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Primary Ovarian Non-Hodgkin's Lymphoma: Retrospective Study of 16 Patients

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Abstract

Background: Primary non-Hodgkin's lymphoma (PONHL) of the ovary is rare disease. Ovarian involvement by NHL is usually secondary, as a part of systemic disease. It is frequently diagnosed as ovarian carcinoma which causes a significant delay in diagnosis and management. Objective: To analyze, to report and to better understand the clinico-pathologic features and results of treatment, and prognostic factors of these tumors. Material & methods: This was a retrospective single institutional work that included 16 cases of primary ovarian non-Hodgkin lymphoma (PONHL) treated in National Cancer Institute-Cairo University from January 2010 till January 2015. All available medical data including the clinical and pathological characteristics, treatment, and outcomes of patients with PONHL are analyzed. Results: Data from 16 patients are obtained. The patient's age ranges from 14 to 55 years (mean 28 years). Ascites is the most common manifestation (75%). Tumor size ranges from 5 to 24 cm (mean 13.1). LDH is elevated in all cases (mean 644 U/L) and CA-125 is elevated in only 4 cases (25%) especially when there is an extensive peritoneal irritation. Ten cases (62.5%) are bilateral with stage IV-E according to the Ann Arbor staging system. The remaining six cases (37.5%) are unilateral with Ann Arbor stage I-E. There are no stage II-E or III-E in the current study. Tumors are classified according to the World Health Organization as follows: diffuse large B-cell lymphoma (10 cases) (62.5%), Burkitt's lymphoma (5 cases) (31%) and only one case of B-lymphoblastic lymphoma/leukemia. All the tumors are of B-cell lineage and are all CD20 positive. All Burkitt's lymphoma cases show higher Ki67 index (4 cases are 100% and one is 88%). The case of B-lymphoblastic lymphoma/leukemia is positive for TDT & CD 10. Surgery is the main treatment modality for primary diagnosis and for staging, although chemotherapy should have been the primary treatment because it is one of the most chemosensitive tumors. Follow-up period ranges from 3 months to 5 years (mean 33 months). Ten patients are alive without disease. Two cases experienced relapse and one case died during chemotherapy treatment. The remaining three cases died from other causes than disease. The median overall sur-

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vival time was not reached yet; however, the mean overall survival was 46.8 monthes; median progression free survival was 36 months. Conclusion: Most patients with PONHL present with symptoms attributable to an ovarian mass which necessitates extensive surgical staging that is not mandatory for lymphomas. More studies will be needed to better define and treat this rare entity.

Keywords

Ovary, Primary Non-Hodgkin's Lymphoma, Report, Outcome

1. Introduction

Non-Hodgkin's lymphoma (NHL) may involve the gynecologic tract. The ovary is the most common anatomic site to be involved. Ovarian involvement by NHL is usually secondary, occurring as a part of systemic disease. The primary involvement of the ovary by NHL is rare and accounts for 0.5% of NHL and 1.5% of all ovarian tumors [1].

2. Materials and Methods

This is a retrospective analysis of 16 patients of primary NHL of the ovary presented to the National Cancer Institute, Cairo University, from January 2010 until January 2015. Cases were identified from the surgical pathology files and clinical information was obtained through reviewing of the medical reports. The surgical and pathological characters were analyzed and each patient record was revised for age, clinical presentation, imaging modalities, pathology, final diagnosis and different treatment modalities given.

Staging includes thorough systemic examination and work-up, with assessment of complete blood cell counts, renal and liver function tests, LDH, CA-125, and imaging studies such as CT scans of the chest, abdomen, and pelvis. Presently, PET-CT scan is the standard imaging modality for NHL. As a primary lymphoma of the ovary, bone marrow involvement should be ruled out. Disease stage was based on Ann Arbor staging system [1].

Histological features were studied using sections routinely stained with hematoxylin-eosin. Each neoplasm was classified according to the recently proposed World Health Organization Classification. Immunohistochemical studies were done using formalin-fixed, paraffin-embedded tissue sections and a variable panel of antibodies specific for the following antigens: CD3, CD20, CD30, CD99, BCL-2, CD10; CD43; LCA; CK; and TdT. Ki67, PLAP & AFP was recorded [2].

Ethical clearance for the conduction of this study was obtained from our institute ethical committee.

3. Inclusion Criteria

The diagnosis of primary ovarian Non Hodgkin's lymphoma (PONHL) was proposed in 1988 by Fox *et al*. [1]. Fox *et al*. proposed a certain criteria for the diagnosis of PONHL: (1) the lymphoma should be confined to the ovary or the adjacent lymph nodes or structures at diagnosis, without evidence of lymphoma elsewhere; (2) the peripheral blood and bone marrow should not contain any abnormal cells; (3) remote involvement should occur at least several months after ovarian involvement.

