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Non-Hodgkin lymphoma of the female genital tract mimicking primary gynecological tumors: a single-center series of 3 cases

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Summary

Introduction: Malignant lymphoma of the female genital tract is quite rare and its presentation may resemble that of other, more common tumors, causing confusion for clinicians. *Case history:* The authors report three patients with a non-Hodgkin lymphoma (NHL) involving the female genital tract: two cases involved the ovary and one involved the uterus. In all patients, the genital tract was the initial site of clinical presentation of a B cell lymphoma. One patient was diagnosed postoperatively and subsequently received chemotherapy; the other two patients were diagnosed by imaging-guided biopsy and were successfully managed by chemotherapy without resection surgery. Two patients were alive, without evidence of disease, and one patient was alive with disease at their most recent follow-up visit. *Conclusion:* The authors' experience emphasizes that lymphoma should be in the differential diagnosis of pelvic gynecological malignancies, and its clinical, biological, and radiological signs must be actively sought. Imaging-guided biopsy should be performed to avoid unnecessary surgery.

Key words: Non-Hodgkin lymphoma; Gynecological tumor; Imaging-guided biopsy.

Introduction

Female genital tract lymphomas are rare diseases, accounting for less than 0.5% of all gynecological cancers [1]. Surgery has a limited role in the treatment of gynecological lymphoma. While debulking clearly improves survival, in proportion to its extent, in many types of malignancy including ovarian cancer, it does not have the same benefit in diseases such as lymphoma that are very chemo- and radiosensitive [2]. The authors report three patients with non-Hodgkin lymphoma (NHL), two of which were successfully managed by chemotherapy without resection surgery. In all three patients, it was initially difficult to distinguish lymphoma from either a malignant ovarian tumor or a leiomyosarcoma. It is important to reach the correct diagnosis in patients with NHL in order to administer the optimal treatment, chemotherapy, and to avoid unnecessary radical surgery.

Case Report

Case 1

A 52-year-old female was referred to the present hospital with a three-month history of abdominal distention and a large pelvic mass apparent on ultrasound. Physical examination revealed leg edema, an adnexal mass, and evidence of ascites. Laboratory results were normal except for an elevated lactate dehydrogenase (LDH) level. Magnetic resonance imaging (MRI) showed moderate ascites, enlarged pelvic lymph nodes, and a pelvic mass with regular margins occupying the entire pelvis. The mass had a low signal on T2-weighted imaging (Figure 1). An ovarian malignancy was suspected and the patient underwent exploratory laparotomy with right salpingo-oophorectomy and omentectomy, and was scheduled for 450 mg of intraperitoneal carboplatin. The pathology results suggested diffuse large B cell lymphoma (DLBCL), transformed from follicular lymphoma (FL) (Figure 1). A whole-body postoperative evaluation that included the bone marrow found no evidence of lymphoma infiltration, although the patient did have a high interleukin-2 receptor (IL2R) blood level. She was successfully treated with four cycles of RCHOP (rituximab, 600 mg; cyclophosphamide, 1,200 mg; vincristine, two mg; doxorubicin, 80 mg; prednisone, 100 mg) followed by three cycles of CHASER (rituximab, 600 mg; cyclophosphamide, 1,900 mg; etoposide, 160 mg; cytarabine, 3,200 mg; dexamethasone, 40 mg) and autologous peripheral blood stem cell transplantation. The patient has been in complete remission for 22 months with no evidence of disease recurrence.

Case 2

A 57-year-old female presented with a two-month history of abdominal distention and leg edema. Contrast-enhanced computed tomography (CT) revealed bilateral pleural effusions, ascites, and bilateral pelvic masses (Figure 2). Laboratory evaluation showed elevated levels of cancer antigen 125 (CA125), and IL2R. An ultrasound-guided needle biopsy was performed and pathological evaluation confirmed FL (Figure 2), grades 1–2. She received two cycles of half-dose CHOP (cyclophosphamide, 500 mg; doxorubicin, 35 mg; prednisone, 50 mg) followed by three cycles of RCHOP (rituximab, 600 mg; cyclophosphamide, 1,000 mg; vincristine, 1.9 mg; doxorubicin, 70 mg; prednisone, 100 mg) and six cycles of bendamustine, 160 mg. She was disease-free at the time of her most recent follow-up.

