

## Original Article

# Lymphoplasmacytic lymphoma-Waldenström macroglobulinemia: an unusual presentation in ovaries, fallopian tubes and uterine cervix

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Received March 31, 2013; Accepted April 30, 2013; Epub May 22, 2013; Published June 1, 2013

**Abstract:** Lymphoplasmacytic lymphoma is an indolent malignancy of B cells and plasma cells. The disease presents in the adults with bone marrow and lymph nodes involvement. Extranodal involvement is rare but has been reported in spleen and liver. Herein, we present a case of a 50-year-old woman who underwent hysterectomy and salpingo-oophorectomy for irregular uterine bleeding. Histologic examination of uterine cervix, uterine walls and fallopian tubes reveal dense lymphoplasmacytic infiltrate that was most pronounced in ovaries. This is the first case report on lymphoplasmacytic lymphoma-Waldenström macroglobulinemia initially presenting and secondarily involving both ovaries and other gynecological organs.

**Keywords:** Lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, ovary

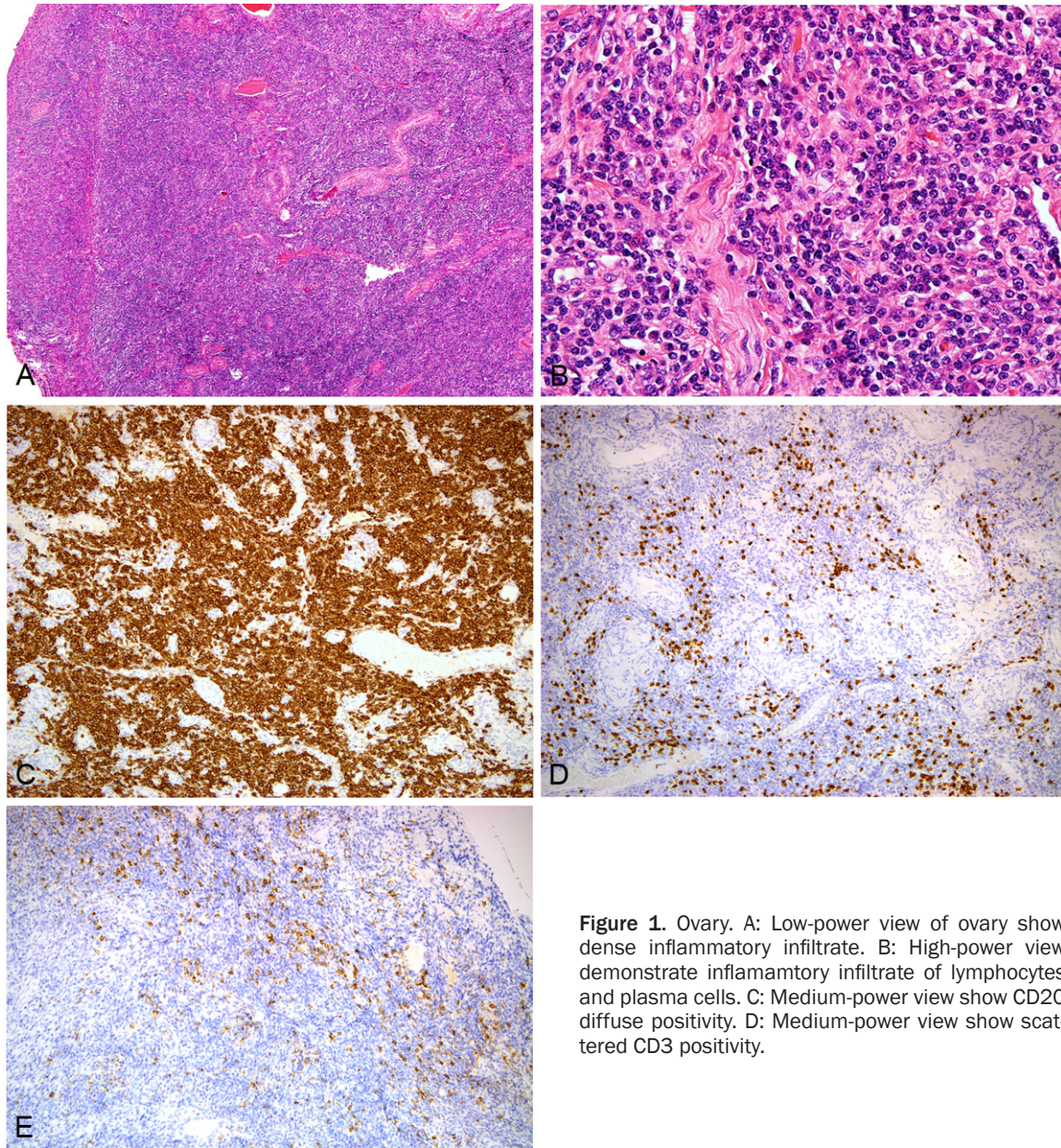
## Introduction

Lymphoplasmacytic lymphoma is an indolent malignancy of B cells and plasma cells. The disease presents in the adults with bone marrow and lymph nodes involvement. Extranodal involvement is rare but has been reported in spleen and liver [1]. The purpose of this case report is to document ovarian, and gynecologic secondary involvement by lymphoplasmacytic lymphoma-Waldenström macroglobulinemia and to describe the potential pitfalls in the histopathologic diagnosis especially in the absence of prior clinical history of lymphoma.

## Report of a case

A 50-year-old postmenopausal woman (gravida 4, para 4), presented with an intermittent low grade fever, night sweats, weight loss and abdominal pain. In addition, she complained of an irregular uterine bleeding. Pap smear was negative for malignancy. Uterine cervical biopsy revealed high grade squamous intraepithelial lesion (HSIL or CIN 2). Initial blood workup showed WBC count  $13 \times 10^9/L$  (high), hemoglo-

bin level 88 g/L (low), hematocrit 0.26 L/L (low), MCV 81 (normal), MCH 27 pg (normal), MCHC 343 g/L (normal), RDW-CV 16% (high), platelet  $409 \times 10^9/L$  (normal). WBC automated differential showed: neutrophils  $4 \times 10^9/L$  (normal), lymphocytes  $6.7 \times 10^9/L$  (high), monocytes  $1.3 \times 10^9/L$  (high), eosinophils  $0.073 \times 10^9/L$  (normal), basophils  $0.087 \times 10^9/L$  (normal). ESR 110 mm/hr (high). PT 12 second, INR 1, aPTT 28 seconds, Fibrinogen 6 g/L (high). Hepatitis B serology was negative, and hepatitis C reactive protein 30 mg/L (high). Abdominal CT scan with contrast in an outside institution revealed diffuse celio-mesenteric