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Original Article

Pathology Section

Primary Ovarian Non-Hodgkin Lymphoma- A Diagnostic Challenge with Clinicopathological Study of Eight Cases

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ABSTRACT

Introduction: The involvement of the Female Genital Tract (FGT) by lymphoma is extremely rare, with ovaries being most commonly affected. Less than 1% of lymphomas present with ovarian involvement and less than 1.5% of ovarian neoplasms are of lymphoid origin. Secondary involvement of ovary by systemic lymphoma is more common than Primary Ovarian Lymphomas (POL) which is usually Primary Ovarian Non-Hodgkin lymphoma (PONHL) of B-cell lineage.

Aim: To understand the clinicopathological and immuno-morphological features of Primary Ovarian Non-Hodgkin lymphoma.

Materials and Methods: This was a descriptive retrospective study conducted at Department of Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka. India, for a duration of 14 years between July 2006 to June 2020. Eight cases of PONHL were identified from departmental archives and clinicopathological and Immunohistochemistry (IHC) findings of these tumours were analysed.

Results: The PONHL constituted 0.4% of all Non-Hodgkin lymphoma (NHL) reported during the study period. The patients age ranged from 13-60 years with a mean age of 34 years. Among eight cases of PONHL, two cases were of Diffuse Large B-Cell Lymphoma (DLBCL), followed by one case each of High-Grade B-Cell Lymphoma, Not Otherwise Specified (HGBL, NOS), Follicular Lymphoma (FL), Burkitt Lymphoma (BL), Plasmablastic Lymphoma (PBL), Precursor B-Lymphoblastic Lymphoma (B-LBL), and precursor T-Lymphoblastic Lymphoma (T-LBL). Seven cases were staged IE (Ann Arbor staging system) while one case was designated as stage IIE.

Conclusion: This was probably the first study on PONHL from India. The diagnosis of PONHL is challenging unless there is a high index of suspicion as these patients present with non specific pelvic symptoms and can be misdiagnosed as other epithelial, stromal or germ cell ovarian neoplasm which differs in treatment and prognosis. Histological examination with IHC and molecular testing are essential to establish a diagnosis.

Keywords: Extra-nodal, Female genital tract tumours, High-grade B-cell lymphoma, Ovarian lymphoma, Ovarian solid tumours

INTRODUCTION

The involvement of the Female Genital Tract (FGT) by lymphoma is extremely rare, with ovaries being most commonly affected, followed by the uterine cervix, uterine corpus, vagina, vulva, and Fallopian Tubes (FT) [1-3]. Less than 1% of lymphomas present with ovarian involvement and less than 1.5% of ovarian neoplasms are of lymphoid origin [4]. Ovarian lymphoma seldom occurs as a primary neoplasm arising from the ovary. The secondary involvement of ovaries, as an initial clinical manifestation of occult nodal disease, or as a manifestation of widely disseminated systemic lymphoma is more common [2,5].

Almost all PONHL of B-cell lineage, with DLBCL being the most common type followed by FL and BL [3,6].

The literature on PONHL is sparse and limited to case reports and a few case series. This was the first case series from India describing eight cases of PONHL. Given the rarity of POL, this case series aimed towards understanding the clinicopathological and immunomorphological features of PONHL. The findings of this study were compared with the previously published studies in the English medical literature.

MATERIALS AND METHODS

This was a descriptive retrospective study conducted at Department of Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India for a duration of 14 years between July 2006 to June 2020. This study strictly followed the Ethical principles laid down by the Institutional Scientific Review Board and Ethical Committee. Eight cases of PONHL were identified from departmental archives between study periods. The cases included both the institutional surgical specimens and review cases.

Inclusion and Exclusion criteria: Cases collected in this study were in accordance with the criteria suggested by Fox H et al., which states that: (a) the lymphoma should be confined to the ovary or regional lymph nodes or structures at diagnosis, without evidence of lymphoma elsewhere; (b) bone marrow and peripheral blood should not contain any abnormal cells; and (c) remote involvement should occur at least several months after ovarian involvement [7].

Study Procedure

The clinical and radiological findings were retrieved from Medical Records Department. Haematoxylin and Eosin (H&E) stained slides of all cases from the routinely processed Formalin-Fixed Paraffin-Embedded (FFPE) tissue was reviewed. IHC was performed using the Horseradish Peroxidase (HRP) polymer method, with 3, 3'-diaminobenzidine tetrahydrochloride (DAB) as a chromogen. The FFPE tissues were sectioned at 4-micron thickness and taken on silane coated slides, dewaxed and heat-induced antigen retrieval was done using the multi-epitope retrieval system, blocked with 2% skimmed milk blocking solution and then incubated with a primary antibody. The bound primary antibody was detected by the addition of secondary antibody conjugated with HRP polymer and DAB chromogen. The slides were counterstained with haematoxylin and covered in a mounting medium. The following antibodies were used depending on the differential diagnosis based on histomorphological features: CD45, CD20, CD79a, CD3, CD7, CD4, CD8, BCL2,

BCL6, CD10, MUM1, CD138, MPO, TdT, EMA, and Ki67. Positive external controls (tonsillar tissue, thymic tissue and known case of myeloid sarcoma) were used along with test samples. Each tumour was typed according to the World Health Organisation (WHO) classification [2]. Bone marrow biopsy was done in all cases for the staging of lymphoma. Basic haematological, biochemical, and serological test results were obtained from case files.

STATISTICAL ANALYSIS

Descriptive statistics were used to analyse the results.

RESULTS

Primary ovarian NHLs constituted 0.4% of all NHLs reported during the study period. Among eight cases of PONHL, two cases were of DLBCL, followed by one case each of High-Grade B-Cell Lymphoma, Not Otherwise Specified (HGBL, NOS), Follicular Lymphoma (FL), Plasmablastic Lymphoma (PBL), B-Lymphoblastic Lymphoma (B-LBL), and precursor T-Lymphoblastic Lymphoma (T-LBL). The clinical and histochemical features have been summarised in [Table/Fig-1].

predominantly solid with occasional cystic areas [Table/Fig-2]. The solid areas were firm to fleshy in consistency. Haemorrhagic and necrotic areas were seen in six cases. Ipsilateral FT were unremarkable in six cases and showed tumour deposits in one case (case no. 3).

