enlarged lymph node near the hepatoduodenal ligament with mass effect on the liver and pancreas, thickening of the ileum.
H	38	Pain	CT	Large pelvic mass without further description in available records

CT – computed tomography; MRI – magnetic resonance imaging; PET – positron emission tomography; TVUS – transvaginal ultrasound.

On final diagnosis, five patients had DLBCL, one (A) had low-grade B cell lymphoma (BCL), one (D) had BCL, and one had follicular lymphoma (F). Patients had stage II disease (n = 4), and stage IV disease (n = 4). The most common sites of disease were one or both ovaries (n = 6), lymph nodes (n = 6), and the cervix (n = 5). Other sites included the uterus (n = 3), parametria (n = 2), bones (n = 2, noted on PET scan), as well as the bowel, stomach, vagina, pelvic side wall, and gluteal fat (all n = 1). A variety of lymph nodes were involved including pericaval, common iliac, pelvic, and inguinal nodes.

All patients in our series except one received systemic chemotherapy under the care of a medical oncologist. Patient A was recommended for observation based on low grade lymphoma and limited disease spread. The most common chemotherapy regimen utilized was R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) which three patients received (C, E, and F). Two (G and H) received CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone), and two (B and D) received DA-R-EPOCH (dose adjusted rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin). Two of these patients also received intrathecal methotrexate for central nervous system prophylaxis (C and D). Five patients received a total of six cycles of their chemotherapy regimen. Patient F was switched to another chemotherapy regimen after progression was noted on imaging after two cycles of R-CHOP, and Patient H received eight cycles of CHOP and radiation to the right lower pelvis. No other patients received radiation. Patient B was offered radiation therapy but declined.

Three patients had complete response to chemotherapy and had NED (no evidence of disease) at time of last follow-up. One of these patients had stage II disease (B), and the other two had stage IV disease (C and E). Patient A who did not receive chemotherapy also had NED at last follow-up. Three patients had progression of disease on their first line of chemotherapy (F, G, and H). All of these patients later underwent autologous peripheral blood stem cell transplant (APBSCT). Patient F tolerated the transplant and had NED at time of last follow-up. Patient G tolerated the transplant but developed recurrent disease. Patient H developed Aspergillus pneumonia during the myeloablative treatment phase and subsequently died. One patient (D) had a recurrence two years after initial chemotherapy. She underwent additional chemotherapy with progression of disease on two regimens and a complete response on the third. She is four years without evidence of disease at the time of her last follow-up. Of note, patients received their chemotherapy under the care of a medical oncologists, and they all continued to also see a gynecologic oncologist for physical exams for surveillance.

4. Discussion

The patients in this series all presented with common gynecologic concerns: pelvic pain, abnormal uterine bleeding, mass related symptoms, or an abnormal pap test. DLBCL is the most common gynecologic lymphoma in both the literature (Crump et al., 2017; Li et al., 2018) and this case series (n = 5/8). About 33 % of patients with DLBCL present with constitutional symptoms (i.e., fevers, fatigue, night sweats) and progressive lymphadenopathy (Caimi et al., 2016). However, these symptoms were absent amongst the patients in this series. Interestingly, two other patients in our institution's pathology database who were ultimately diagnosed with a primary gynecologic lymphoma first presented with non-gynecologic symptoms: one with fatigue and fevers, and the other with weakness and sensory loss due to leptomeningeal spread of an ovarian DLBCL. These patients were therefore referred to and evaluated primarily by Medical Oncology. This observation underscores the diversity of presentations for gynecologic lymphomas.

On examination and imaging, two patients had cervical masses (A, B), one had an endometrial lesion (G), and the remaining five patients had complex pelvic masses involving the uterus and adnexal structures. Currently, there are no specific imaging findings that can be considered characteristic of lymphomas on the typical radiologic modalities (e.g.,

Table 2
Surgical procedures and tissue diagnosis of primary gynecologic lymphomas.

