International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Primary Ovarian Non-Hodgkin Lymphoma Diffuse Large B-Cell, Anaplastic Variant

Reported a Case

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Abstract: ***Introduction: Non Hodgkin's lymphoma may involve gynecologic tract. Secondary involvement by NHL from the other site is often occurred as part of systemic disease and ovary is the more common site to be involved. However, primary ovarian NHL is very rare. Case description: a 31 year old woman complained of abdominal pain, fever and shortness of breath. Abdominal ultrasonography reveals a large solid mass of the right ovary and multiple paraaortic lymphadenopathy. There was a significant increase in serum CA-125 and LDH. Frozen section examination was conducted and found a gelatinous, yellowish-white color, solid ovarian mass, 11x7, 5x4, 5cm in size that filled the entire tissue. Microscopically, the cells arranged in a diffuse pattern and had an anaplastic morphology. Mitoses were numerous. The conclusion of the frozen section was a malignancy, tends to be Germ Cell Tumor. The diagnosis was then confirmed by routine histopathology examination and found diffuse, solid sheets and linear anaplastic cell tumor. Differential diagnosis of Non Hodgkin Lymphoma, Undifferentiated carcinoma and Embryonal carcinoma were made and immunohistochemical examination was done. The results showed as follow: CD45 and CD20 were diffusely positive, TdT and CD3 was negative and Ki67 was positive in 90% tumor cells. Conclusion: Based on histopathology and immunohistochemical examination, this case was concluded as Non-Hodgkin's lymphoma, diffuse large B cell, anaplastic variant, stage IIIE. This patient has a total IPI score of 4 and a poor prognosis. The patient was reported dead.***

Keywords: ovarian tumor, anaplastic cell, non hodgkin lymphoma, immunohistochemistry

1.Introduction

Non Hodgkin's lymphoma may involved gynecologic tract. Secondary involvement by NHL from the other site is often occured as part of systemic disease and ovary is the more common site to be involved. However, primary ovarian NHL is very rare. The incidence is less than 0.5% of all lymphomas and 1.5% of all ovarian tumors. The rarity of this tumor leads to misdiagnosis with other ovarian malignancies including epithelial ovarian and germ cell tumors.[1,2]

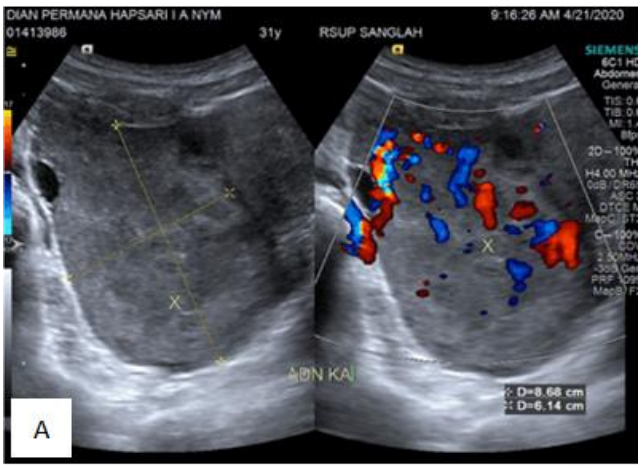
We reported the case of ovarian Non Hodgkin's Lymphoma, Diffuse Large B Cell, Anaplastic variant that suggested as malignant germ cell tumor in previously frozen section examination.

2.Material and Methods

A 31-year-old woman complained of abdominal pain since 2 days before admitted to the hospital. Abdominal pain is said to be sudden and not relieved by painkillers. The patient also experienced significant weight loss in the last 2 years. About 2 weeks earlier the patient had complained of fever for 10 days accompanied by complaints of shortness of breath. The patient also underwent two SARS COV-2 PCR swab tests and the results were negative. Other complaints such as vaginal bleeding or vaginal discharge were denied by the patient. The patient had no previous history of serious illness.

Ultrasound examination of the upper and lower abdomen revealed a solid mass in the right adnexa, measuring approximately 8.6x6.1 cm, suggesting a right ovarian mass (Fig. 1A). Multiple paraaortic lymphadenopathies and bilateral pleural effusion were also found. There were no morphology abnormalities of the gallbladder, liver, pancreas, right and left kidney, and bladder. An AP chest radiograph (Fig. 1B) shows bilateral pleural effusion and pneumonia.