Histopathological and Immunohistochemical Findings [Table 3a-f,4a-d]

Both cases of DLBCL (case no. 1, and 2) showed diffuse sheets of large lymphoid cells (centroblastic type) with a moderate amount of cytoplasm and nucleus size more than twice of normal lymphocyte. The nuclear contours were irregular or round with vesicular to granular chromatin and solitary or multiple nucleoli and frequent mitosis [Table/Fig-3a,4a]. Among these two DLBCL cases, one was Germinal Centre B-cell (GCB) type (CD10+, BCL6+, and MUM1+ in <30% of neoplastic cells) [Table/Fig-3b-e], while other was of the Activated B-Cell (ABC) type (MUM1+, BCL6+, and CD10-) [Table/Fig-4b-d]. The neoplastic lymphoid cells had replaced the ovarian stroma. Both cases had a high proliferative index which varied from 70% to 90% [Table/Fig-3f].

Case No.	Age (years)	Presentation	Side	Size (cm)	Diagnosis	Immunophenotype	Ann Arbor stage	Therapy	Follow-up/Outcome
1.	60	Pain in abdomen, Pelvic mass	L	5	DLBCL- GCB type	LCA+, CD20+, CD10+, BCL6+, MUM1 patchy + in <30% of neoplastic cells, MPO-, CD138-, Ki67- 80%	IE	USO	Died, 1 month
2.	41	Pain in abdomen	R	7.6	DLBCL- ABC type	LCA+, CD20+, MUM1+, BCL6+, CD10-, BCL2-, Ki67- 70%	IE	TAH-BSO, CT, RT	No evidence of disease, 4.5 years
3.	28	Pain in abdomen, Pelvic mass	R	24	HGBL, NOS	LCA+, CD20+, BCL6+, CD10+, MUM1-, BCL2-, C-MYC-, Ki67- 90% [FISH for C-MYC rearrangement: Negative]	IIE	TAH-BSO, CT	Undergoing treatment, 1 year
4.	38	Pain in abdomen	L	7.5	Follicular lymphoma (FL)	LCA+, CD20+, CD10+, BCL2+, BCL6+ Ki67- 80%	IE	TAH-BSO, CT	Died, disease free for a year
5.	17	Pain in abdomen, Pelvic mass	R	12	Burkitt's lymphoma (BL)	LCA+, CD20+, CD10+, Ki67- 95%, TdT-, C-MYC+	IE	USO	Refused further treatment
6.	13	Pain in abdomen, Pelvic mass	R	10.6	B-lymphoblastic lymphoma (B-LBL)	LCA+, CD20+, TdT+, CD10+, Ki67- 80%	IE	USO	Refused further treatment
7.	41	Pain in abdomen, Pelvic mass	B/L	10, 10	T-lymphoblastic lymphoma (T-LBL)	LCA+, TdT+, CD3+, Ki67% - 90%	IE	TAH-BSO, CT	No evidence of disease, 5 years
8.	36	Pain in abdomen, Pelvic mass	R	8	Plasmablastic lymphoma (PL)	LCA-, CD138+, CD38+, MUM1+ [EBER-ISH for EVB Negative]	IE	TAH-BSO, CT	No evidence of disease, 7 years

[Table/Fig-1]: Clinical and immunohistochemical features of PONHL in present study.
R: Right ovary; L: Left ovary; B/L: Bilateral ovaries; DLBCL: Diffuse large B-cell lymphoma; ABC: Activated B-cell type; GCB: Germinal centre B-cell type; HGBL: High grade B-cell lymphoma; NOS: Otherwise non specified; FISH: Fluorescence in situ hybridization; EBER-ISH: Epstein-Barr virus encoded RNA in situ hybridization; EBV: Epstein-Barr virus; TAH-BSO: Transabdominal hysterectomy with bilateral salpingo-oophorectomy; USO: Unilateral salpingo-oophorectomy; CT: Chemotherapy; RT: Radiotherapy

Clinicopathological Characteristics

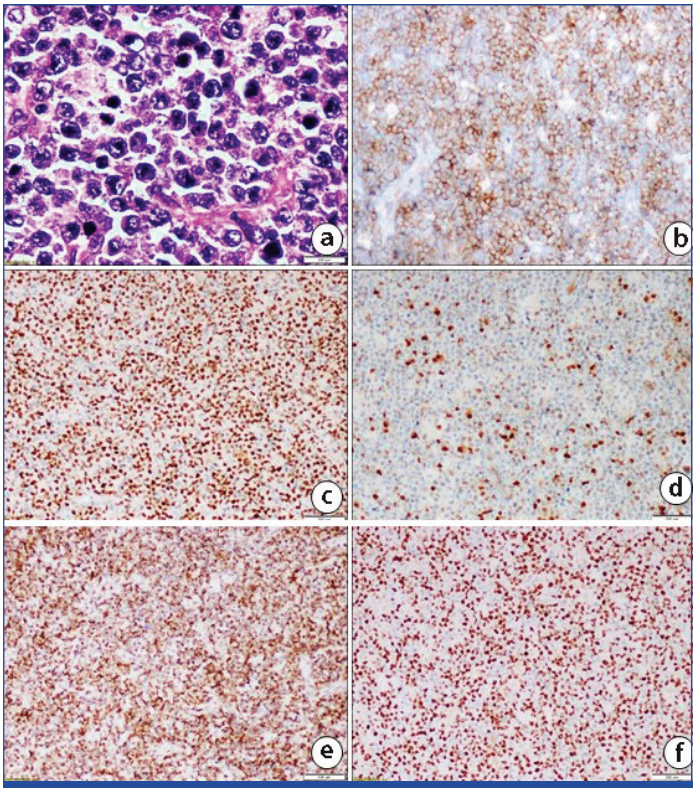
The patients ranged in age from 13-60 years with a mean age of 34 years. All eight cases presented with pain in the abdomen with six patients also complaining of a pelvic mass. Three patients had a history of vaginal bleeding/menorrhagia. While seven tumours were unilateral, one patient presented with bilateral tumour masses [Table/Fig-1], case no. 7). Of the seven unilateral tumours, five were right-sided and two involved the left ovary. Ultra-sonographic findings were non specific and suggestive of predominantly solid neoplasm in five cases and solid cystic neoplasm in three cases. Seven cases were localised to the ovary (Ann Arbor stage IE) and one case was designated as stage IIE because of involvement of the omentum and mesenteric lymph node (case no. 3). There was no evidence of generalised lymphadenopathy. Bone marrow and peripheral blood were not involved by lymphoma in any case. Serum LDH and CA125 levels were elevated in all cases with the mean values being 1473 U/L and 134 U/mL, respectively. One case was positive for HBsAg (case no. 2).