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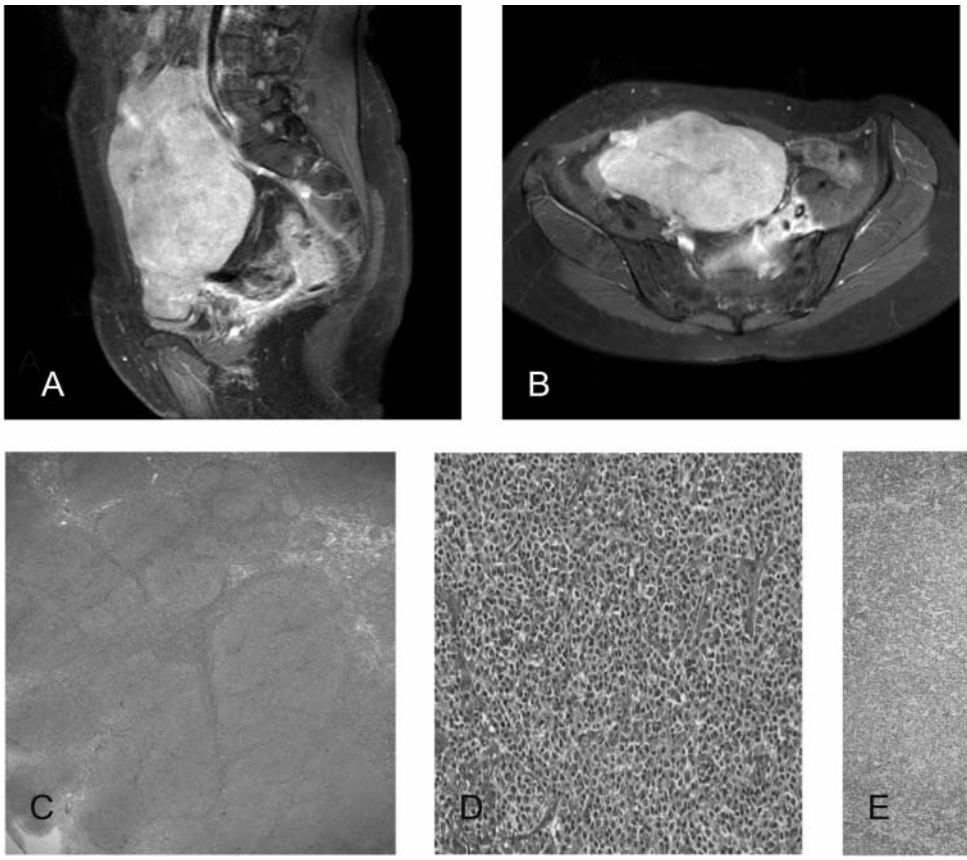

Figure 1. — Imaging and histopathological findings, Case 1. (A) Sagittal view and (B) axial view: preoperative contrast magnetic resonance imaging (MRI). (C, D) Photomicrographs showing large tumor cells with large nuclei and prominent nucleoli (Hematoxylin and eosin [HE] staining; C: magnification, ×40 ; D: magnification, ×400). (E) Immunohistochemistry showing CD20 positivity (magnification, x400).

