

Primary ovarian non-Hodgkin's lymphoma: a case series and a review of literature

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DOI: [10.31083/j.ejgo.2021.03.2377](https://doi.org/10.31083/j.ejgo.2021.03.2377)

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Submitted: 12 January 2021 Revised: 16 February 2021 Accepted: 26 February 2021 Published: 15 June 2021

Objectives: We report nine cases of primary ovarian non-Hodgkin's lymphoma (PONHL). **Materials and methods:** From January 2000 to February 2020, we retrospectively analyzed nine patients with PONHL admitted to our hospital. Their clinicopathologic features, treatments, and outcomes were summarized. **Results:** This study included eight cases of DLBCLs and one case of T-cell origin. Their presentations included abdominal pain, abdominal distension, and a pelvic mass, and one had a history of B symptoms. Imaging features revealed large, solid, and homogenous adnexal lesions. Four cases had bilateral ovary involvement and one had abdominal bloody ascites. Intraoperative frozen section analysis showed that five patients had lymphoma, and four had incorrect diagnoses. All patients received surgical treatment and adjuvant chemotherapy. Three patients died of their disease, and six are alive and cancer-free. **Conclusions:** Preoperative diagnosis of PONHL is difficult. Correct frozen section analysis is a key determinant for guiding conservative therapy. Adjuvant R-CHOP chemotherapy might be an effective regimen.

Keywords

Lymphoma and non-Hodgkin's disease; Ovarian tumors; Ovarian lymphoma; Primary ovarian lymphoma

1. Introduction

Primary ovarian non-Hodgkin's lymphoma (PONHL) is an extremely rare neoplasm, accounting for only 0.5% of all non-Hodgkin's lymphomas (NHLs) and only 1.5% of all ovarian neoplasms [1]. Clinical manifestations include abdominal pain, abdominal distension, and a rapidly growing pelvic mass. The majority of cases with PONHL are of B-cell origin, of which diffuse large B cell lymphoma (DLBCL) is the most common [1, 2]. Fox *et al.* [3] proposed the following criteria for the diagnosis of PONHL: the disease is confined to ovarian regional lymph nodes or adjacent organs at diagnosis, no abnormal cells are found in the bone marrow or peripheral blood, and any extraovarian lymphomatous lesions that may develop, occur several months after the appearance of the ovarian lesion. When these criteria are strictly applied, the diagnosis of PONHL becomes extremely rare.

Due to its rarity and atypical clinical symptoms, it is difficult to distinguish PONHL from other ovarian malignancies before surgery, and there is no standard therapeutic manage-

ment. In this study, we analyzed nine patients with PONHL retrospectively.

2. Materials and methods

Medical charts were reviewed for patients diagnosed with PONHL, who were treated at Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) between January 2000 and February 2020. The pathology of these nine cases were reviewed by a senior pathologist. The histological classification was based on the World Health Organization 2017 classification, and the staging was based on the Ann Arbor system. Survival was defined as the time between the date of unequivocal diagnosis of lymphoma and the date of last follow-up or death.

3. Results

3.1 Age

The patient age ranged from 23 to 52 years (mean, 36).

3.2 Symptoms and signs

Three patients presented with abdominal pain, one with abdominal distention, and one with constipation, three patients had pelvic masses that were discovered incidentally, and the remaining one patient had a history of B symptoms including fever and weight loss.

3.3 Laboratory tests and imaging examinations

Laboratory tests for carbohydrate antigen 125 (CA125) and lactate dehydrogenase (LDH) were performed for all patients. LDH was high in three patients, ranging from 474–1001 U/L (reference range, 80–220 IU/L). CA125 was elevated in two patients, with a maximum value of 561 U/mL (normal is <35). All patients had undergone an ultrasound (US) scan and pelvic computed tomography (CT) scan. PONHL appeared as a well-defined, solid, homogenous, and hypoechoic adnexal lesion with moderate to high vascularity on color Doppler. On the CT images, lymphomatous deposits were hypodense and homogenous and showed mild enhancement (Fig. 1). However, lymphoma was not considered preoperatively in any patient.