Gross Appearance

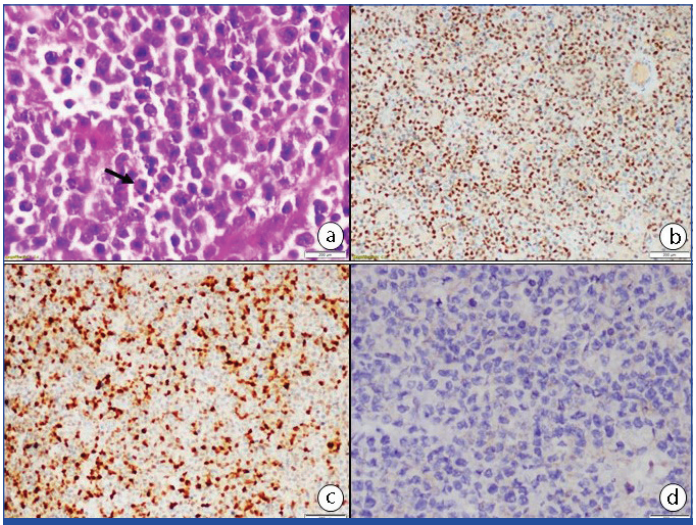
Tumour size was ranging from 8 to 26 cm (mean=10.75 cm) in maximum dimension. Grossly, the ovarian capsule was intact in seven cases and breeched in one (case no. 3). All tumours were

[Table/Fig-2]: Gross appearance of a specimen of transabdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO) showing right ovarian neoplasm which is predominantly solid and cystic with focal areas of haemorrhage. The left ovary showed predominantly haemorrhagic areas. Bilateral FT and uterus were unremarkable in this case.

The third case showed diffuse sheets of medium sized neoplastic lymphoid cells with scattered large cells and intermixed tingible

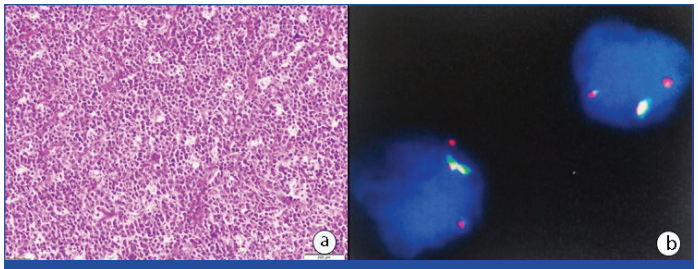


[Table/Fig-3a-f]: Immunomorphological features of ovarian DLBCL-GCB type showing diffuse sheets of large neoplastic lymphoid cells with a moderate amount of cytoplasm with irregular nucleus having vesicular chromatin, visible nucleoli, and frequent mitosis (a) (H&E stain, ×400). The neoplastic cells are immunoreactive for CD10 (membranous) (magnification ×200) (b), BCL6 (nuclear) (magnification ×100) (c), MUM1 nuclear positivity in <30% of tumour cells (magnification ×100) (d); and BCL-2 (nuclear and cytoplasmic) (magnification ×100) (e). The neoplasm is showing a high proliferative index with Ki67 (magnification ×100) (f) (immunoperoxidase stain, HRP polymer method).



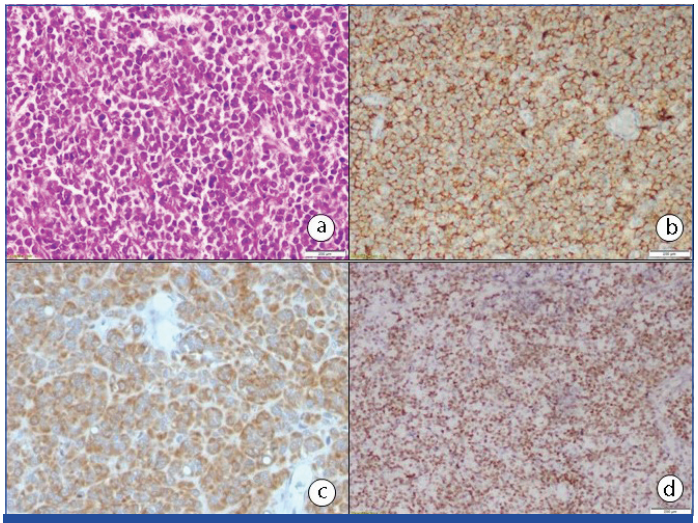
[Table/Fig-4a-d]: Immunomorphological features of ovarian DLBCL- ABC type showing histomorphology similar to DLBCL-ABC type (magnification x400) (a). These neoplastic cells are immunoreactive for BCL-6 (nuclear) (magnification x100) (b), MUM1 (nuclear positivity in >40% of tumour cells) (magnification x100) (c), while non-reactive to CD10 (magnification x200) (d) (immunoperoxidase stain, HRP polymer method).

body macrophages imparting a starry sky pattern. The morphological features of this case were intermediate between DLBCL and BL [Table/Fig-5a]. On IHC, the tumour cells were immunoreactive for LCA, CD20, CD10 and BCL6. Fluorescence In-Situ Hybridisation (FISH) for *C-MYC* rearrangement was performed to rule out BL. FISH showed 2 to 8 fusion signals of break-apart probe in most of the neoplastic nuclei and hence was interpreted to be negative for *C-MYC* rearrangement [Table/Fig-5b]. The molecular tests to identify double-hit (MYC, BCL2 or BCL6) or triple-hit lymphoma (MYC, BCL2 and BCL6) signatures could not be performed. Hence, we labelled this neoplasm as HGBL, NOS.



[Table/Fig-5]: HGBL, NOS showing diffuse sheet of monotonous medium sized neoplastic lymphoid cells with conspicuous sclerotic band and intermixed tingible body macrophages appearing morphological features intermediate between DLBCL and BL (H&E stain, x200) (a). FISH for C-MYC showing three fusion signals of break-apart probe in each neoplastic nuclei (b) (magnification x1000).