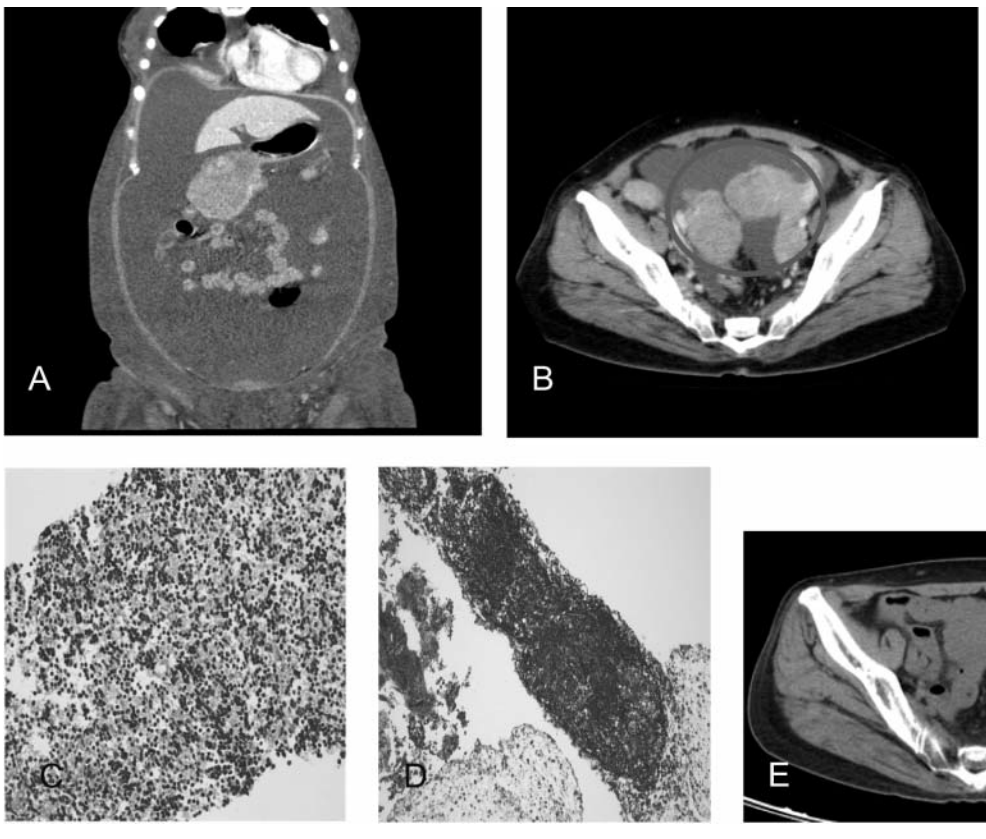

Figure 2. — Imaging and histopathological findings, Case 2. (A) Coronal view and (B) axial view: computed tomography (CT). (C) Photomicrograph showing follicular lymphoma cells with condensed chromatin (HE staining; magnification, ×100). (D) Immunohistochemistry showing CD20 positivity (magnification, ×40). (E) Follow-up CT showing evidence of treatment response.

