

Case report

Symptomatic ovarian involvement as the initial presentation of primary mediastinal large b-cell lymphoma

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ABSTRACT

Primary mediastinal large B-cell lymphoma (PMLBCL) is a mature aggressive B-cell lymphoma which affects mainly young and middle-aged women. The majority of patients present with bulky mediastinal lymphadenopathy. Extranodal involvement is a rare phenomenon at disease presentation. Herein, we describe a case of a young female with PMLBCL presenting with symptomatic, bulky ovarian involvement. The 23-year old patient presented at the Emergency Department with abdominal pain. The chest X-ray film revealed a mediastinal mass and CT scan revealed a large pelvic mass, possibly involving the ovaries. Due to the development of signs of acute abdomen, she was urgently transferred to the operation room where surgical resection of the right ovary and the adjacent mass was performed. The histological examination of the resected material revealed proliferation of PMLBCL cells. This is the first report in the scientific literature describing symptomatic ovarian mass as the initial mode of presentation of PMLBCL.

1. Introduction

Primary mediastinal large B-cell lymphoma (PMLBCL) is a mature aggressive B-cell lymphoma which is recognized as a distinct entity in the WHO classification based on its clinical, immunophenotypic and cytogenetic characteristics (Swerdlow et al., 2017). PMLBCL is an uncommon thymic neoplasm of B-cell origin accounting for approximately 2.5% of non-Hodgkin lymphomas (NHL) (Swerdlow et al., 2017). Unlike most cases of diffuse large B-cell lymphoma (DLBCL), PMLBCL typically affects young and middle-aged adults with a female predominance (Vassilakopoulos et al., 2012; Savage et al., 2006; Vassilakopoulos et al., 2021). The majority of patients present with bulky mediastinal lymphadenopathy often causing dyspnea, dry cough and occasionally the superior vena cava syndrome. The tumor frequently invades the adjacent structures, including lungs, chest wall and pericardium. In general,

involvement of extrathoracic distal extranodal sites is a rare event at disease presentation; only a small percentage of patients (approximately 5%) may suffer from renal, liver, adrenal or gastrointestinal involvement (Karakatsanis et al., 2021). However, this is more common at progression or relapse of PMLBCL, where the kidney, central nervous system (CNS), adrenals and ovaries are more commonly affected (Swerdlow et al., 2017; Papageorgiou et al., 2013; Bishop et al., 1999). Herein, we present a young female patient, who presented at the Emergency Department with symptomatic, bulky ovarian tumor at diagnosis and was finally diagnosed as PMLBCL with a clinically silent bulky mediastinal mass. Ovarian involvement has been very rarely described at initial diagnosis of PMLBCL, and has never been reported as the presenting feature, which renders the present case unique.

Abbreviations: PMLBCL, Primary Mediastinal Large B-Cell Lymphoma.

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2. Case presentation

A 23-year old female presented at the Emergency Department of Kalamata General Hospital with abdominal pain of sudden onset in December 2020. She reported night sweats without fever accompanied with weight loss (approximately 6 kg, 9.4% of body weight) during the last semester. On physical examination she had right lower quadrant tenderness on abdominal palpation, but she also had signs of the superior vena cava syndrome (Fig. 1a). The complete blood count was as follows: white blood cells $7.12 \times 10^9/L$ (neutrophils 86.8%, lymphocytes 6.5%, monocytes 5.3%, eosinophils 1.1%), red blood cell count $4.44 \times 10^{12}/L$, hematocrit 38.1%, hemoglobin 12.9 g/dL and platelets $204 \times 10^9/L$. Serum biochemistry was within normal range, except for a highly elevated LDH level (663 IU/L, 2.82-fold above the upper normal limit of 235 IU/L). A pregnancy test was negative. The chest X-ray film revealed a large mediastinal mass and a small right pleural effusion, which were confirmed on CT scan measuring 15 cm at the maximal diameter (Fig. 1b). Furthermore, no contrast enhanced CT (NCECT) of the abdomen revealed a large (11 × 8.3 cm), solid shaped pelvic mass, located at the Douglas pouch and possibly involving the right ovary as well as the presence of free fluid in *cul de sac* (Fig. 1c). The mass was slightly inhomogeneous with smooth borders and appeared to mildly compress the upper wall of the urinary bladder without infiltrating it. Due to the progressively worsening clinical picture and the development of signs of acute abdomen, she was urgently transferred to the operation room where laparotomy via Pfannenstiel-Kerr incision was performed. Macroscopic findings of the right ovary were not consistent with a healthy tissue and -since a frozen section biopsy was not possible- the entire right ovary and the adjacent mass were removed. Once the ovary was resected, adequate hemostasis was performed in order to minimize bleeding risk.