4. Results

4.1. Clinical Features

Sixteen cases of Primary ovarian NHL were included in this study. The patients ranged in age from 14 to 55 years (mean 28years). The most common presenting signs or symptoms were: ascites (n = 12) (75%); pelvic pain (n = 10) (62.5%); constitutional symptoms (B-symptoms) (n = 9) (56%); menstrual disturbances (n = 7) (44%) & distension (n = 6) (37.5%). All tumors were bilateral (10 cases) (62.5%) apart of six cases (37.5%). No bone marrow infiltration was seen in this study. Neoplasms were grossly identified and ranged in size from 5 to 24 cm (mean 13.1 cm; median 13.5 cm). LDH was elevated in all our cases at presentation (mean = 644 U/L), while CA125 was elevated in only four cases (25%). Tumors were staged as per Ann Arbor staging system of lymphoma where six cases were stage I-E (37.5%) & ten cases were IV-E (62.5%). There were no stage II-E or

III-E in the current study which seems to be a deficiency in this system in staging of patients with primary extralymphatic site lymphoma.

IPI is the most useful prognostic tool in estimating the likelihood of survival with conventional chemotherapy, and was calculated based on age (greater than 60 years), performance status, elevated serum lactate dehydrogenase (LDH) level, staging (stage III or IV disease), and more than one extranodal site. One point is assigned for each risk factor. Low risk (0 - 1 points) (5-year survival of 73%), low-intermediate risk (2 points) (5-year survival of 51%), high-intermediate risk (3 points) (5-year survival of 43%) and high risk (4 - 5 points) (5-year survival of 26%). In this study we had ten cases of high intermediate risk (62.5%) & the other six (37.5%) remaining were low IPI risk group [3]. **Figure 1**, **Figure 2** present two of our cases.

4.2. Histological Subtypes and Immunohistochemical Findings

All cases were pan-B markers positive include CD19; CD20; CD79a. 8 tumors (50%) were diffuse large B-cell lymphoma (DLBCL) with PLAP, AFP, CK, Inhibin, CD45 RO negative, and CD19; CD22; CD10 −/+; Sig + was positive.6 cases (38%) of Burkitt's lymphoma showed high KI67% index (4 cases 100% and 2 cases 88%), CD10 CD43 were positive. We found only 2 cases (12%) of B-lymphoblastic lymphoma/leukemia with CD 10 & TdT were positively expressed while CD5 was negative (**Table 1**).

4.3. Treatment

Various combinations of surgery and chemotherapy were given. All patients were treated by a form of surgery in an attempt for surgical staging and obtaining a tissue diagnosis as usually the provisional diagnosis was an ovarian carcinoma: four cases (25%) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, another four (25%) underwent unilateral salpingo-oophorectomy; and eight cases (50%) underwent bilateral salpingo-oophorectomy. Appendicectomy and ileal loop resection anastomosis was done in four separate cases (25%) as part of the surgical procedure. six cases (37.5%) had positive peritoneal nodules and four cases (25%) had infiltrations of para-aortic group of lymph nodes. All patients received chemotherapy after their surgery according the lymphoma subtype.

Figure 1. CT axial and coronal view of two different patients in our study; one presenting with bilateral adnexal cystic lesions and the other with right adnexal mass.

Figure 2. The postoperative specimen of 3 different case in our study, the first underwent TAH with bilateral SO and infracolicomentectomy associated with Appendicectomy, the second case underwent the formal TAH + BSO with total omentectomy, the third case underwent bilateral SO only with infracolicomentectomy as she was not consented on hysterectomy.

Table 1. Different histological types in the current study.

Histological subtype	No. (16)
Diffuse large B-cell lymphoma (DLBCL)	10 (~63%)
Burkitt's lymphoma	5 (~31%)
B-lymphoblastic lymphoma/leukemia	1 (~6%)

Burkitt's lymphoma (BL) is a highly aggressive lymphoma presenting mainly at extranodal sites. **Three distinct clinical forms** of Burkitt's lymphoma could be recognized: endemic(African), sporadic (nonendemic/non-African) and immunodeficiency associated furthermore, cases from Middle East show higher extranodal involvement rates than sporadic forms [4]-[6].