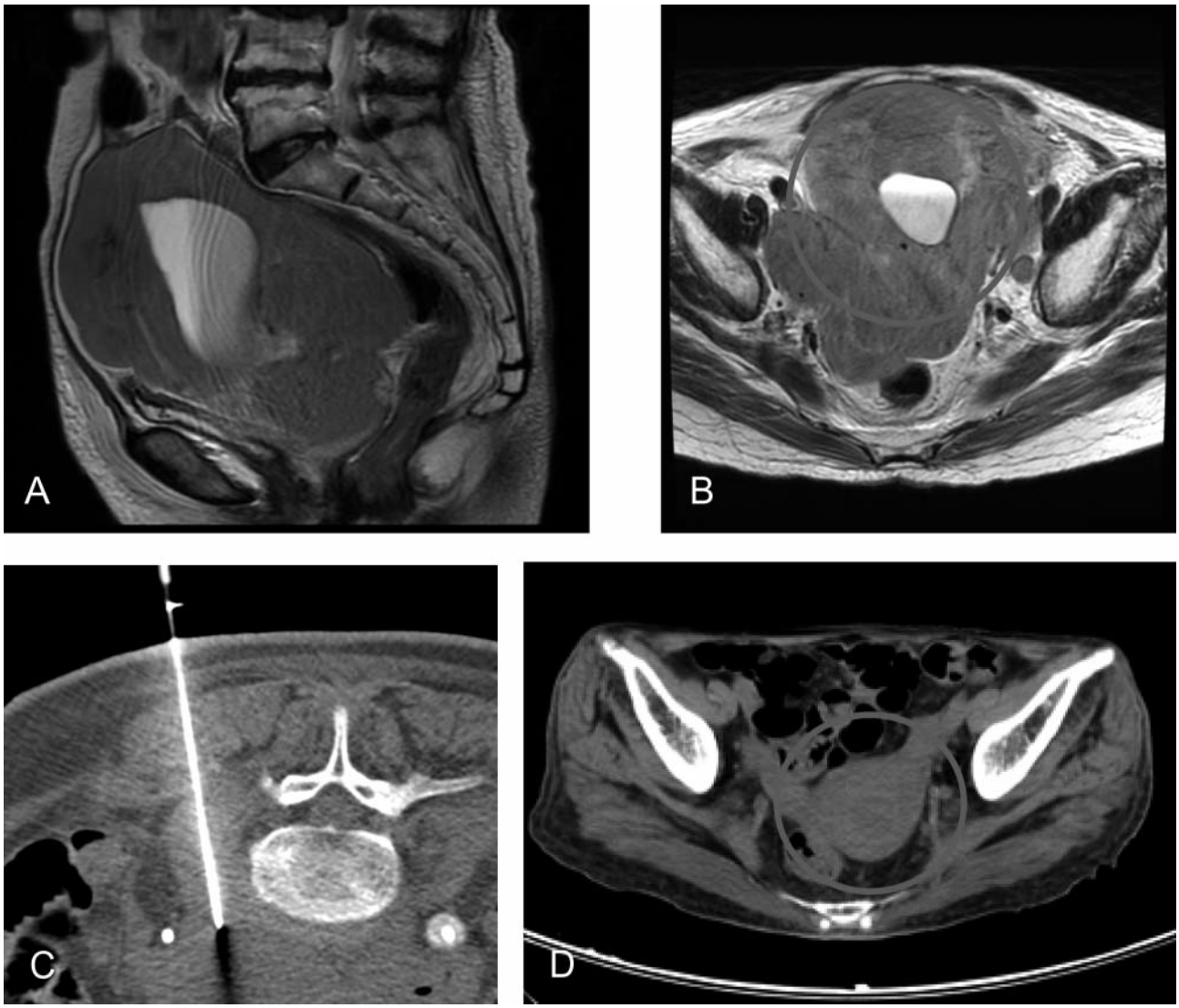

Figure 3. — Imaging findings, Case 3. (A) Sagittal view and (B) axial view: MRI. (C) CT-guided para-aortic lymph node biopsy. (D) Follow-up CT showing a reduction in tumor size after chemotherapy.

Case 3

An 83-year-old woman presented with a one-month history of pelvic pain and anorexia. Physical examination revealed a supraclavicular lymph node enlarged to two cm, and marked lower-leg edema. Ultrasound examination detected an enlarged uterus, 13 cm in length. Laboratory results were normal except for elevated LDH and IL2R levels. MRI showed a uterine mass with low signal on T2-weighted images, and enlarged pelvic and para-aortic lymph nodes (Figure 3). The differential diagnosis, based on the MRI findings, included leiomyosarcoma and malignant lymphoma. A bone marrow biopsy revealed lymphoma-cell infiltration. A CT-guided needle biopsy of both the uterine mass and a para-aortic lymph node confirmed DLBCL. She was treated with eight cycles of RCHOP (rituximab, 500 mg; cyclophosphamide, 380 mg; vincristine, 0.7 mg; doxorubicin, 25 mg; prednisone 60 mg). The patient has been in partial remission after primary chemotherapy. Table 1 summarizes the clinical information of the three patients.

Discussion

NHL types represent 90% of all lymphomas [3]. Usually, these cancers occur in the lymph nodes or in other lymphoid tissue such as the spleen, Waldeyer's tonsillar ring, the thymus, and in bone marrow. Extranodal NHL accounts for 20–24% of all disease, most frequently arising from the gastrointestinal tract, lung, nervous system, and skin [3, 4].

Female genital tract lymphomas are very rare, and less than 1% of patients with any type of lymphoma present initially with ovarian enlargement. In autopsy studies of patients with NHL, the uterus was found to be involved in approximately 0.5% of cases [4, 5]. Regardless of the site of involvement, DLBCL is the most frequent histological subtype [4]. In this series, the authors encountered one patient with DLBCL, one with FL, and one with DLBCL

Table 1. — Patients with non-Hodgkin lymphoma.

	Case 1	Case 2	Case 3
Age (years)	52	57	83
Presentation	Abdominal distention	Abdominal distention	Pelvic pain, anorexia
B symptoms	Absent	Absent	Absent
Hepatosplenomegaly	Absent	Absent	Absent
Extranodal site	Ovary	Ovary	Uterus
Diagnosis	DLBCL (transformed from FL)	FL Grade 1–2	DLBCL
Stage	IV A	IV A	IV B
IPI/ FLIPI	High intermediate risk	High risk	High risk
CA125	1,136 IU/ml	3,254 IU/ml	245 IU/ml
LDH	335 IU/L	441 IU/L	310 IU/L
IL2R	5,221 IU/ml	1,024 IU/ml	7,248 IU/ml
CD20	+	+	+
CD10	+	+	
CD19	ND	ND	+
CD4	+	ND	+
CD5	_	_	_
CD7	+	ND	ND
BCL2	+	+	_
Therapy	Surgery, chemotherapy	Chemotherapy	Chemotherapy
Response	CR	CR	PR

DLBLC: diffuse large B cell lymphoma; FL: follicular lymphoma;
IPI: international prognostic index;
FLIPI: follicular lymphoma international prognostic index; CA: cancer antigen;
LDH: lactate dehydrogenase; IL2R: interleukin-2 receptor;
BCL2: B cell lymphoma 2; ND: not detected; CR: complete remission;
PR: partial remission

transformed from FL. Histological transformation from indolent follicular lymphoma to a diffuse aggressive lymphoma reportedly occurs in 10–70% of cases and is associated with a poor prognosis [3]. The present patient, however, experienced complete remission and remains disease-free, 22 months after treatment.