On blood examination, there was an increase in SGOT 125.5 U/L (11-27 U/L), SGPT 56.40 U/L (11-34), and ALP 208 U/L (42-98). HBsAg and Anti HCV were non-reactive. Several examinations of tumor markers were performed, including AFP 0.88 IU/mL, CA 19-9 7.54 U/mL, Beta-HCG <0.10, and CEA 0.30 (within normal limits), while there was an increase in CA-125 1449 U/mL and LDH 2725 U/L. The results of complete blood count were as follows: Hemoglobin 13.46 g/dL (within normal limits), Hematocrit 44.24% (within normal limits), Platelets 65.76x10 3 /µL (decreased), WBC 13.72x10 3 /µL (slightly increased). Because there were complaints of fever and thrombocytopenia, the patient was also examined for Dengue NS I Ag, Anti DHF IgM, and IgG, but showed negative results.



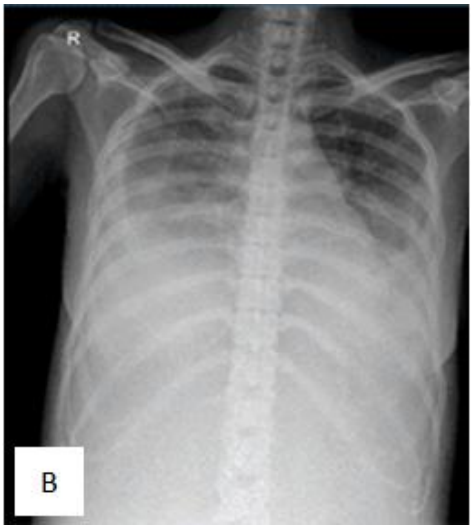
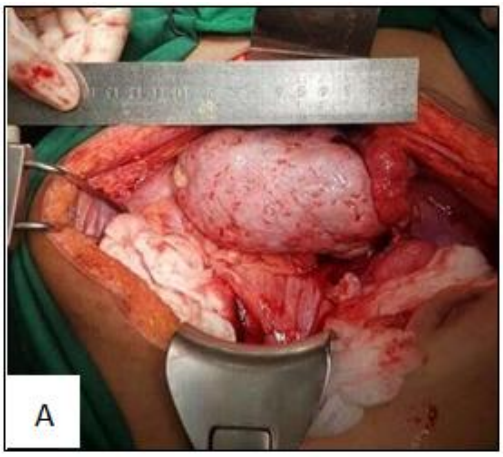


Figure 1: Radiological examination. **A.** Ultrasound of the abdomen reveals a solid mass, measuring about 8.6x6.1 cm, which suggests a right ovarian mass. **B.** AP chest radiograph showing bilateral pleural effusion and pneumonia.

One week after the patient was admitted to the hospital with complaints of abdominal pain, surgery (Figure 2A) was performed on the ovarian tumor, and the tissue was sent to the Anatomical Pathology Laboratory for a Frozen Section. The preparation was received in a medium jar containing 1 piece of ovarian and tubal tissue measuring 11x7.5x4.5 cm, the tubal structure was 4 cm long, and 1 cm in diameter. On the ovary slices, a solid mass filled the entire tissue was seen, the consistency is gelatinous, with a yellowish-white color (Fig.2B).