Case	Source of tissue for diagnosis	Procedures	Intraoperative pathology	Diagnosis	Sites
A	LEEP, surgical specimen for additional tissue	RA-TLH/BSO, left pelvic LN dissection	N/a	Low grade BCL, stage II	Cervix, right ovary, common iliac lymph LN
B	Cervical biopsy	–	N/a	DLBCL, stage II (bulky)	Cervix, vagina, pelvic and inguinal nodes
C	Surgical specimen	Radical hysterectomy, BSO, pelvic LND, rectosigmoid resection with anastomosis, debulking	Malignant epithelioid neoplasm	DLBCL, stage IV (bulky)	Cervix, uterus, ovaries, parametria, pelvic LN, rectum, stomach, gluteal fat, multiple osseous lesions
D	Surgical specimen	TAH/BSO, tumor debulking	Blue cell tumor	BCL, stage IV (bulky)	Cervix, ovaries, peritoneum, multiple osseous lesions
E	Surgical specimen	TAH/BSO, omental biopsies, LND	N/a	DLBCL, stage IV (bulky)	Right fallopian tube, ovary, uterus, pericaval LN
F	Surgical specimen	TAH, BSO, LND, debulking	N/a	Follicular center lymphoma, stage II (bulky)	Cervix, left ovary, fallopian tube, parametria, pelvic LN
G	Dilation and curettage (in OR)	(After chemotherapy) TAH/BSO for persistent bleeding	N/a	DLBCL, stage IV	Uterus, pulmonary nodules, diffuse LN involvement
H	Surgical specimen	Laparotomy, oophorectomy, pelvic wall mass resection, appendectomy	N/a	DLBCL, stage II (bulky)	Ovary, fallopian tube, pelvic side wall

BCL – B cell lymphoma; BSO – bilateral salpingo-oophorectomy; DLBCL – diffuse large B cell lymphoma; LEEP – loop electrosurgical excision procedure; LN – lymph node; LND – lymph node dissection; OR – operating room; RA – robotic-assisted; TAH – total abdominal hysterectomy; TLH – total laparoscopic hysterectomy.

Table 3
Treatments and response in patients with gynecologic lymphomas.

Case	Initial treatment	Response to systemic therapy	Subsequent treatment	Current status
A	Surgery, then observation	–	–	Surveillance (1 year without disease at last follow-up)
B	DA-R-EPOCH x6 cycles	Complete	Offered radiation, but declined	Surveillance (2 years without disease at last follow-up)
C	Surgery, R-CHOP x6 cycles, IT-MTX x2	Complete	–	Surveillance (2 years without disease at last follow-up)
D	Surgery, DA-R-EPOCH x6 cycles, IT-MTX x2	Complete, then recurrence (2 years later)	R-ICE (progression), umbralisib (progression), bendamustine and rituximab x6 cycles (complete response)	Surveillance (4 years without disease at last follow-up)
E	Surgery, R-CHOP x6 cycles	Complete	–	Surveillance (20 years without disease at last follow-up)
F	Surgery, R-CHOP x2 cycles	Progression	DHAP x2 cycles (partial response), APBSCT	Surveillance (1 year without disease at last follow-up)
G	CHOP x6 cycles	Progression	Surgery for symptom management, DLBCL in specimen. APBSCT	Recurrent disease 2 years later at last follow-up
H	Surgery, CHOP x8 cycles, radiation to pelvis	Progression	APBSCT	Deceased

APBSCT – autologous peripheral blood stem cell transplant; DA-R-EPOCH – dose adjusted rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; DHAP – dexamethasone, high-dose cytarabine, and cisplatin; f/u – follow-up; IT-MTX – intrathecal methotrexate; R-CHOP – rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone; R-ICE – rituximab, ifosfamide, carboplatin, and etoposide).

ultrasound, CT scan, MRI). Lymphomas are FDG (fluorodeoxyglucose) avid, but PET scans are not routinely used for gynecologic complaints. Additionally, many gynecologic malignancies are also FDG avid, and therefore would be unlikely to differentiate a lymphoma from a more common carcinomatous or sarcomatous malignancy.