The histological examination of the resected material revealed diffuse proliferation of large lymphoid cells with polymorphic nuclei and a wide rim of cytoplasm while localized there were sustained ovarian follicles. This finding further supports the ovarian origin of the resected mass. The immunophenotype of the neoplastic cells was CD20+, CD79a+, PAX-5+, LCA+, BCL2+, Multiple myeloma 1/ Interferon regulatory factor 4 protein (MUM1/IRF4)+, p63+ and BCL6+ in the vast majority of the cells and CD3-, AE1/AE3-, CD30-, CD10-, CD21-, CD15-, ALK-, CD23-, CD5-; c-myc was positive in 55% of cells. The proliferation rate as estimated by Ki-67 was 75%. Additional immunophenotypic analysis was performed for programmed death ligand 1 (PDL-1) which was positive in 100% of the neoplastic cells, further supporting the diagnosis of PMLBCL in combination with the clinical

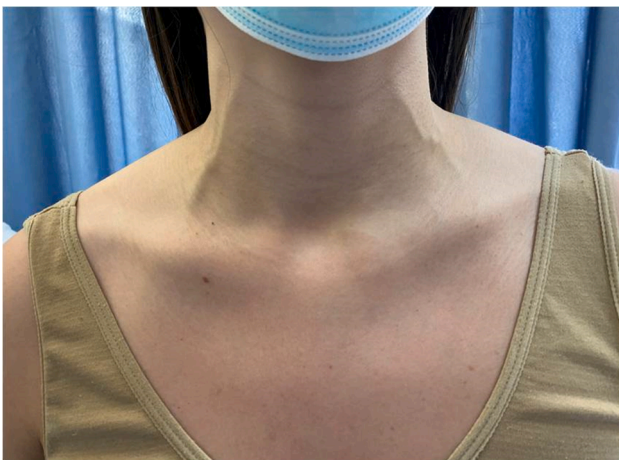


Fig. 1a. Asymptomatic jugular vein distention of the patient due to bulky mediastinal lymphadenopathy consistent with superior vena cava syndrome (SVCS).



Fig. 1b. Chest CT scan- revealing the large mediastinal mass measuring 15 cm at the maximal diameter and a small right pleural effusion.



Fig. 1c. No Contrast Enhanced CT of the abdomen revealing a large pelvic mass (thick arrow) with smooth borders, indistinguishable from the ovaries. Note the small amount of ascites (thin arrow).

findings (Fig. 2). Furthermore, bone marrow was negative for infiltration. Following recovery from surgery, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0. Complete staging with PET/CT scan demonstrated increased 18FDG uptake in the lymphatic mass of the posterior and middle mediastinum as well as the right peribronchial nodes (SUVmax: 19.36) (Fig. 1d). Based on the above data, the clinical stage was IVB, the International Prognostic Index (IPI) was 2 and the age-adjusted IPI was also 2 falling into the low/intermediate and high/intermediate risk group respectively. However, this case is considered as “high-risk” based on extranodal involvement and highly elevated LDH (>2xULN) or bulky disease according to the scoring system, which was recently published by our group (Vassilakopoulos et al., 2021).

The patient received six cycles of the R-da-EPOCH chemotherapy protocol with rapid response based on radiological findings. Interim CT scan evaluation showed partial response, whereas final disease assessment with PET/CT scan was consistent with complete metabolic remission. Routine follow-up is performed every three months with physical examination and CT evaluation of the chest and the abdomen; the patient still remains in complete remission 15 months post-treatment initiation. In addition, the patient was empirically treated with five intrathecal (i.t.) infusions of methotrexate/dexamethasone due to the ovarian localization. According to the applied chemotherapy protocol (R-da- EPOCH) patients with more than one extranodal site and an elevated LDH should receive prophylactic CNS treatment with i.t. methotrexate twice per cycle for the last four cycles. Although ovarian involvement is not an indisputable, well established risk factor for CNS relapse in DLBCL, many physicians consider such cases as high risk and provide prophylactic CNS- directed therapy (Kanemasa et al., 2016; Schmitz et al., 2016; Hollender et al., 2002). In projection to this