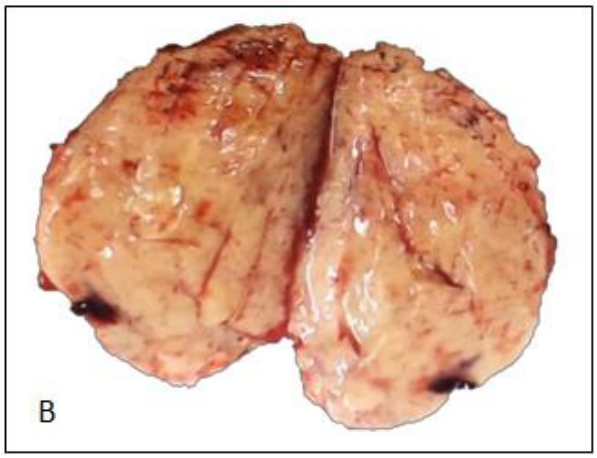
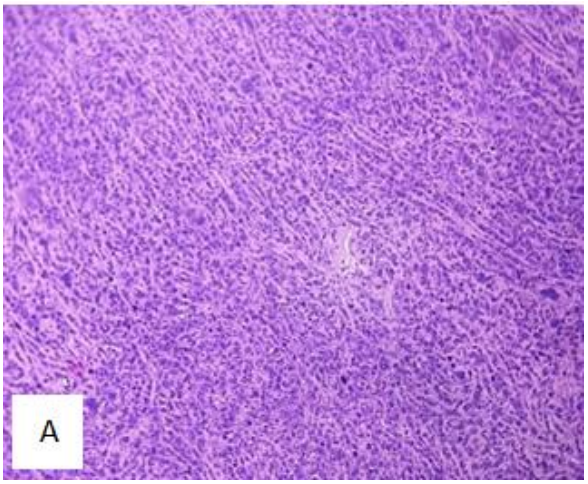


Figure 2: A. Photo during operation. B. Tumour slices showed a solid tumour with yellowish-white color

Microscopically, frozen section specimen showed pieces of ovarian tumor tissue consist of anaplastic cells proliferation forming in solid sheets and diffuse pattern infiltrative between the connective tissue stroma. These cells were characterized by extensive eosinophilic cytoplasm, marked nuclear pleomorphism with multinucleated nuclei and irregular nuclear membranes. Mitosis were numerous. The conclusion of frozen section examination was a malignancy, tends to be a Germ Cell Tumor.

The Frozen Section diagnosis was then confirmed with routine histopathology examination and found the tumor mass consists of anaplastic cells forming in a diffuse, solid sheet, storiform, and linear file pattern. Tumor cells had large, spherical, pleomorphic and partly grooved nuclei, irregular nuclear membrane, coarse chromatin and prominent nucleoli. The distribution of bizarre cells and several Reed Sternberg-like cells were also seen. Mitoses were numerous, consisting of normal and abnormal mitoses. An extensive necrosis area were also found. The tubal tissue also contains the infiltration of malignant cells from the mucosal layer to the serous layer as well as connective tissue, fat, and the walls of the peritubular blood vessels. Based on conventional morphological features above the diagnosis of high-grade malignant tumor tends to be a Non-Hodgkin's lymphoma (anaplastic variant DLBCL) was made, with differential diagnosis of Undifferentiated carcinoma and Embryonic carcinoma with a choriocarcinoma component. Omental resection was also performed, and malignant cell infiltration was found in the omentum. The results of the immunohistochemical examination (Figure 4) were as follows: CD 45 and CD20 were diffusely positive, CD 3 was negative, and Ki 67 was positive in 90% of tumor cells. From the clinical picture, radiology, histopathology, and immunohistochemical examination, this case was concluded as Non-Hodgkin's lymphoma. Diffuse large B-cell, anaplastic variant, stage IIIE.

While waiting for the diagnosis to be confirmed histopathologically and immunohistochemically, the patient's general condition continued to be improved so that she could receive RCHOP chemotherapy. However, the patient's condition continued to deteriorate after the operation. The patient continued to have a fever, electrolyte disturbances, hypoalbuminemia, and respiratory distress. After entering one type of chemotherapy agent (doxorubicin), the patient's condition worsened and finally, the patient died.



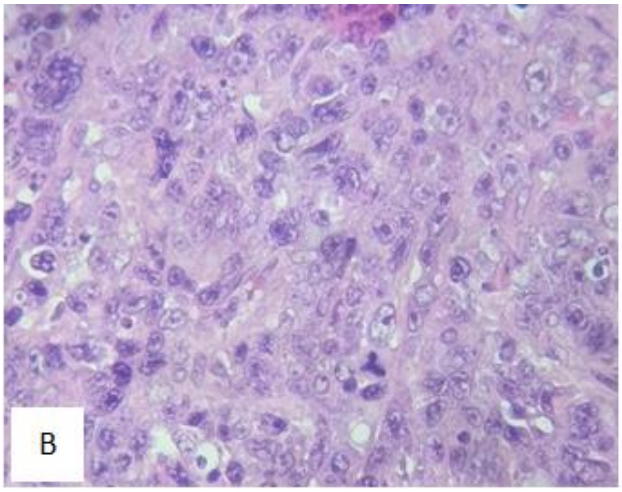


Figure 3: Microscopic view of routine histopathological examination. (A) The tumor mass is composed of anaplastic cells that form a diffuse and *linear file structure. (*B) Tumor cells with bizzare nuclei dan abnormal mitosis. HE 400x magnification.