Because of rarity of PONHL, there are no standard guidelines on its management. All our cases were treated in various fashions including surgery & chemotherapy. The available literature for management of an adnexal mass supports surgery as the gold standard for primary evaluation. This consensus may be attributable to the difficulty in diagnosing PONHL preoperatively, therefore requiring excision of the tumor to make the right diagnosis. Although there is a propensity for primary ovarian NHL to be bilateral in nature (41% - 71%), there are no other characteristics that would distinguish it from other ovarian cancers. Therefore, the most proper treatment for primary ovarian NHL is to surgically excise the tumor although chemotherapy should have been the primary treatment because it is one of the most chemosensitive tumors [3].

In our study, all of our 16 cases had a form of surgery performed.

The protocol for chemotherapy used in diffuse large B-cell histology is the standard CHOP regimen. Routine addition of rituximab to CHOP regimen for CD-20 positive disease should be advocated [3].

CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 in the first day of cycle, and prednisone100 mg orally in first to fifth days of each cycle) [7].

Cases of Burkitt's lymphoma received the standard treatment of intensive combination of chemotherapy. These regimens result in cure rates of up to 90% in patients with low stage disease and 60% - 80% in those with advanced disease [8]. After surgical resection, the patient was treated with multiagent chemotherapy CODOX-M-IVAC and central nervous system prophylaxis with intrathecal Ara-c and methotrexate. Four full cycles of chemotherapy were planned [9].

CODOX-M-IVAC (**Table 2**)

Case of B-lymphoblastic lymphoma/leukemia received chemotherapy as per NCCN guidelines (induction, consolidation & maintenance with CNS prophylaxis). Patients receive induction therapy with combinations of drugs, including vincristine, prednisone, cyclophosphamide, doxorubicin, and L-asparaginase, which are given over 4 - 6 wk. Patients then receive consolidation (intensification) with multiagent therapy additionally, including cytarabine and methotrexate; there is no role for radiation or surgical treatment in patients in the induction phase. Maintenance therapy includes 6-mercaptopurine, methotrexate, steroids, and vincristine; intrathecal methotrexate was administered throughout the cycles [10]-[12].

4.4. Survival

The follow-up of these patients remain the same as for NHL. After documentation of complete remission, the patient should be assessed clinically (history and physical examination) at 3-month follow-ups for 2 years, every 6 months for the next 2 years, and yearly thereafter. Repeat contrast-enhanced CT or PET-CT should be performed at follow-up only if there is a clinical suspicion of relapse.

During the period of follow-up (median 31 months, ranging from 3 months to 5 years), one patients (~6%) died during chemotherapy. Another two patients (12.5%) experienced relapse and 3 patients (~19%) died from other causes than ovarian lymphoms. At end of our study ten patients (62.5%) were still alive free of the disease.

The median overall 5 years survival for all cases was not reached yet. The mean OS was 46.8 months, The median PFS was 36 months (**Figure 3** & **Figure 4**).

5. Discussion

NHL uncommonly involves the gynecologic tract. However, when involved by NHL, the ovary is one of the most common anatomic sites [1]. PONHL may mimic the more often occurring tumors including advanced

Table 2. CODOX-MVAC regimen.

CODOX-M (cycle 1 & 3)

Cyclophosphamide: 800 mg/m^2 IV on day 1.

Doxorubicin: 40 mg/m^2 IV on day 1.

Vincristine: 1.5 mg/m^2 IV on days 1 and 8 (cycle 1). Days 1, 8 and 15 (cycle 3).

Methotrexate: 1200 mg/m^2 IV over one hour on day 10, then 240 mg/m^2 per hour for the next 23 h.

Leucovorin rescue: begins 36 h from the start of the methotrexate infusion.