One case of FL (case no. 4) showed closely packed irregular follicles with randomly distributed centroblasts and centrocytes [Table/Fig-6a]. There were average seven large nucleolated cells per high power field, rendering it grade 2 FL. The neoplastic lymphoid cells were positive for CD20, CD10, BCL2, and BCL6 [Table/Fig-6b-d].



[Table/Fig-6]: Immunomorphological features of ovarian FL showing neoplastic lymphoid cells forming a vague follicular pattern with mixed centroblastic-centrocytic cells (grade 2) (a) (H&E stain, x400). The neoplastic lymphoid cells are positive for CD20 (membranous) (magnification x400) (b), BCL2 (cytoplasmic) (magnification x400), and BCL6 (nuclear) (magnification x100) (immunoperoxidase stain, HRP polymer method).

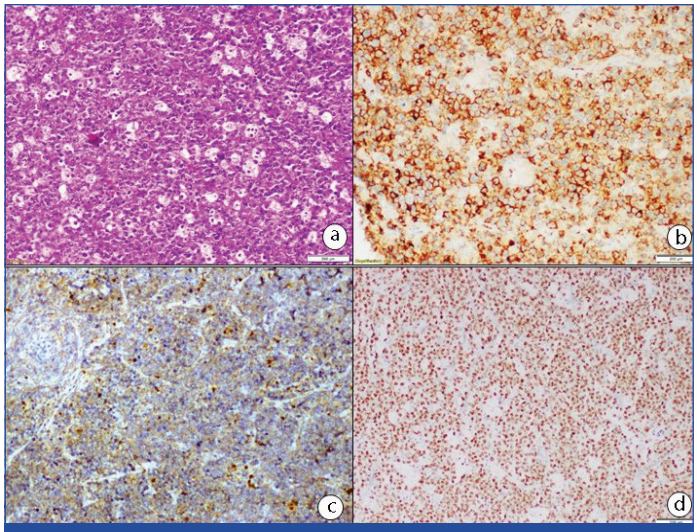
The BL case (case no. 5) was composed of a monotonous population of medium sized neoplastic cells and tingible body macrophages giving a starry sky appearance [Table/Fig-7a]. These cells had round to slightly irregular nuclear contours, with vesicular chromatin and high mitotic rate. These neoplastic cells were positive for CD20 and CD10 and negative for TdT. The Ki67 proliferating index was approaching 100% [Table/Fig-7b-d].

There was one case each of precursor B-LBL and T-LBL respectively. Both cases showed sheets of small to medium sized tumour cells with round to oval, indented nuclei with coarsely clumped chromatin with indistinct to prominent nucleoli. Numerous mitoses were present. While the B-LBL case was positive for CD20 and TdT and the T-LBL case was positive for CD3 and TdT. Both cases showed a Ki67 index of >90% [Table/Fig-8a-d,9a-d].

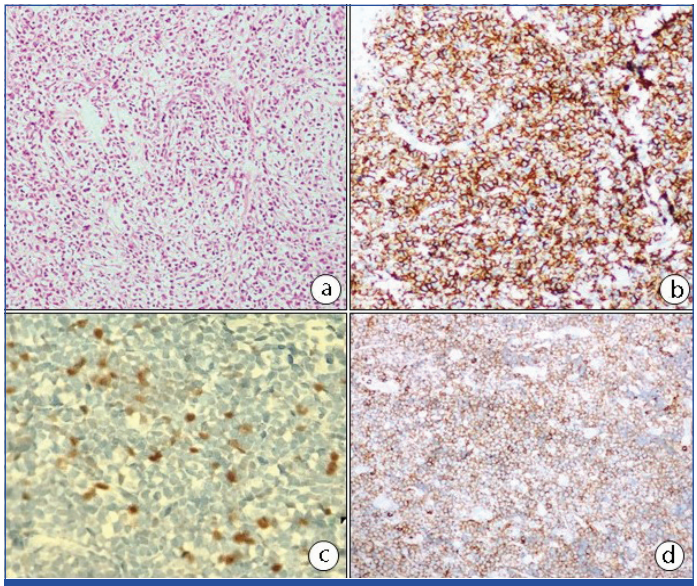
One case of PBL showed sheets of large plasmacytoid cells with large vesicular nuclei, prominent nucleoli with abundant cytoplasm [Table/Fig-10a-d]. These cells were immunoreactive for CD38, CD138, and MUM1.

Treatment and Follow-up

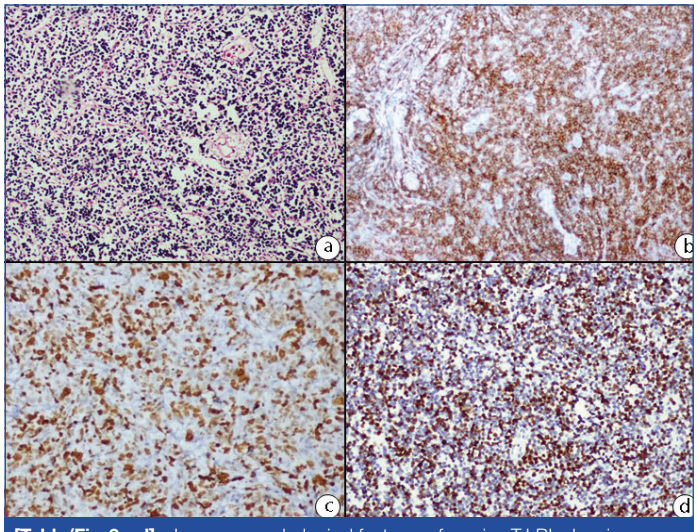
Varying combinations of surgery, Chemotherapy (CT), and Radiotherapy (RT) were used to treat these patients. Five of the eight cases underwent transabdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO), whereas the remaining three patients underwent unilateral salpingo-oophorectomy with tumour debulking surgery. Five patients received adjuvant CT and one received a combination of CT and RT.