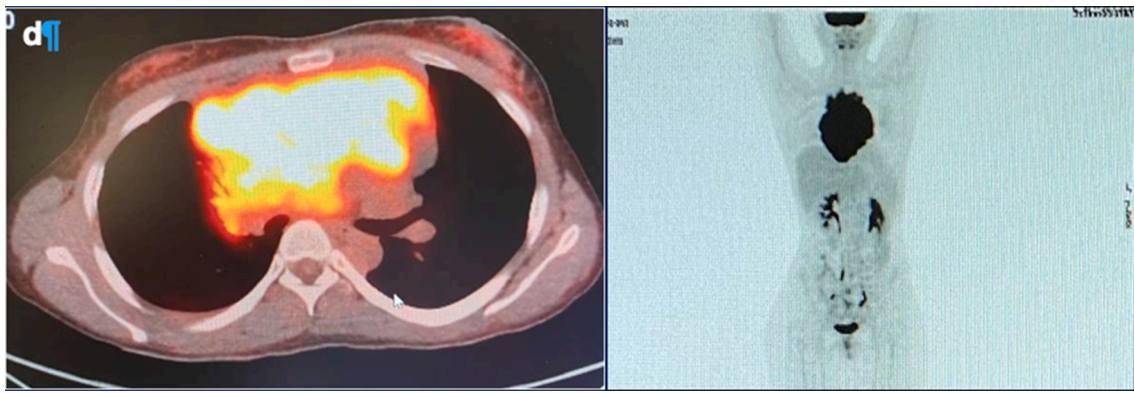


Fig. 1d. Whole body PET/CT scan- highly increased ^{18}F FDG uptake in a very bulky mediastinal mass (SUVmax: 19.36).

strategy and despite that the patient reported here was not fulfilling the prespecified protocol criteria, she received i.t. CNS prophylaxis.

3. Discussion

PMLBCL presents in the vast majority of the patients with a localized, usually bulky, mediastinal mass occupying the thymic area and frequently invading the surrounding tissues. Subdiaphragmatic spread, especially to extranodal sites, is very rare at disease presentation, but more common at disease progression. Ovarian involvement is very rarely observed. There is limited data describing ovarian infiltration by PMLBCL at initial diagnosis, as commented below. Ovarian involvement has been an incidental finding during imaging staging evaluation being totally asymptomatic, as there is no previously published case of symptomatic ovarian involvement as part of the initial clinical presentation of PMLBCL. Herein, we describe a young female presenting with acute abdomen due to rapid enlargement of a right ovarian mass and finally diagnosed as PMLBCL, which makes this case unique in the literature. The clinical (demographic and anatomic) and histologic findings and the expression of p63 and PDL-1 by the tumor cells established the diagnosis of PMLBCL versus that of DLBCL.

Lymphoma rarely presents with infiltration of the female reproductive organs. However, ovarian involvement in general is a well-established manifestation in NHL. According to data published in the 60's and 70's based on autopsy findings, the frequency of this event may vary from 7 to 26% of all lymphoma cases (Chorlton et al., 1974; Woodruff et al., 1963; Lathrop et al., 1967). In a recent review by Vang et al, authors collected all NHL cases involving the female genital tract, which were diagnosed in the Pathology Department of M.D. Anderson Cancer Center. The collected cases were segregated into two groups: localized NHL and NHL that involved the female genital tract as a part of systemic disease. In total 88 cases were evaluated. Approximately 41% of all cases (36/88) involved the ovaries according to clinicopathological findings; 4% (4/88) were localized and 29% (26/88) were disseminated NHLs. DLBCL appeared to be the most common histological type accounting for 50% and 69% of early- and advanced-stage NHL, respectively. Burkitt's and follicular lymphoma were the next most common NHL subtypes in these case series (Vang et al., 2001). Although DLBCL is the most common underlying histology in female genital tract (and ovarian) NHL, such involvement remains very rare even within the DLBCL population. According to a recent report on 678 female patients with DLBCL, the ovaries were infiltrated in 1% (10/678) of the cases, uterus in 2% (14/678), while both ovaries and uterus were affected in less than 1% (3/678) of the cases. Furthermore, rare cases of extranodal marginal zone lymphomas (EMZL) involving the female reproductive tract has been reported. However, based on the analysis of 4,994 EMZL cases of the Surveillance, Epidemiology, and End Results (SEER) program (after the exclusion of 2,702 gastric MALT lymphomas), vulva, vagina, cervix uteri, corpus uteri, ovary and other urogenital sites were

described as extremely rare localizations of the disease with each one reported in less than 16 cases (corresponding to less than 0.3% of all EMZL) (Khalil et al., 2014; Diamantopoulos et al., 2019).