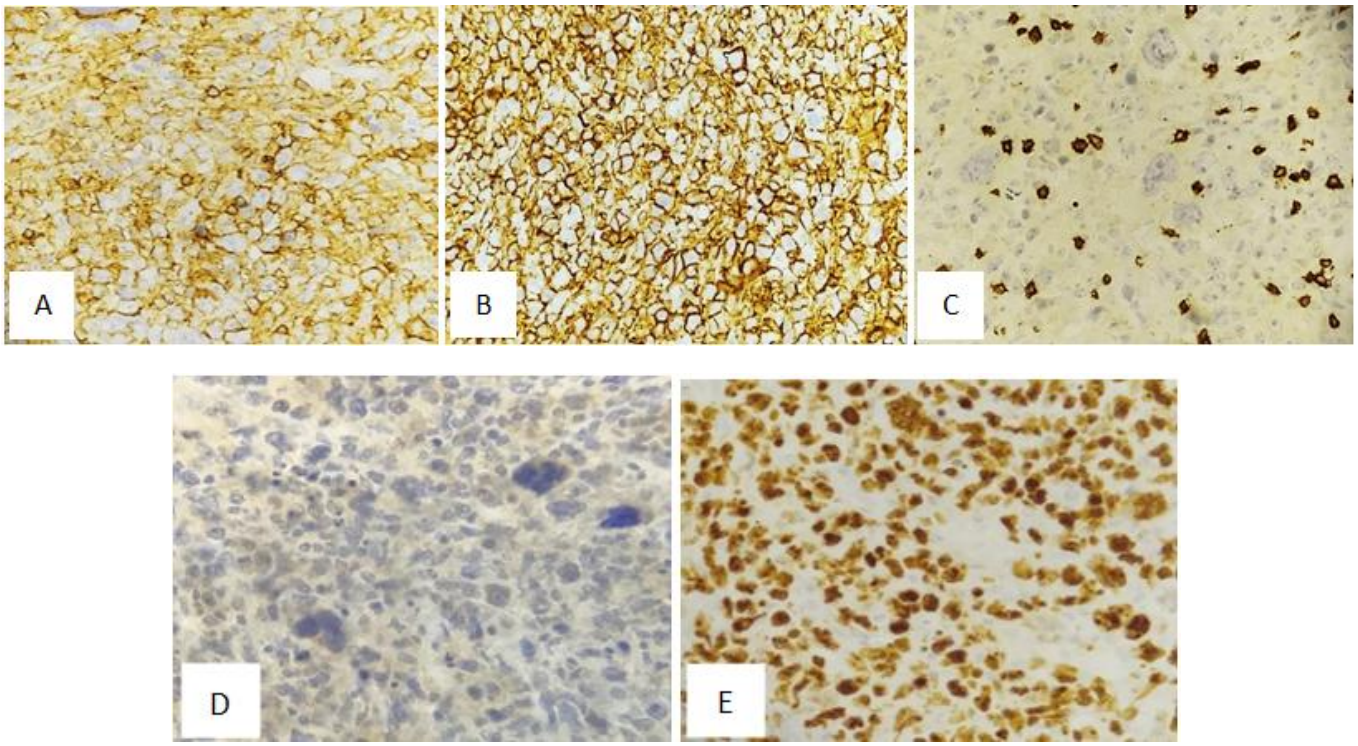


Figure 4: Immunohistochemical review (x400). A. CD45 stains diffusely positive on the membrane. B. CD 20 stains diffusely positive on the membrane. C. CD3 negative. D. TdT Negative. E. Ki 67 is positive in 90% of tumor cell nuclei.