and retro-peritoneal lymphadenopathy. Patient underwent hysterectomy and bilateral salpingo-oophorectomy, gross examination was unremarkable. Microscopic examination of the uterine cervix, uterine walls and fallopian tubes revealed dense lymphoplasmacytic mainly cuffing blood vessels without evidence of vascular injury. Examination of ovaries was striking with prominent diffuse infiltrate composed of lymphocytes and plasma cells in medullary location. The infiltrating cells exhibited mature nuclear detail and chromatin distribution (**Figure 1A, 1B**).



**Figure 1.** Ovary. A: Low-power view of ovary show dense inflammatory infiltrate. B: High-power view demonstrate inflammatory infiltrate of lymphocytes and plasma cells. C: Medium-power view show CD20 diffuse positivity. D: Medium-power view show scattered CD3 positivity.

Histopathologic differential diagnosis is outlined in **Table 1** and is discussed below.

Acute and chronic salpingo-oophoritis in the clinical context of pelvic inflammatory disease (PID) enters the histopathologic differential diagnosis. However, neutrophils and foamy histiocytes are missing from the current case. In addition, clinical history and microbial studies were not supportive of this possibility.

Autoimmune oophoritis associated with ovarian failure. Patients of reproductive age presents with amenorrhea and infertility (primary or

secondary). On histology, dense lymphoplasmacytic inflammatory cell infiltrate will be centered on cortical follicles. Some follicles may be destroyed [2]. The current case, is a post-menopausal porous woman and ovarian inflammation was not related to cortical follicles instead it was medullary in location.

Giant cell arteritis more common in uterine cervix but rarely involves ovary [3].

There was no clinical history of systemic arteritis or polymyalgia rheumatic in the patient. The inflammation was mainly perivascular with no

**Table 1.** Histopathologic differential diagnoses of current case

Histopathologic Differential Diagnoses
Chronic oophoritis/pelvic inflammatory disease
Autoimmune oophoritis
Giant cell arteritis/other vasculitis
Small cell carcinoma (primary and metastatic)
Undifferentiated carcinoma (primary and metastatic)
Diffuse adult granulosa cell tumor
Desmoplastic small round cell tumor
Primitive neuroectodermal tumor (PNET)
Lymphoma and leukemia (primary and secondary)

evidence of fibrinoid necrosis of the vessel wall or intraluminal thrombi. In the ovary the inflammation was centered in the medullary portion and spared ovarian cortex. Microscopic examination in giant cell arteritis demonstrates segmental involvement of small and medium sized arteries. Elastic laminae are destroyed and inflammation is composed of multinucleate giant cells, lymphocytes and histiocytes [4].