To our knowledge, there are only five studies evaluating the frequency of ovarian involvement in PMLBCL either at initial diagnosis or at the time of the relapse. However, no patient in these series was reported to present with symptomatic ovarian disease, as already stated. More specifically, in 1986 Perrone et al reported a retrospective analysis of 60 patients with PMLBCL, 25 of whom relapsed, evaluating the main clinical and pathological characteristics of the disease (Perrone et al., 1986). Among other sites, ovaries were involved in two out of these 25 relapsing cases. Ovarian involvement at relapse of PMLBCL was also reported by Lazzarino et al, where specific issues concerning the disease's aggressive behavior and modality of spread were analyzed (Lazzarino et al., 1993). Among 30 patients with PMLBCL during a 10-year period (1982–1992), only one, who had presented with localized mediastinal disease at initial diagnosis, developed ovarian infiltration at the time of disease progression. Ovaries have been very rarely described as an extranodal site of involvement at initial diagnosis of PMLBCL. Depuydt et al retrospectively studied ten patients diagnosed with PMLBCL from 1983 to 1993 and observed right ovarian involvement by CT imaging in a single patient at the time of diagnosis (Depuydt et al., 1995). Furthermore, in 1999, Bishop et al evaluated the frequency of CNS involvement in PMLBCL through a review of 23 patients. Among other findings, authors describe five cases with ovarian infiltration; two at disease diagnosis and three at relapse, among this very rare and highly selected subpopulation of PMLBCL patients who experience CNS dissemination at some point of the disease course (Bishop et al., 1999). Finally, a few months ago our group published the first report on the incidence and prognostic significance of subdiaphragmatic extranodal site involvement in PMLBCL evaluating data of a large patient series treated in the cooperating Hellenic and Cypriot haematology departments. According to these results, ovarian involvement was described in only three out of 455 (0.7% or 1.0% when only females were considered) newly diagnosed PMLBCL patients (Karakatsanis et al., 2021).

4. Conclusion

In conclusion, ovarian involvement is very uncommon in PMLBCL and can be seen in different clinical settings; more frequently at disease relapse or progression and rarely at presentation. CT staging may provide useful information regarding the actual incidence of subclinical ovarian involvement in this entity, since the majority of the cases are clinically silent as far as the ovarian disease is concerned; however, it is not clear whether PET/CT may actually increase the rate of the detection of ovarian involvement. This unique case represents the first report in the scientific literature describing symptomatic ovarian mass as the initial mode of presentation of PMLBCL.