CNS prophylaxis

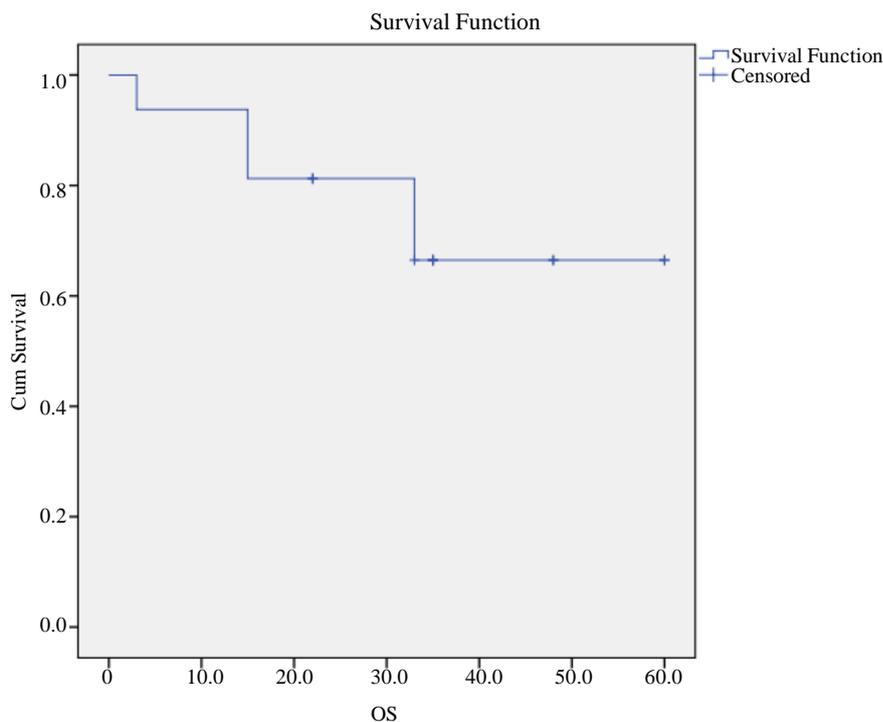Intrathecal cytarabine 70 mg on days 1 and 3.

Intrathecal methotrexate 12 mg on day 15.

IVAC (cycles two and four)

Ifosfamide: 1500 mg/m^2 IV on days 1 through 5 with mesnauroprotection.

Etoposide: 60 mg/m^2 IV on days 1 through 5.
Cytarabine: 2.0 gm/m^2 IV every 12 h on days 1 and 2 (four doses).

Figure 3. Overall survival of all cases.

epithelial carcinoma and, therefore, the correct diagnosis and ideal treatment should have been missed without histopathological examination which is usually after surgical exploration [2] [13].

Early studies debated even the possible occurrence of primary lymphoma in the ovary. The presence of preexisting benign lymphoid cells in the ovary is obviously required for development of a primary malignant lymphatic tumor. Skodras *et al.* [8] as well as Suzuki *et al.* [14] reported the presence of B and T lymphocytes scattered within the ovary. These findings further strengthened the assumption that non-Hodgkin lymphomas may even arise from ovarian tissue.

In the current study, we collected 16 PONHL cases, which seemed had arisen in the ovary *i.e.* primary. All cases were analyzed to further understand their clinico-pathologic and immunophenotypic features. Patients were defined to have PONHL as per Fox *et al.* criteria [1] [15] as previously mentioned.
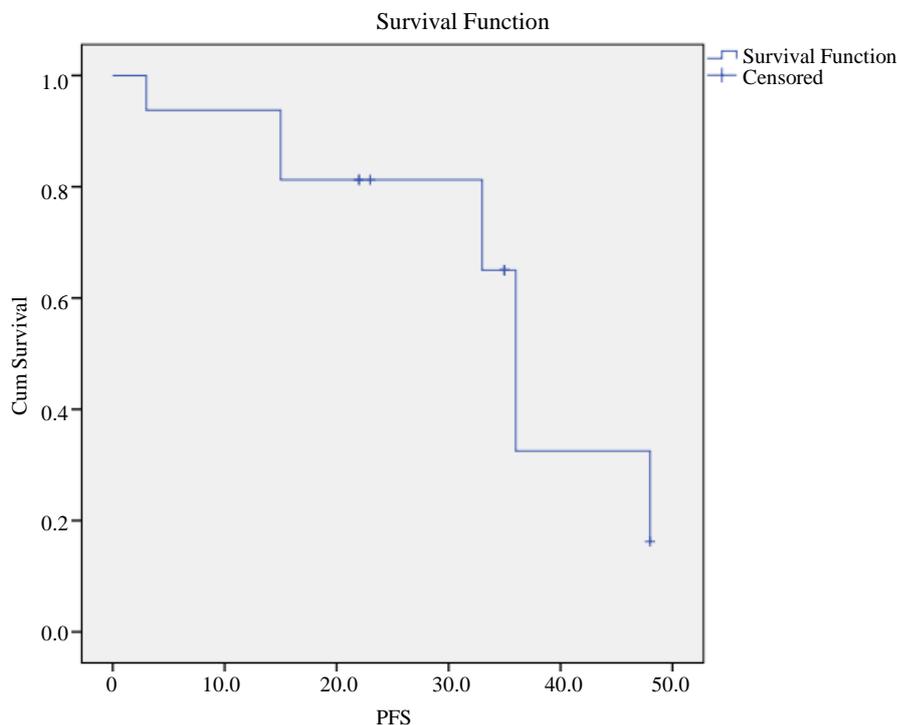
Figure 4. Progression free survival of cases.