Small cell carcinoma primary or metastatic may be considered in the differential diagnosis. This tumor would be evident grossly as large solid mass. The cells will be cohesive and arrange in sheets, islands or trabeculae, with high nuclear to cytoplasmic ratio, high mitotic rate and nuclear debris. If there is any doubt immunohistochemistry can be employed to rule out this possibility. TTF-1 immunostain is positive in tumors of pulmonary origin while negative in ovarian primary.

Another entity in the differential is undifferentiated carcinoma primary and metastatic, clinical history will be valuable to pinpoint origin.

Diffuse adult granulosa cell tumor is a consideration. It occurs in postmenopausal women and elicits endocrine manifestations such as uterine bleeding. The nuclei are uniform, pale and variably grooved. Inhibin and calretinin immunostains are useful.

Desmoplastic small round cell tumor (DSRCT) intra-abdominal type is rare; it arises from serosal surfaces and may involve the ovary. DSRCT is a disease of young adults, usually males. The desmoplastic stroma is not seen in the current case. These tumors are positive for cytokeratins, neuron specific enolase and desmin [5, 6].

Primitive neuroectodermal tumor (PNET); monomorphic population arranged in sheets and nests with variable rosette-like structures.

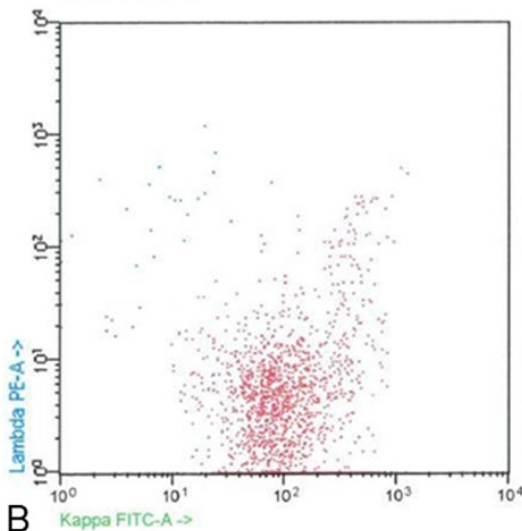
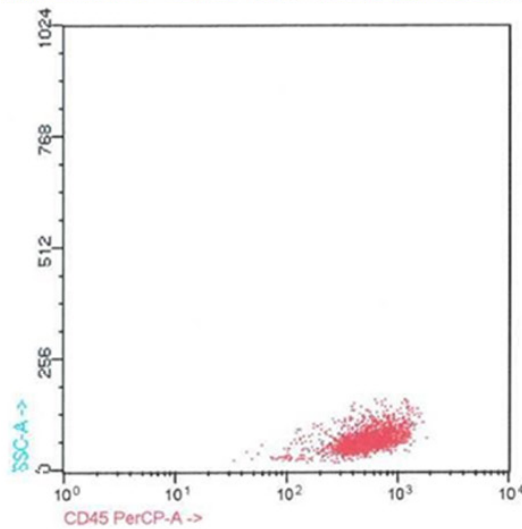
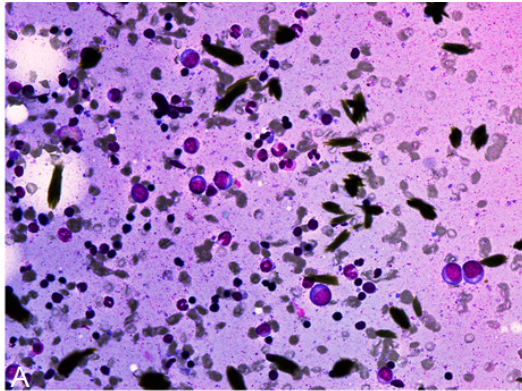
Primary lymphoma of ovary is rare and can be of Burkitt's, T or B cell types. Neoplastic cells infiltrate ovarian parenchyma in diffuse fashion and insinuate in between existing structures [7, 8].

Lymphomas secondarily involving ovary(s) are seen in up to 25% of advanced cases. Majority of cases will have concomitant lymphadenopathy. Grossly, the ovarian surface is smooth and parenchymal involvement can be partial or complete. Bi-laterality is encountered in 60% of cases. Burkitt, diffuse large B cell, follicular lymphoma, plasmacytoma, Hodgkin lymphoma and many others were reported [9-14].

If myeloid leukemia or granulocytic sarcoma is suspected then CD68, CD44 and myeloperoxidase should be performed.