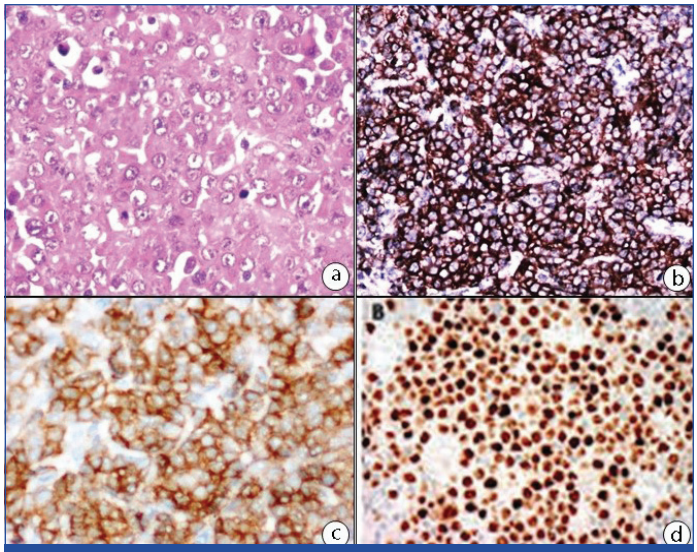
[Table/Fig-7a-d]: Immunomorphological features of ovarian BL showing a monotonous population of medium-sized neoplastic cells and tingible body macrophages displaying starry sky appearance (a) (H&E stain, x400). Neoplastic lymphoid cells expressing CD20 (membranous) (magnification x400) (b), CD10 (membranous) (magnification x100) (c) and a high Ki67 proliferating index >90% (magnification x100) (d) (immunoperoxidase stain, HRP polymer method).



[Table/Fig-8a-d]: Immunomorphological features of ovarian B-LBL showing sheets of small to medium-sized tumour cells with imperceptibly irregular nuclei with coarsely clumped chromatin and indistinct nucleoli (a) (H&E stain, x200). These cells are positive for CD20 (membranous) (magnification x200) (b), TdT (nuclear) (magnification x400) (c), and CD10 (membranous) (magnification x200) (d) (immunoperoxidase stain, HRP polymer method).



[Table/Fig-9a-d]: Immunomorphological features of ovarian T-LBL showing histomorphological features similar to B-LBL (magnification x200) (a). T-LBL neoplastic cells show immunopositivity for CD3 (membranous) (magnification x200) (b), TdT (nuclear) (magnification x400) (c) with high ki67 proliferative index (>90%) (magnification x100) (d) (immunoperoxidase stain, HRP polymer method).



[Table/Fig-10a-d]: Immuno-morphological features of ovarian PBL showing sheets of large plasmacytoid cells with abundant cytoplasm, large vesicular nuclei with prominent nucleoli (a) (H&E stain, x400). These cells are immunoreactive for CD138 (membranous) (magnification x400) (b), CD38 (membranous) (magnification x400) (c), and MUM1 (nuclear) (magnification x400) (d) (immunoperoxidase stain, HRP polymer method).

The chemotherapeutic regimen consisted of R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Clinical follow-up ranged from five months to seven years (mean four years). Three patients were alive and disease-free at the last follow-up and one patient is undergoing treatment. Also, while two patients succumbed to disease, the remaining two patients refused further treatment after surgery and were lost to follow-up.

DISCUSSION

Primary lymphomas of the FGT are rare with ovaries being the most common site to be involved [2]. This can be seen in the study by Nasioudis D et al., who reviewed 697 cases of primary lymphomas of FGT and concluded that POL constituted 37% of cases followed by cervix (21.4%), and uterus (16.5%) [3].

Histogenesis of PONHL is unclear but it is considered to arise from hilar lymphoid tissue, from lymphocytes in an inflammatory infiltrate in ovarian stroma, or from lymphoid tissue in a teratoma of ovary [7-10]. The present study reported eight cases of PONHL according to criteria suggested by Fox H et al., [7]. However, Paladugu RR et al., found these criteria to be insufficiently stringent and suggested that there should be 60 months of disease free interval following surgical treatment of the ovarian lesion [11]. This criterion is difficult to apply practically and makes the possibility of lymphomas to arise primarily in the ovary exceedingly rare. For instance, Chorlton I et al., reported 54 cases of POL, of them only five tumours can be eligible for this diagnosis if this criterion is adopted [12]. Similarly, only two tumours in this series would qualify this criterion.

Lymphomas of the ovary affect patients of any age, but most often in the third and fourth decade [6]. In this study patients age ranged from 13 to 60 years with a mean age of 34 years [Table/Fig-11]. Patients of ovarian lymphoma usually present with complaints of abdominal pain, pelvic mass, abnormal vaginal bleeding, and ascites [13,14]. B-symptoms like fever, night sweats, fatigue, or weight loss are seen in 10%-33% of the patients [6,15]. Also, most of the PONHL patients present with elevated CA125 and LDH similar to other ovarian neoplasms [14,16]. CA125 and LDH levels were elevated in all cases whereas B-symptoms were not seen in patients of the present study. Vang R et al., reported that unilateral ovarian involvement was commoner than bilateral involvement with no predilection to side, in localised stage I_E diseases [4]. All eight cases of PONHL in this study were low stage NHLs, seven of which presented with unilateral disease.

Sr. No.	Authors (year of publication)	Country	Duration (years)	No. of cases	P, S, U	Age range (years)	Histological subtype (n)
1.	Chorlton I et al., 1974 [12]	Washington, DC	-	19	19P	7-59	BL(1), LLPD (7), LLMD (4), LLWD (2), RS (4), HL-MC(1)
2	Paladugu RR et al., 1980 [11]	California	-	11	3P, 8S	17-69	DSCL (2), F&D SCL (2), DLCL (3), BL (2), LL (1), DSNCL (1)
3.	Osborne BM and Robboy SJ 1983 [17]	Boston, Massachusetts	-	40	40P	2-74	LCIBL (13), DSNCL (11), DLCL (10), FSCCL (2), FMCL (2), FLCL (2)
4.	Fox H et al., 1988 [7]	Manchester	-	34	3P, 31S	7-71	DLBCL (6), FL (6), Histiocytic lymphoma (5), DULBCL (2), BL (7), PTLL (2), LL (6)
5.	Monterroso V et al.,1993 [15]	Maryland USA	38 (1953-1991)	39	4P, 27S, 8U	2-77	BL (21)*, DLBCL (8), FL grade III (4), F&D SCL (1), PTCL (1), F&D LCL (2), DLCL (2)
6.	Dimopoulos MA et al., 1997 [6]	Houstan, Texas	20 (1974-1993)	14	14P	22-69	DLCL (9), DSNCL (3), LL (2)
7.	Vang R et al., 2001 [5]	Houston USA	-	8	8P	29-62	FL grade III (1), FL grade II (1), DLBCL (3), BL (1), PTLL (1), ALCL (1)
8.	Kosari F et al., 2005 [22]	Germany	30 (1974-2004)	45	45P	-	DLBCL (25), BL (5), FL-I (5), FL-II (1), FL-III (4), PBLL (1)
9.	Zhao XY et al., 2011 [14]	China	10 (1997-2006)	14	14P	29-72	DLBCL (13), PBLL (1)
10.	Sun J et al., 2015 [16]	Beijing	14 (1999 to 2012)	14	14P	13-74	DLBCL (12), BL (2)
11.	Present study	India	14 (2006-2020)	8	8P	13-60	DLBCL (3), FL (1), BL (1), PBL (1), PBLL (1), PTLL (1)