This distinction between primary and secondary lymphomas was usually made postoperatively, when the diagnosis of ovarian lymphoma was established and when its extension was evaluated. In this study the sure diagnosis was made postoperative as the preliminary diagnosis was usually an ovarian carcinoma [16].

PONHL can occur at any age. The mean age of our patients was 28 years.

Patients usually sought medical attention for pelvic complaints, menstrual abnormalities or B-symptoms. In our study the commonest manifestation was abdominal enlargement as a result of ascitec fluid accumulation which was noted in 75% of the patients (**Table 3**). This was matching with Vang R. *et al.* (2001) [2].

The neoplasms identified were large, up to 24 cm, which misleaded the primary diagnosis unless some form of surgical procedure was done to confirm the diagnosis and staging of the disease our results was in concordance with Yadav B. *et al.* (2014) and Kumar N. *et al.* (2014) [3] [16].

LDH was found high in all our cases (>280 U/L), while 4 cases (25%) showed high CA125 at presentation (>35 U/ml). Approximately; 90% of women with advanced ovarian cancer have elevated levels of CA-125 in their blood serum, making CA-125 a useful tool for detecting ovarian cancer after the onset of symptoms. Although CA-125 is a sensitive marker, it lacks specificity for confirming the diagnosis of epithelial ovarian tumors. High serum levels of CA-125 have been reported sometimes in ovarian lymphoma, particularly in cases with extensive infiltration of the pelvic peritoneum, which was matching with our data [13].

As previously discussed by Senol Tetal (2014) [13].

Staging of the PONHLs are as difficult as categorizing them as primary and secondary. Disease stage was based on Ann Arbor staging system (**Table 4**, **Table 5**). It seems to be inadequate for the extranodal lymphomas. Bilateral involvement upgrades the staging as stage IV, despite absence of involvement in the other sites. This upgrading needs further clarification. Bilateralism is more common as shown in many publications, (81%) of our cases presented as a bilateral ovarian disease this was confirmed by Yadav B.S. *et al.* (2001); Azizoglu C. *et al.* (2001) and Zhao X. *et al.* (2011) [3] [17] [18]. In this study we had 10 cases of high intermediate risk (62%) & the other 6 (38%) remaining were low IPI risk group [17].

Literatures suggest that nearly all primary lymphomas (92%) of the ovary are B-cell neoplasms, all the sixteen cases were in line. The most common types were DLBCL (8 cases) and Burkitt's lymphoma (6 cases) and 2 cases were B-lymphoblastic lymphoma/leukemia. All of cases in this report had immunohistochemical evaluation showed strong staining for pan B markers (CD19; CD20; CD79a) [17] [18].

Table 3. Patient characters in our study.

Patient characteristics	No. (16)
Age	
≥18 years	8 (50%)
<18 years	8 (50%)
Symptomatology	
1-Ascites	12 (75%)
2-Pelvic pain	10 (62.5%)
3-Constitutional symptoms	9 (56%)
4-Menstrual irregularities	7 (44%)
5-Distension	6 (37.5%)
Size of the tumor	
≥10 cm	12 (75%)
<10 cm	4 (25%)
Bilaterality	
Bilateral disease	10 (62.5%)
Unilateral disease	6 (37.5%)

Table 4. Staging of the disease is done according to Ann Arbor staging system (Table 2).

Stage	Description
I-E	Patients with disease limited in unilateral ovary.
II-E	Disease involved one ovary and one area of lymph node around the same ovary.
III-E	Involvement of lymph node sites on both sides of the diaphragm with or without involvement of an extra-lymphatic site *i.e*. ovary (IIIE), spleen (IIIS), or both (IIISE).
IV-E	Bilateral ovary involvement or lymphoma cells found in the ascites.
A	Asymptomatic
B	Fever, night sweats, or weight loss of more than 10%

E (extralymphatic site according to the original Ann Arbor system).

Table 5. Staging of patients in our study.

Staging	No. (16)
Stage I-E	6 (38%)
Stage IV-E	10 (62%)

Mean follow-up period in our data was 31 months, during which two patients relapsed & one recorded case death during treatment & other three other died from unrelated causes.

6. Conclusion

Primary lymphoma of the ovary is a rare disease; it represents a challenge for Oncology team for proper diagnosis, staging & management. Ann Arbor staging system is deficient. Best treatment option seems to be primary chemotherapy if possible. Physicians should be aware of this rare presentation to avoid radical surgical resection, which seems to be unnecessary. Useful diagnostic markers should be defined to avoid extensive surgical unnecessary staging.

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