The following immunostains were performed: CD3, CD5, CD10, CD20, CD23, CD138, cyclin D1, kappa and lambda. CD3 and CD5 were similar and stained few T cells. CD10 and cyclin D1 were negative. CD20 was positive and stained the majority of infiltrating cells. CD138 was positive in a significant proportion of infiltrate albeit less than CD20 (**Figure 1C-E**). Both kappa and lambda were positive. There were no endometrial pathology and the lining endometrium showed atrophic pattern. Uterine cervix showed no residual dysplasia. The case was signed out with a comment on the unusual inflammatory infiltrate. Clinico-radiologic investigation of patient's lymphadenopathy and lymph node biopsy to exclude lymphoplasma-cytic proliferative disorder was recommended. The patient was directed to hemato-oncology. Pelvic MRI was performed and showed bilateral iliac, inguinal and para-aortic lymphadenopathy. An in house CT scan with contrast of neck, chest and abdomen was performed. The study demonstrated bilateral axillary, celio-mesenteric and retroperitoneal lymphadenopathy. Blood workup showed WBC count  $12 \times 10^9/L$  (high), hemoglobin level 81 g/L (low), hematocrit 0.27 L/L (low), MCV 79 (low), MCH 24 pg (low), MCHC 304 g/L (low), RDW-CV 16% (high), platelet  $504 \times 10^9/L$  (high). WBC automated differential showed: neutrophils  $4 \times 10^9/L$  (normal), lymphocytes  $5.5 \times 10^9/L$  (high), monocytes  $1.7 \times$

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**Figure 2.** Bone marrow aspirate and immunoflowcytometry. A: High-power view show small clusters of plasmacytoid lymphoid cells interspersed among other bone marrow elements. B: Immunograph demonstrate clonal kappa light chain restricted B cell population (Wright Giemsa, [A]).

$10^9/L$  (high), eosinophils  $0.203 \times 10^9/L$  (normal), basophils  $0.090 \times 10^9/L$  (normal). Serum

IgA  $0.53 \text{ g/L}$  (low), serum IgG  $47 \text{ g/L}$  (high), and serum IgM  $47 \text{ g/L}$  (high). Serum kappa was  $1867 \text{ mg/L}$ , lambda  $162 \text{ mg/L}$  (high) and serum kappa/lambda ratio  $11.5$ . Blood film review revealed  $1+$  target cells and  $3+$  rouleaux formation. Serum immunofixation confirmed a monoclonal protein band quantified at  $59.5 \text{ g/L}$  without immunoparesis. IgA was suppressed on quantification. Immunofixation identified the M-Protein band as IgM kappa.

Bone marrow aspirate and biopsy of iliac crest were done. The aspirate showed normoblastic erythropoiesis (22%), granulopoiesis of adequate activity and maturation (45%). Small plasmacytoid lymphoid cells and occasional plasma cells were identified in increased numbers (33%). Megakaryocytes were present in adequate numbers. Bone marrow biopsy revealed moderately hypercellular marrow heavily infiltrated by polymorphic mixture of small lymphocytes, plasma cells, plasmacytoid cells and fewer eosinophils. The normal marrow elements were reduced. Reticulin stain was increased in a diffuse fashion. Immunohistochemistry for CD3, CD20 and CD138 was done. The majority of cells were CD20 positive and moderate numbers were positive for CD138. CD3 stained a minority of T cells. Bone marrow immunophenotyping highlighted the presence of 14% clonal B cells (Kappa light chain restricted) that are positive with CD45+, CD19+, CD20+, CD22+, CD79b+, Surface IgM+ and FMC7+, with partially positive CD38+ (**Figure 2A, 2B**). The cells were negative with CD5-, CD10-, CD23-, CD103- and TDT-. Approximately 65% of cells were myeloid precursors and 20% were T cells.

The findings are consistent with a mature B cell neoplasm which together with peripheral blood, marrow findings and presence of an IgM large paraprotein is consistent with Lymphoplasmacytic Lymphoma- Waldenström's macroglobulinaemia (WHO Classification).

In summary this is the first reported case in the literature of bilateral ovarian involvement by lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy. The patient underwent hysterectomy and bilateral salpingo-oophorectomy for irregular uterine bleeding, the dense lymphoplasmacytic infiltrate in cervical, uterine, fallopian walls and in ovarian medulla was unusual especially in

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the absence of clinical history of lymphoma. The possibility of lymphoplasmacytic proliferative disorder especially marginal zone lymphoma was raised in the hysterectomy pathology report. Lymphoma work up followed and indeed lymphadenopathy, bone marrow involvement and monoclonal IgM paraproteinemia were documented.

### Conflict of interest statement

No conflict of interest to declare.

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