Fig. 1. Computed tomography scan show low-density shadow replacing the left (A), right (B) and bilateral (C) ovary (arrow).

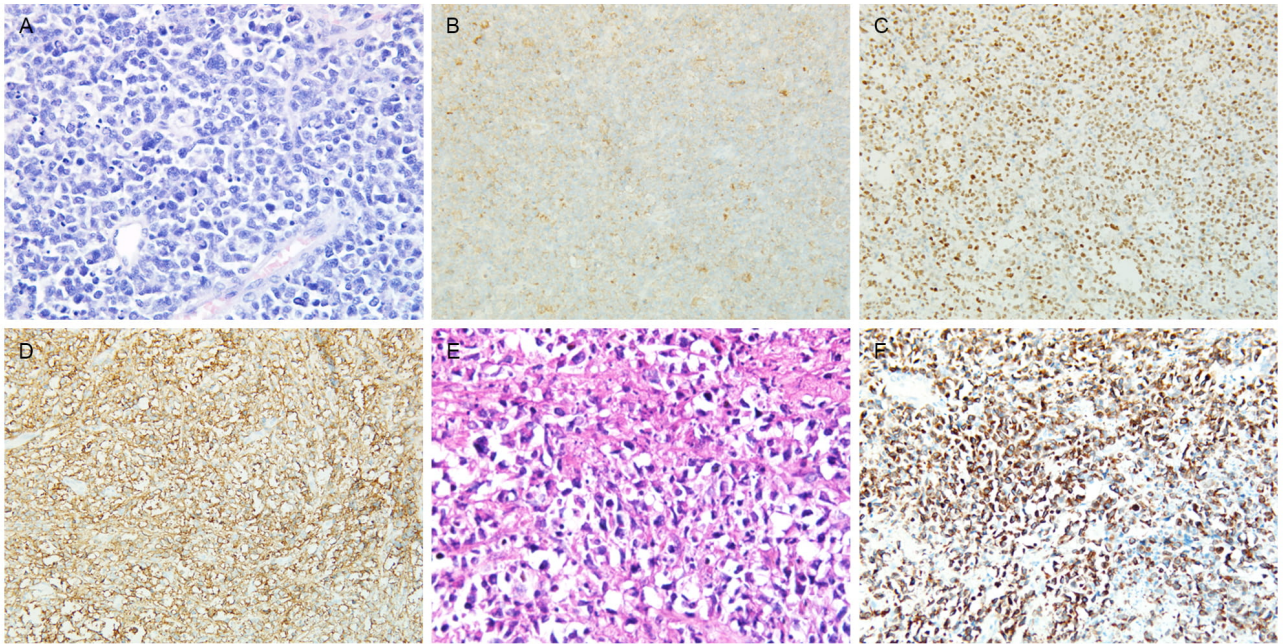


Fig. 2. Morphological and immunohistochemical aspect of primary ovarian non-Hodgkin lymphoma (PONHL). Primary ovarian Diffuse large B cell type (DLBCL) (hematoxylin eosin stain for A, $\times 400$), primary ovarian NK/T-cell type lymphoma (hematoxylin eosin stain for E, $\times 400$). The slides show neoplastic B-cell CD10 (B), BCL-6 (C) and CD20 (D) positive, neoplastic T-cell CD3 (F) positive (immunohistochemical stain for B, C, D, F, $\times 200$).

3.4 Surgical therapy

Three patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO), one received bilateral adnexectomy, and three were treated by adnexectomy, one of whom underwent staging surgery concurrently including adnexectomy, pelvic lymphadenectomy, and omentectomy. The remaining patient underwent debulking surgery for intraoperative misdiagnosis of ovarian carcinoma. According to the Ann Arbor staging system, the overall evaluation revealed two patients in stage I and seven in stage II.