[Table/Fig-11]: Comparison of histological subtypes of ovarian lymphoma reported in various major studies.
ALCL: Anaplastic large cell lymphoma; BL: Burkitt's lymphoma; DLBCL: Diffuse large B-cell lymphoma; DLCL: Diffuse large cell lymphoma; DSCL: Diffuse small cell lymphoma; DSNCL: Diffuse small cell noncleaved lymphoma; DULBCL: Diffuse undifferentiated large cell lymphoma; F&D LCL: Follicular and diffuse large cell lymphoma; F&D SCL: Follicular and diffuse small cell lymphoma; FLCL: Follicular large cell lymphoma; FL: Follicular lymphoma; FMCL: Follicular mixed cell lymphoma; FSCCL: Follicular small cell cleaved lymphoma; HL-MC: Hodgkin lymphoma, mixed cellularity type; LCIBL: Large cell immunoblastic lymphoma; LL: Lymphoblastic lymphoma; LLMD: Lymphocytic lymphoma, moderately differentiated; LLPD: Lymphocytic lymphoma, poorly differentiated; LLWD: Lymphocytic lymphoma well differentiated; P: Primary; PBLL: Precursor B-lymphoblastic lymphoma; PTLL: Precursor T-lymphoblastic lymphoma; RS: Reticulum cell sarcoma; S: Secondary; U: Unclassified
*Eight cases were diagnosed according to morphologic criteria alone

Macroscopically, ovarian lymphomas have been reported as unilateral or bilateral mass forming solid tumours which vary in size from 4 to 20 cm (median size 8-12 cm) [5,14,16]. The common differential diagnosis of solid ovarian tumours includes Brenner tumours, teratomas, dysgerminomas, ovarian fibromas, ovarian thecomas, granulosa cell tumours, and Krukenberg tumours [17,18]. It is necessary to differentiate PONHL from advanced epithelial carcinoma as both can present with similar clinical features like elevated tumour markers and ascites [19,20]. Lymphoblastic Lymphoma (LL) can be confused with other small round cell tumours so an optimal panel of IHC should be used to classify ovarian lymphoma [21].

Commonly, lymphomas of the ovaries are of B-cell lineage with previous studies revealing DLBCL to be the most common subtype of PONHL followed by BL and FL, a finding consistent with this series [Table/Fig-11] [3-5,7,14-17,22].

Histologically, ovarian DLBCL shows centroblast, immunoblast, and/or multilobed cells arranged in diffuse sheets, nests, and cords associated with sclerosis [16-20]. In present study, two cases showed typical immuno-morphological features of DLBCL while one case showed morphological features intermediate between DLBCL and BL which warranted further molecular analysis to classify this lymphoma as double-hit/ triple-hit lymphoma (HGBL with MYC and BCL2 and/or BCL6 rearrangements) or HGBL, NOS (HGCL that lack defined genetic rearrangements or unable to classify as DLBCL or BL). This case was labelled as HGBL, NOS as molecular test could not be performed due to poor economic status of patient. DLBCL-GCB type is commoner than ABC type as describe by Xu H et al., who reported seven cases of GCB subtype in their study on nine ovarian DLBCLs [23]. Molecular pathogenesis of DLBCL shows clonal rearrangement of IG genes. Cao XX et al., suggested that 50% of cases have *MYD88* p.Leu256Pro mutation and 25% have CD79BB p.Tyr196 mutation (with or without *MYD88* p.Leu256Pro) [24]. Khattar P et al., conducted a molecular analysis of ovarian DLBCL and concluded that most *MYD88* mutated cases had an NGCB immunophenotype while somatic mutations of EZH2 and GNA13 are restricted to GCB DLBCL cases [18]. Xu H et al., also stated that *NOTCH3* and *HDAC4* mutations are commonly identified in the GCB subtype of DLBCL involving the ovaries but not in the conventional type [23].

Histologically, primary ovarian FL shows mixed diffuse and follicular growth patterns and high grade cytological features as compared to secondary involvement by systemic disease [2]. Özsan N et al., studied 16 cases of ovarian FL and concluded that FL presenting in the ovary comprised of two distinct biological subsets: one group showed features of nodal FL, including presentation as an advanced-stage disease with low histologic grade, BCL2 immunoreactivity, and presence of IGH@/BCL2 translocation. The second group included cases that presented with the disease usually confined to one ovary, showing a higher histologic grade, loss CD10 and BCL2 immunoreactivity and absence of IGH@/BCL2 fusion. This latter group may represent the true primary ovarian FL as it shows distinct biological and immunologic characteristics similar to higher-grade/low-stage FL presenting at other extra-nodal sites [25]. Ovarian FL in the present study can be categorised in the second group as it was confined to one ovary with histological grade 2.

BL is an aggressive undifferentiated B-cell NHL which accounts for 5-20% of FGT lymphomas [2]. It is characterised by frequent extra-nodal site presentation, an extremely rapid growth rate with a short doubling time, and usually *MYC* translocation [3,4,22]. Stepniak A et al., reviewed 21 cases of primary ovarian BL and formulated 4 factors suggestive of primary ovarian BL which include: young age at presentation, bilateral ovarian involvement, rapid progression, and high LDH levels [26]. While Stepniak A et al., reported that 67% of their primary ovarian BL cases presented with bilateral ovarian involvement, the case of BL in this series involved only the right ovary. Pathogenesis of BL is characterised by deregulation of MYC expression by translocation of *MYC* to an *IG* gene locus. The diagnosis of BL can be made based on of criteria suggested by Haralambieva E et al., [27]. These include: a Ki-67 index of ~90%, breakpoints in the MYC gene, CD10 positivity with an absence of BCL2 expression [27].