Gynecological lymphomas usually occur in the fifth decade of life, although the age of presentation ranges from 20–80 years. The presentation is usually similar to that of other genital tumors, namely an abdominal or pelvic mass often accompanied by pain, intermittent vaginal bleeding, and vaginal discharge [6]. However, lymphoma presents different diagnostic and therapeutic implications than other genital tract malignancies.

Genital lymphomas may be underdiagnosed, both because lymphoma is unexpected at this site and because it may be misdiagnosed as another type of malignant tumor. If patients present with an isolated pelvic mass, there may be few signs to suggest the diagnosis of lymphoma. Often, lymphoma patients will complain of systemic symptoms, known as B symptoms, that include fever, night sweats, and weight loss. Clinical examination focuses on the detection of palpable adenopathy or liver/spleen infiltration [7]. The present patients exhibited none of these findings, except the patient featured in Case 3 who presented with cervical lymphadenopathy.

The key to diagnosing lymphoma in the genital organs is first to suspect it. Ferrozzi *et al.* [8] reported the most typical imaging patterns of ovarian NHL: the lesion exceeds five cm in diameter and is frequently bilateral and homogeneous; ultrasonography shows homogeneous, hypoechoic, mildly vascularized tumors; CT reveals clear-cut, hypodense lesions, with mild contrast enhancement; MRI reveals homogeneous masses, with low signal intensity on T1-weighted images and slightly hyperintensity on T2-weighted images; gadolinium T1-weighted images show mild enhancement. Ferrozzi *et al.* emphasized that a diagnosis of ovarian lymphoma may be considered when bilateral ovarian tumors appear to be homogeneous and ascites is absent [8].

Park *et al*. described varying imaging features of uterine lymphoma, emphasizing that these findings closely resemble those of other malignancies. Diffuse enlargement of the uterus without disruption of the endometrial epithelium is reported to be a characteristic finding for lymphoma involving the uterine body. The tumor is heterogeneous on CT due to regions of necrosis and hemorrhage. Areas of calcification can also be present [9].

Since the imaging findings of genital tract lymphoma are often not specific, patients should undergo systemic evaluation prior to surgery. This should include bone marrow biopsy, biochemical analysis of IL2R and soluble LDH, as well as cytology and flow cytometry of fluid from cavitary effusions [8]. Increased IL2R and high soluble LDH levels reportedly have clinical and prognostic significance in patients with malignant lymphoma, and can help to predict the diagnosis [10, 11]. In this series, all three patients had high IL2R and soluble LDH levels, and one patient demonstrated bone marrow infiltration. Although bone marrow investigation does not always contribute helpful information, a positive result can save an unnecessary operation and prevent delayed initiation of chemotherapy.

Histopathological evaluation and immunohistochemical staining of biopsy specimens are usually required for the definitive diagnosis of lymphoma. Core needle biopsy may be helpful in the diagnosis of lymphoma located deep in the abdomen or retroperitoneum, and may allow the patient to avoid laparotomy. However, as the present first patient demonstrated, most genital lymphomas are diagnosed after surgery, particularly when the disease is located in the ovaries. The authors' experience with Case 1 helped them to suspect lymphoma in the next two patients, and were therefore able to confirm the diagnosis by histopathological evaluation of tissue obtained by a guided needle biopsy, avoiding laparotomy.

Currently, there is no consensus on a specific recommended treatment for extranodal genital lymphoma. According to the literature, the mainstay of treatment is chemotherapy and, to a minor extent, radiotherapy [6]. New treatment modalities such as the use of monoclonal antibodies, high-dose chemotherapy, or allogenic transplantation have improved treatment results over the last decade [2]. In the review by Dursun *et al.* evaluating 31 cases of extranodal genital lymphoma, eight patients were treated with chemotherapy alone and no relapses were observed; follow-up ranged from six months to eight years [12]. Signorelli *et al.* reported 12 patients treated with chemotherapy and observed nine complete responses [6]. In the case reported by Yamada *et al.*, the patient remained in complete remission six years after appropriate chemotherapy, with no surgical procedure required other than biopsy [1]. Complete remission was established in the present case report in two of the three patients after chemotherapy; two of them were disease-free at the time of the most recent follow-up examination.

In conclusion, lymphomas affecting the female genital tract are uncommon and often pose a diagnostic challenge, as their presentation may resemble other, more frequently seen tumors. Guided needle biopsy can help to reach the correct diagnosis. Many genital-tract lymphomas can be cured, and in many other cases survival can be prolonged [2]. Therefore, patients presenting with a pelvic mass should be evaluated for the criteria of malignant lymphoma before surgery is planned. If lymphoma is present, treatment will consist of biopsy and adapted chemotherapy rather than surgery.

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