3.5 Pathology findings

The tumor size ranged from 3 to 22.0 cm, and six patients (66.7%) had a tumor >10 cm in size. Five (44.4%) tumors were unilateral, and four were bilateral. We detected that 200 mL of bloody ascites accumulated in the abdomen of one patient. The masses were nodular in appearance. Intraoperatively, tumors were resected for frozen section analysis. Five

patients were confirmed to have lymphoma, and four had an incorrect diagnosis (including one case misdiagnosed as dysgerminoma, one misdiagnosed as ovarian cortical hyperplasia, one misdiagnosed as a malignant ovarian tumor, and one had an unclear diagnosis of dysgerminoma or lymphoma). Microscopically, DLBCL ($n = 8$) was the most common NHL histology found in our patients, and there was one case of natural killer/T-cell lymphoma (NKTL $n = 1$). Immunophenotypic analysis revealed one tumor expressing at least one pan-B-cell antigen (cluster of differentiation 20 [CD20], CD79a, CD10, B-cell lymphoma 2 [Bcl-2], Bcl-6), and one tumor expressing CD3 T-cell antigens. In addition, based on the classification criteria of Han *et al.* [4], eight DLBCLs in our series were subclassified according to the expression of CD10, Bcl-6, and multiple myeloma oncogene 1 (MUM1); six (75%) were considered germinal center B cell (GCB); and two (25%) were considered non-GCB (Fig. 2).

Table 1. Clinical characteristics of patients with PONHL.

N	Symp	Age yr	LDH	Ascites	CA125 (U/mL)	Side and Size (cm)	IFSA	Histologic type	Immuno-phenotype	Surgery	Chemo	Stage	IPI	Outcome	Survival (mo)
1	Abd pain	50	N	NEG	14	Left: 8 Right: 21	lymphoma	DLBCL (non-GCB)	CD20+, CD10-, BCL-6-	TAH + BSO	CHOP	IIE A	0	DWD	10 m
2	Abd distension	23	↑	POS	561	Right: 17	dysgerminoma or lymphoma	DLBCL(GCB)	CD20+, CD10+	RSO + staging	R-CHOP	IIE A	4	DWD	11 m
3	Abd pain	32	N	NEG	31	Left: 15 Right: 6	lymphoma	DLBCL (GCB)	CD20+, CD10+, BCL-6+	BSO	CHOP*	IIE A	1	AWD	181 m
4	Incidental finding	29	N	NEG	11	Right: 7	dysgerminoma	DLBCL (GCB)	CD20+, CD10+, BCL-6+	RSO	CHOP	IA	1	AWD	164 m
5	Incidental finding	36	N	NEG	19	Left: 19	lymphoma	DLBCL (non-GCB)	CD20+, CD10-, BCL-6-	LSO	R-CHOP	IA	0	AWD	92 m
6	Constipation	49	N	NEG	21	Left: 14 Right: 5	lymphoma	DLBCL (GCB)	CD20+, CD10+, BCL-6+	TAH + BSO	R-CHOP #	IIE B	0	AWD	85 m
7	Incidental finding	51	↑	NEG	338	Right: 3	ovarian cortical hyperplasia	DLBCL (GCB)	CD20+, CD10+	TAH + BSO	R-CHOP #	IIE A	2	AWD	53 m
8	Fever	32	N	NEG	33	Right: 11	lymphoma	DLBCL (GCB)	CD20+, BCL6+	RSO	R-CHOP	IIEA	1	AWD	57 m
9	Abd pain	52	↑	NEG	27	Left: 22 Right: 8	malignant ovarian tumor	NKTL	CD3+	Debulking	CHOP	IIE A	1	DWD	14 m

Bi, bilateral; L, left; R, right; NEG, negative; POS, positive; m, month; Symp, Symptoms; Abd, abdominal; Chemo, chemotherapy; CR, complete remission; PD, progressive disease; N¹, number; N, normal; DWD, dead with disease; AWD, alive with disease; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RSO, right salpingo-oophorectomy; IFSA, Intraoperative Frozen Section Analysis; NKTL, natural killer/T-cell lymphoma.

*: further treatment with stem cell transplantation. #: further treatment with bioimmunotherapy.

3.6 Adjuvant therapy

Five patients received six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), and four received six cycles of CHOP. Among them, two patients still received bioimmunotherapy and one underwent stem cell transplantation.