PBL is a high-grade NHL, usually seen in the oral cavity of immunodeficient patients, usually Human Immunodeficiency Virus (HIV) positive [28]. Extra-oral PBL arising in the ovary is very rare and not related to immunodeficiency [29]. Epstein-Barr Virus (EBV) is an important aetiological factor is seen in 70% of PBL cases [30]. In addition to EBV infection, recent studies have identified the presence of MYC gene rearrangements as an important

pathogenic mechanism of PBL [31]. The neoplastic cells in PBL are immunonegative for CD20 with the expression of CD138, CD38, CD79a, IRF4/MUM1, cytoplasmic immunoglobulins (most frequently IgG), either kappa or lambda light chain restriction, and a high Ki-67 proliferation index (usually ≥80%) [32]. Cases of PBL which are seen in HIV-negative individuals have shown EBV association in 17% of cases [33]. The present case of PBL was negative for HIV and did not express EBER by ISH.

The LL of the ovary is rarely seen and usually presents as secondary involvement than a primary lymphoma [2]. Case studies by Dimopoulos MA et al., Fox H et al., and Paladugu RR et al., reported only one, six, and two cases of LL, respectively [6,7,11]. Histologically, it shows small to medium sized blasts with scant cytoplasm and convoluted nuclei which are uniformly immunoreactive for TdT. While B- ALL cells are positive for B lineage markers (CD19, CD20, CD79a), and CD10; T- ALL shows positivity for T-cell lineage markers (CD3, CD7), CD1a+, CD10+/-, and/or CD4/CD8 double+ [21,34]. Clonality of IGH or T-cell Receptor (TR) can be demonstrated by molecular analysis [2].

The POL are staged as other extra-nodal NHLs (Ann Arbor staging system) or by Lugano staging system [2,3]. Most studies on ovarian NHL have included both primary and secondary cases of ovarian lymphoma [7,12,20]. Less than 10% of all ovarian NHLs reported in the literature are presumably PONHLs [6,17]. This distinction is of considerable importance because primary extra-nodal lymphomas have a less aggressive disease course with a five-year survival rate of 80% as compared to lymphomas with secondary involvement of the ovaries, which have a five-year survival rate of only 33% [6].

PONHL treatment relies on histology, type, and clinical staging. Cancer-Directed Surgery (CDS) was performed in 90.3% of ovarian lymphoma cases in a study by Nasioudis D et al., [3]. Dimopoulos MA et al., reported and reviewed the treatment aspect of ovarian lymphomas and recommend that they should be treated with curative intent with combination CT regimens appropriate for their specific histology [6].

In the present study, ovarian involvement by systemic NHL/leukaemia was ruled out by the absence of generalised lymphadenopathy, bone marrow, and peripheral blood involvement. Also, of the six patients who agreed to further management, three patients show no evidence of disease on follow-up (median follow-up duration, 5 years). The prognosis is better in patients with localised disease. Various reports in the literature suggest the survival rate of PONHL cases ranges from 0% to 36%, with an average survival time of less than 3 years [6,15,18,19].

Nasioudis D et al., reported five-year Cancer-Specific Survival (CSS) of 70.8% for ovarian lymphoma [3]. Inaccurate or delayed diagnosis of ovarian lymphoma contributes to their poor prognosis as compared to nodal lymphoma [7]. While unilateral ovarian involvement and/or focal involvement of the ovary may be considered as indicators of good prognosis; the rapid growth of a pelvic mass, severe systemic symptoms, bilateral ovarian tumours, and advanced stage may be indicative of poor prognosis [14-17].

Limitation(s)

The results of the present study highlight the histopathologic features of PONHL and the prognostic impact of this diagnosis. However, due to the rarity of PONHL, the data needs to be interpreted with caution due to the limited number of patients. Also, further molecular analysis would have been beneficial could not be performed due to poor economic status of patients.

CONCLUSION(S)

To conclude, PONHL is a very rare disease with the majority of cases showing a B-cell phenotype. We have described probably the first case series of PONHL from India. They present with non specific pelvic symptoms and can be misdiagnosed as other epithelial, stromal, or germ cell ovarian tumours. Tissue biopsy coupled with IHC and molecular testing is essential to establish a diagnosis, especially in young females. Low stage PONHL has a good prognosis if optimally treated with combined CT with or without surgery.

REFERENCES

[1] Ferry JA. Hematologic Neoplasms and Selected Tumourlike Lesions Involving the Female Reproductive Organs. In: Kurman R., Hedrick Ellenson L, Ronnett B. (eds). Blaustein's Pathology of the Female Genital Tract. 7th ed. Cham: Springer, 2019; 1377-1403.

[2] Moch, Holger (editors). Female genital tumours: WHO Classification of Tumours, 5th ed. vol 4. Lyon: International Agency for Research on Cancer. 2020. 463-475.

[3] Nasioudis D, Kampaktsis PN, Frey M, Witkin SS, Holcomb K. Primary lymphoma of the female genital tract: An analysis of 697 cases. Gynecol Oncol. 2017;145(2):305-09.

[4] Vang R, Medeiros LJ, Fuller GN, Sarris AH, Deavers M. Non-Hodgkin's lymphoma involving the gynecologic tract: A review of 88 cases. Adv Anat Pathol. 2001;8(4):200-17.

[5] Vang R, Medeiros LJ, Warnke RA, Higgins JP, Deavers MT. Ovarian non-Hodgkin's lymphoma: A clinicopathologic study of eight primary cases. Mod Pathol. 2001;14(11):1093-99.

[6] Dimopoulos MA, Daliani D, Pugh W, Gershenson D, Cabanillas F, Sarris AH. Primary ovarian non-Hodgkin's lymphoma: Outcome after treatment with combination chemotherapy. Gynecol Oncol. 1997;64(3):446-50.