3.Results & Discussion

Primary lymphoma in the ovary is very rare, the incidence is <0.5% of all lymphomas and 1.5% of all ovarian tumors. This may be due to the absence of lymphoid tissue in the ovaries. Because the cases are rare, the diagnosis is often confused with epithelial ovarian or germ cell tumors.[1, 2, 3] Ovarian lymphoma can affect patients with a wide age range, from children to the elderly, with the median age being in the fourth or fifth decade. The most common primary lymphoma in the ovary is the diffuse large B-cell type lymphoma (DLBCL), followed by Burkitt's lymphoma, follicular lymphoma, and less commonly B and T lymphoblastic lymphoma.[1]

The etiology of DLBCL is not yet known. These tumors usually appear de novo (primary) but can also be transformed from less aggressive (secondary) lymphomas, such as lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, or Hodgkin's lymphoma nodular lymphocyte predominance. Underlying immunodeficiency is a significant risk factor. DLBCL occurring in immunodeficient patients is more often positive for EBV than in sporadic cases. In cases of DLBCL without overt immunodeficiency, the rate of EBV infection varies from 3% in western populations to about 10% in Asian and Latin American populations.4 From the anamnesis, the patient in this case had no history of severe disease or previous immunodeficiency. This patient's EBV status has also not been examined.

Most common patient complaints are abdominal pain and an increase in abdominal circumference. Some patients also experience weight loss, fatigue, fever, or abnormal vaginal bleeding. Ascites are common. Sometimes ovarian lymphoma is found incidentally.[1] The patient in this case had complaints of abdominal pain, fever, shortness of breath, and weight loss.

The radiological features of lymphomas are usually non-specific and may mimic benign or malignant conditions.[3, 5] Radiological examination of lymphoma is commonly used to stage disease, to guide percutaneous biopsy, and also to evaluate response to

therapy.[5] On abdominal ultrasound examination of this case, a solid mass was found, which suggested that it came from the right ovary. Multiple paraaortic lymphadenopathies and bilateral pleural effusion were also found.

Complete blood counts are usually performed in new lymphoma patients to evaluate for bone marrow involvement, which may reveal anemia, thrombocytopenia, and/or leukopenia. A comprehensive metabolic panel consisting of liver function, kidney function, serum electrolytes, and lactate dehydrogenase (LDH) tests is also necessary.[6] CA (carbohydrate antigen)-125 is expressed on the surface of mesothelial cells, gastric mucosa, female urogenital tract, and ovarian epithelium. This protein has long been used as a tumor marker and also for ovarian cancer follow-up. However, an increase in the serum CA-125 value is not specific because it can be seen in various malignancies such as gynecologic carcinoma, lymphoma, mesothelioma, immature teratoma, as well as carcinomas of the pancreas, colon, breast, and lung.[7] LDH is widely distributed in various body tissues such as muscle and liver cells as well as hemopoietic cells. Therefore, elevated LDH levels can be seen in some cases such as myocardial infarction, myopathy, liver dysfunction, and also malignancy.[8] On blood examination, this patient found an increase in the value of CA-125 (1449 U/mL) and LDH (2725 U/L), besides that the patient also had thrombocytopenia.

Although the accuracy of the Frozen Section in some literature is stated to be quite high in distinguishing benign or malignant tumors (ranging from 86-97%), the Frozen Section has several limitations in establishing the diagnosis, including the limited number of samples examined, thicker sections of the preparation compared to that of the frozen section. permanent preparations, and the presence of freezing artifacts that can cover cell details. Misdiagnosis can be caused by sampling error, erroneous interpretation, or suboptimal preparations.9 From the microscopic examination of the Frozen Section, the diagnosis of this patient was concluded as a malignancy, predisposed to Germ Cell Tumor, due to the presence of pleomorphic cells with multinucleated nuclei resembling malignant syncytiotrophoblast cells found in choriocarcinoma. And also because this patient is young, the most common tumor is Germ Cell Tumor.

Most primary lymphomas in the ovary are unilateral. Tumor size ranges from microscopic (which is usually found incidentally) to large with an average diameter of 8-15 cm. The outer surface is usually intact and may be smooth or nodular. with a soft to dense consistency and chewy. On incision, the tumor is usually white, brown, or gray-pink. A minority of cases may show cystic degeneration, areas of hemorrhage, or necrosis. Secondary ovarian lymphoma is usually bilateral and on average smaller in size than primary ovarian lymphoma.[1] On macroscopic examination of this case, the tumor was 11x7.5x4.5 cm in size, which on the slices appeared to be a solid mass with a gelatinous consistency and yellowish white.