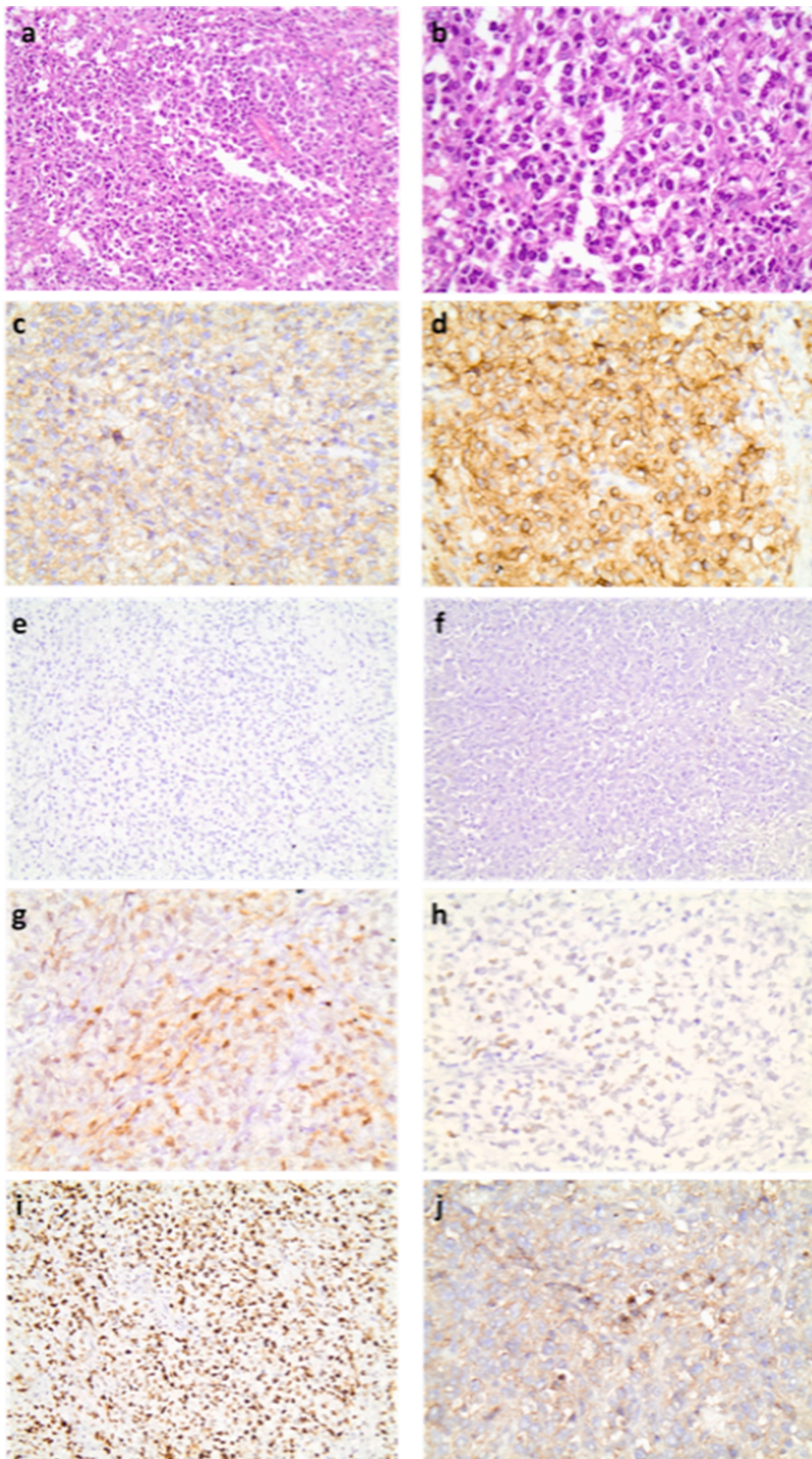


Fig. 2. a. Hematoxylin-eosin stain (X200): diffuse proliferation of large lymphoid cells with polymorphic nuclei with a prominent single nucleolus and eosinophilic cytoplasm b. hematoxylin-eosin stain (X400): a wide rim of cytoplasm producing clear cell morphology at sites c. CD20 immunostain (X400): diffuse cytoplasmic positivity d. CD79a immunostain (X400): diffuse cytoplasmic positivity e. CD30 immunostain (X200): the neoplastic cells are negative f. CD23 immunostain (X200): the neoplastic cells are negative g. MUM-1 immunostain (X400): the majority of the neoplastic lymphoid cells show nuclear staining h. c-myc immunostain (X400): about half (>40%) of the lymphoid cells show nuclear staining i. Ki67 immunostain (X200): proliferation index is high, about 75–80% j. PDL1 immunostain (X400): diffuse membranous positivity, evident at all neoplastic lymphoid cells.

Ethical statement

The subject provided informed consent and patient anonymity has been preserved.

CRedit authorship contribution statement

Alexia Piperidou: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Ioannis Drandakis:** Data curation, Writing – review & editing. **Maria-Aikaterini Lefaki:** Data curation, Writing – review & editing. **Eleftheria Lakiotaki:** Conceptualization, Writing – review & editing. **Helen Plyta:** Data curation. **Georgia Sypsa:** Writing – review & editing. **Maria Tsolakou-Dalekou:** Data curation. **Maria Androulaki:** . **Fotios Panitsas:** Data curation, Writing – review & editing. **Eleni Plata:** Data curation, Writing – review & editing. **Penelope Korkolopoulou:** Writing – review & editing. **Theodoros P. Vassilakopoulos:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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