Thus, one of the major challenges with gynecologic lymphomas is the role of surgical management. Six patients (A, C, D, E, F, and H) were definitively diagnosed with lymphoma only after surgical resection of a pelvic mass. Only patient B was managed without a large surgical resection, and patient G had a TAH/BSO for symptomatic management. Per National Comprehensive Cancer Network® (NCCN) guidelines, complete cytoreduction is not indicated in known cases of lymphoma (NCCN Clinical Practice Guidelines, 2024). This results in a quandary of management for gynecologic oncologists who typically avoid percutaneous biopsies of isolated pelvic masses out of concern for potentially upstaging; however, this implies that pelvic masses which are non-epithelial ovarian cancers may receive a more extensive surgery than necessary unless there is high suspicion intra-operatively that might facilitate a frozen section.

Intraoperative frozen consultation may be helpful in surgical decision-making. While it is exceedingly difficult to render a definitive diagnosis of lymphoma in this setting, through both gross and microscopic examination, the pathologist would likely be able to raise the suspicion of a hematolymphoid malignancy or at least convey that the tumor is not a common gynecologic entity. Common gross findings in hematolymphoid malignancy include diffuse or nodular enlargement of the involved site with white-tan, soft, fleshy cut surface. On microscopic examination, a diffuse proliferation of round blue cells is seen. Touch cytology preparation may also be useful in identifying atypical lymphoid cells. The differential diagnosis is unfortunately broad and may include poorly differentiated or undifferentiated carcinoma, dysgerminoma, adult granulosa cell tumor, and reactive lymphoid hyperplasia. Examples of intraoperative diagnoses may include “round blue cell tumor” or “malignant neoplasm, cannot exclude lymphoma”. If a diagnosis of lymphoma is suspected, fresh tissue sample should be obtained for further hematopathology diagnostic workup. Combining both intraoperative pathologic finding and clinical picture (i.e. presence of other symptoms or unusual imaging or operative findings) is necessary to determine the best course of action. Ultimately, given the difficulties in obtaining a definitive diagnosis of lymphoma intraoperatively, an otherwise resectable tumor of suspected gynecologic origin should be resected as planned intraoperatively. However, in cases with ambiguity where lymphoma remains on the differential diagnosis, it may be

reasonable to defer more radical or potentially morbid procedures and await a final pathology diagnosis.

Medical treatment for DLBCL is well established. The typical first-line chemotherapy is R-CHOP, which leads to a cure in about 50–60 % of patients regardless of site of origin. Outcomes are poor for patients that do not respond to R-CHOP therapy (Liu and Barta, 2019). Patients with disease <7.5 cm should receive four to six cycles of R-CHOP depending on interim imaging response, and those with bulky disease (≥ 7.5 cm) should receive six cycles of R-CHOP with consideration of radiation therapy (NCCN Clinical Practice Guidelines, 2024). However, given its rarity, there are limited data regarding bulky disease, as that many clinical trials exclude those patients (Rojek and Smith, 2022). There are also no guidelines available for patients who have had bulky disease resected, as is the case for many of the patients presented here. Of note, recent evidence suggests that complete surgical resection of DLBCL may be associated with a survival benefit in patients less than 60 years old with stage I or II DLBCL (Schmitz et al., 2020), but further evidence is needed. Regardless, questions remain regarding whether these patients still need radiation and/or as many cycles of chemotherapy, and some data suggest treating resected DLBCL as non-bulky disease (Rojek and Smith, 2022). The majority of the patients in this series received six cycles of chemotherapy, and one patient ultimately received radiation (H). All patients received adjuvant therapy under the direction of medical oncologists with specific lymphoma expertise.

In conclusion, gynecologic lymphomas pose a unique challenge to gynecologists. Although a rare diagnosis, better identification of and management guidelines for gynecologic lymphomas are needed to enhance outcomes and reduce risks of treatment. Unfortunately, few diagnostic clues exist for this rare pathology, and intra-operative pathology is often inconclusive. Collaboration with medical oncologists is important for appropriate medical management once a diagnosis is made. Identifying unique features prior to radical and potentially morbid surgical resections may be a fruitful avenue for further investigation.

CRediT authorship contribution statement

Alexandra J. Lamacki: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Caroline Montag:** Writing – original draft, Investigation, Data curation. **Elizabeth Kertowidjojo:** Writing – review & editing, Formal analysis, Data curation. **S. Diane Yamada:** Writing – review & editing, Conceptualization. **Katherine C. Kurnit:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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