[7] Fox H, Langley FA, Govan AD, Hill AS, Bennett MH. Malignant lymphoma presenting as an ovarian tumour: A clinicopathological analysis of 34 cases. Br J Obstet Gynaecol. 1988;95(4):386-90.

[8] Woodruff JD, Costillo RD, Novak ER. Lymphoma of the ovary-a study of 35 cases from the Ovarian Tumour Registry of the American Gynecological Socicty. Am J Obstet Gynecol. 1963;85:912-18.

[9] Walther O. On lymphosarcomatosis of the female genital organs. Arch gynecol. 1934;157(1):44-64.

[10] Durfee HA, Clark BF, Peers JH. Primary lymphosarcoma of the ovary: Report of a case. Am J Cancer. 1937;30(3):567-73.

[11] Paladugu RR, Bearman RM, Rappaport H. Malignant lymphoma with primary manifestation in the gonad a clinicopathologic study of 38 patients. Cancer. 1980;45(3):561-71.

[12] Chorlton I, Norris HJ, King FM. Malignant reticulo-endothelial disease involving the ovary as a primary manifestation. A series of 19 lymphomas and 1 granulocytic sarcoma. Cancer. 1974;34(2):397-407.

[13] Lagoo AS, Robboy SJ. Lymphoma of the female genital tract: Current status. Int J Gynecol Pathol. 2006;25(1):01-21.

[14] Zhao XY, Hong XN, Cao JN, Leaw SJ, Guo Y, Li ZT, et al. Clinical features and treatment outcomes of 14 cases of primary ovarian non-Hodgkin's lymphoma: A single-center experience. Med Oncol. 2011;28(4):1559-64.

[15] Monterroso V, Jaffe ES, Merino MJ, Medeiros LJ. Malignant lymphomas involving the ovary. A clinicopathologic analysis of 39 cases. Am J Surg Pathol. 1993;17(2):154-70.

[16] Sun J, Zhang J, Ling Q, Luo Y, Wu S, Liang Z, et al. Primary diffuse large B-cell lymphoma of the ovary is of a germinal centre B-cell-like phenotype. Virchows Arch. 2015;466(1):93-100.

[17] Osborne BM, Robboy SJ. Lymphomas or leukaemia presenting as ovarian tumours. An analysis of 42 cases. Cancer. 1983;52(10):1933-43.

[18] Khattar P, Bedi P, Gonzalez M, Zhong M, Yin C, Huang W, et al. Genomic analysis reveals distinct subtypes in two rare cases of primary ovarian lymphoma. Pathol Res Pract. 2018;214(4):593-98.

[19] Hu R, Miao M, Zhang R, Li Y, Li J, Zhu K, et al. Ovary involvement of diffuse large B-cell lymphoma. Am J Case Rep. 2012;13:96-98.

[20] Senol T, Doger E, Kahramanoglu I, Geduk A, Kole E, Yucesoy I, et al. Five cases of Non-Hodgkin B-cell lymphoma of the ovary. Case Rep Obstet Gynecol. 2014;2014:392758.

[21] Yadav R, Sharma MC, Karak AK, Agarwal N, Kumar R, Kumar L. Natural history of primary precursor B lymphoblastic lymphoma of the ovary: Report of a rare case. J Obstet Gynaecol Res. 2013;39(2):611-16.

[22] Kosari F, Daneshbod Y, Parwaresch R, Krams M, Wacker HH. Lymphomas of the female genital tract: a study of 186 cases and review of the literature. Am J Surg pathol. 2005;29(11):1512-20.

[23] Xu H, Duan N, Wang Y, Sun N, Ge S, Li H, et al. The clinicopathological and genetic features of ovarian diffuse large B-cell lymphoma. Pathology. 2020;52(2):206-12.

[24] Cao XX, Li J, Cai H, Zhang W, Duan MH, Zhou DB. Patients with primary breast and primary female genital tract diffuse large B cell lymphoma have a high frequency of MYD88 and CD79B mutations. Ann Hematol. 2017;96(11):1867-71.

[25] Özsan N, Bedke BJ, Law ME, Inwards DJ, Ketterling RP, Knudson RA, et al. Clinicopathologic and genetic characterisation of follicular lymphomas presenting in the ovary reveals 2 distinct subgroups. Am J Surg Pathol. 2011;35(11):1691-99.

[26] Stepniak A, Czuczwar P, Szkodziak P, Wozniakowska E, Wozniak S, Paszkowski T. Primary ovarian Burkitt's lymphoma: A rare oncological problem in gynaecology: A review of literature. Arch Gynecol Obstet. 2017;296(4):653-60.

[27] Haralambieva E, Boerma EJ, van Imhoff GW, Rosati S, Schuuring E, Müller-Hermelink HK, et al. Clinical, immunophenotypic, and genetic analysis of adult lymphomas with morphologic features of Burkitt lymphoma. Am J Surg Pathol. 2005;29:1086-94.

[28] Castillo JJ, Reagan JL. Plasmablastic lymphoma: A systematic review. Sci World J. 2011;11:687-96.
[29] Tomaselli T, Rollo D, Tarsitano F, Trezzi R, Crescini C. Lymphoplasmacytic lymphoma or plasmacytoma of the ovary? A case report and a literature review. Ital J Gynaecol Obstet. 2016;28(2):17-20.
[30] Castillo JJ, Bibas M, Miranda RN. The biology and treatment of plasmablastic lymphoma. Blood. 2015;125(15):2323-30.
[31] Bogusz AM, Seegmiller AC, Garcia R, Shang P, Ashfaq R, Chen W. Plasmablastic lymphomas with MYC/IgH rearrangement: Report of three cases and review of the literature. Am J Clin Pathol. 2009;132(4):597-605.
[32] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al.* World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue. Revised Edition. Lyon: IARC; 2017. Pp. 291-97.
[33] Hadžisejdić I, Babarović E, Vranić L, Duletić Načinović A, Lučin K, Krašević M, et al. Unusual presentation of plasmablastic lymphoma involving ovarian mature cystic teratoma: A case report. Diagn Pathol. 2017;12(1):01-07.
[34] Sakurai N, Tateoka K, Taguchi J, Terada T. Primary precursor B-cell lymphoblastic lymphoma of the ovary: Case report and review of the literature. Int J Gynecol Pathol. 2008;27(3):412-17.

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