3.7 Prognosis

After a follow-up of 10–181 months (median, 57 months), six patients were still alive and free of disease. One patient succumbed to the disease 10 months after initial diagnosis due to primary chemoresistance. The other two patients who received tumor debulking or staging surgery, died 11 and 14 months after diagnosis, respectively; both presented with increased LDH, and one had an International Prognostic Index (IPI) score ≥ 3 . The median overall survival (OS) in patients with DLBCL was 71 months (range, 10–181 months), which was better than that observed with T-cell lymphoma (14 months). In addition, the median OS in patients with GCB was 71 months (range, 11–181 months), which was better than that observed with non-GCB subtype (51 months, range 10–92 months). The primary clinicopathological features of the nine cases are summarized in Table 1.

4. Discussion

Because normal ovaries are devoid of any lymphoid tissue, the true origin of PONHL remains unclear. However, histopathological studies have confirmed the presence of variable numbers of lymphocytes in examined ovaries [5, 6], which provides a theoretical basis for the occurrence of PONHL. Nevertheless, it is speculated that on rare occasions, chronic inflammation stimulates the occurrence of reactive lymphocytes [2]. It has been postulated that the composition of the microenvironment and the particular immunological interaction between B cells in lymphoma and reactive T cells may have important effects on tumor biology [7].

Preoperative diagnosis is often difficult. As in our case series, the presentation similar to that of other ovarian malignancies can easily be misdiagnosed as ovarian cancer preoperatively. B symptoms such as fever, night sweats or weight loss have been reported in 10–33% of the patients [8]. Ascites may be present, but it is rare [2]. In this study, one patient had B symptoms (11.1%), and another had a small amount of bloody ascites. In Monterroso's report [6], ascites was not present in any of the four patients with PONHL. Another report studying 40 cases of ovarian lymphoma, found that ascites was only present in 2 cases [9]. This is significantly different from the 75% incidence of ascites in advanced ovarian cancer. Therefore, for patients with an obvious pelvic mass and lack of ascites, clinicians should consider the possibility of this disease and be particularly vigilant for B symptoms.

In our study, CA125 was elevated in two cases, with a maximum value of 561 U/mL, and LDH was high in three patients. CA125 does not appear to be directly secreted by lymphoma cells but is produced by mesothelial cells in response to lymphokines released by NHL cells. Hence, ele-

vated CA125 in lymphoma patients is not as obvious as in ovarian cancer patients [8]. However, lymphoma cells can secrete LDH, which is a useful marker of lymphoma cells associated with proliferative activity [10]. In our study, all three patients with elevated LDH had stage II disease. The elevation of LDH was more specific to PONHL than CA125, which can be used as a diagnostic clue.

PONHLs are large ovarian masses, mostly between 8 and 15 cm [2], and bilateral ovarian involvement occurs in 36% to 71% of cases [1, 11]. In our study, imaging scan indicated homogeneous low-density lesions with mild enhancement, similar to the study by Nasioudis [1]. Six cases (66.7%) had masses ≥ 10 cm and 4 (44.4%) had bilateral involvement. However, Uccella [7] reported that primary testicular DLBCL usually presents as a large mass, and common sites of secondary involvement include the contralateral testis. Therefore, PONHL should be considered when a solid homogenous large ovarian mass or bilateral ovarian involvement is seen in the absence of ascites [1, 12].

Histopathological examination is key to the diagnosis of this rare disease. In this study, the majority of cases with PONHL were of B-cell origin (80–95%). Regarding NHL subtypes, our findings support previous evidence of DLBCL being the most common type of NHL in gynecologic organs [2, 8]. Senol *et al.* [13] reported five cases of PONHL, all of which were DLBCLs. Because lymphomatous infiltrates may have many patterns, NHL categories might be confused with a granulosa cell tumor, a dysgerminoma, a primary or metastatic poorly differentiated ovarian cancer, and small cell carcinoma, finally resulting in a histopathology misdiagnosis, making frozen section diagnosis even harder [2, 12]. In one report, two of three patients with pelvic masses underwent intraoperative frozen section examination; one was misdiagnosed as having fibroma, and the other diagnosis was unclear as lymphoma or sarcoma [14]. Ahmad *et al.* [12] reported that among 36 cases of lymphoma of the female reproductive system, 28 had unclear intraoperative frozen diagnoses. In our study, four patients had incorrect frozen section diagnoses.

To avoid misdiagnosis, an immunohistochemical work-up is mandatory. Specific immunohistochemistry is often used for classification. A screening panel consisting of CD3, CD20, and cytokeratin is useful in determining whether the tumor is a B-cell lymphoma (CD20+), T-cell lymphoma (CD3+), or carcinoma (cytokeratin+) [15]. In the 4th edition of the World Health Organization classification of lymphoma, patients with DLBCLs were further divided into GCB and non-GCB types according to the expression of CD10, Bcl-6, and MUM-1, with a positive rate of 60% for GCB type [16]. Among the eight patients with DLBCL in our series, six (75%) had GCB type, which is higher than the reported rate, and two had non-GCB type. This high incidence of GCB might be related to the very small number of cases in this study. Although lymphoma originates in the ovary, immunohistochemical detection and classification

based on lymphoma are particularly important for diagnosis, treatment, and prognostication.

There is no widely accepted consensus on the treatment for PONHL due to its rarity. Because imaging-guided biopsy cannot be routinely recommended due to the inherent risk of upstaging, it is generally believed that PONHL should initially be treated with surgical resection [1]. However, there is no evidence that debulking surgery is superior to simple hysterectomy or adnexectomy [1, 8]. In this study, two cases underwent staging and debulking surgery; however, these two patients did not gain any survival benefits, while four of five patients who had received TAH/BSO or BSO achieved long-term survival.

After the diagnosis of PONHL, a standard adjuvant chemotherapy regimen used for aggressive or advanced NHL such as R-CHOP is usually administered [1]. Yun's study [11] of PONHL patients who received R-CHOP demonstrated similar outcomes to those with nodal NHLs. In our study, four of five patients, who had received R-CHOP, achieved long-term survival.

Some experts recommend fertility-sparing treatment for younger PONHL patients, but there have been no reports with regard to successful fertility in these PONHL patients in the literature [1]. In this study, two patients who desired fertility-sparing treated were treated with adnexectomy. Although not pregnant, no recurrence occurred in either patient. However, there have been patients with primary cervical lymphoma, who achieved fertility after being treated with chemotherapy alone, which provides us with referenceable experiences [17].

Dimopoulos *et al.* [18] reported that localized ovarian lymphomas treated with modern combination chemotherapy have a favorable prognosis, with a long-term survival of 75%, similar to that of NHL. The IPI score is a significant prognostic factor for survival in PONHL patients with primary NHL [8]. However, it appears to provide limited information because all lymphomas are localized, as our data show. B-cell lymphomas generally respond better to chemotherapy than T-cell lymphomas, and therefore have a better prognosis [2, 3]. Gutierrez's study [16] found that the 5-year survival rates for GCB and non-GCB were 59% and 30%, respectively. This study showed that the median OS in patients with DLBCL was 71 months (range, 10–181 months), which is better than that observed in T-cell lymphoma (14 months). In addition, the prognosis was better for patients with GCB subtype compared to non-GCB subtype (71 vs. 51 months).

5. Conclusions

In general, awareness of this disease among clinicians, radiologists, and pathologists is critical. Avoiding intraoperative misdiagnosis is a key determinant for guiding conservative operations. Fertility preservation surgery is also worth discussing.

Author contributions

HTX conceived and designed the drafts, wrote the paper, authored or reviewed drafts of the paper. LZ prepared figures and/or tables. KW authored or reviewed drafts of the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

To ensure anonymity of the patients, the database was depersonalized; therefore, our study did not involve human subjects. We received confirmation from the Medical Ethics Review Committee of the Tianjin Medical University Cancer Institute and Hospital that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that official institutional review board approval is not required.

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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