DLBCL is a neoplasm of medium or large B-cell lymphoid, in which the nucleus size is equal to, or greater than, the normal size of macrophages, or more than twice the size of normal lymphocytes, and exhibits a diffuse growth pattern.[4] The histology of DLBCL in the ovary is similar to that seen in the extra-ovarian area, although in the ovary the lymphoma is associated with sclerosis and the neoplastic cells may form cords and clusters that resemble carcinoma or may have an elongated shape with a storiform growth pattern that resembles a tumor. Spindle cell sarcoma.[1] DLBCL has three common morphological variants namely centroblasts, immunoblastic, and anaplastic variants. The centroblasts variant is the most common. Centroblasts are medium to large lymphoid cells with oval-round morphology, vesicular nuclei containing fine chromatin, with 2-4 nucleoli. The cytoplasm is usually narrow, amphophilic, or basophilic. The immunoblastic variant has a centrally located nucleolus with basophilic cytoplasm. Immunoblasts with plasmacytoid differentiation may also be found. The anaplastic variant is characterized by large to very large cells with bizarre pleomorphic nuclei that may resemble Hodgkin/Reed-Sternberg cells, and may also resemble anaplastic large cell lymphoma (ALCL). The cells may exhibit a sinusoidal pattern and/or a cohesive growth pattern that resembles undifferentiated carcinoma. The anaplastic variant was biologically and clinically unassociated with (ALCL), which is a cytotoxic T-cell derivative, and was not associated with either ALK-positive large B-cell lymphoma, which lacks CD20 and CD30 expression.[4] On a microscopic picture of the histopathological preparation of this case, it was found that the tumor mass consisted of anaplastic cells that formed a diffuse, solid sheet, storiform and linear file structure. Tumor cells with large spherical nuclei, pleomorphic, coarse chromatin, prominent nucleus, irregular nuclear membrane, and partly grooved. The distribution of bizarre cells with multiple nuclei with extensive eosinophilic cytoplasm and several Reed Sternberg-like cells was also seen so that conventional morphology, this case was concluded as a high-grade malignant tumor tending to be Non-Hodgkin's lymphoma (DLBCL anaplastic variant) DD/ Undifferentiated carcinoma DD/ Embryonic carcinoma with a choriocarcinoma component.

DLBCL neoplastic cells typically express pan-B cell markers such as CD19, CD20, CD22, CD79a, and PAX5. Surface and cytoplasmic immunoglobulins (generally IgM, followed by IgG and IgA) can be demonstrated in 50-75% of cases. The Ki-67 proliferative index is usually high (>40% and may be >90% in some cases).[1, 4] Immunohistochemical examination results were as follows: CD 3 negative, CD 20 diffusely positive, CD 45 diffusely positive, and Ki 67 positive in 90% of tumor cells. From the histopathology and immunohistochemical appearance, the two differential diagnoses can be ruled out because the tumor is diffusely positive with CD45 and CD20 staining, whereas in carcinoma and germ cell tumors it is usually negative.

Staging of Non-Hodgkin's lymphoma is the same as that of Hodgkin's lymphoma, using the Ann Arbor staging classification which can be seen in Table 1.10 The patient, in this case, was in stage IIIE because the involved organs were located on both sides of the diaphragm and there was omental involvement and pleural effusion.

Table 1: Ann Arbor 10 Staging Classification

Stage	Description
I	Involvement of a single lymphatic site (eg, nodal region, Waldeyer ring, thymus, or spleen) (I); or localized involvement of a single extra lymphatic organ or site in the absence of lymph node involvement (IE).
II	Involvement of a single lymphatic site (eg, nodal region, Waldeyer ring, thymus, or spleen) (I); or localized involvement of a single extra lymphatic organ or site in the absence of lymph node involvement (IE).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by extra lymphatic extension associated with involvement of adjacent lymph nodes (IIIE) or with involvement of the spleen (IIIS) or both (IIIE, S).
IV	Diffuse or disseminated involvement of one or more extra lymphatic organs, with or without associated lymph node involvement; or isolated extra lymphatic organ involvement in the absence of involvement of adjacent regional lymph nodes, but in association with the disease at a distant site. Stage IV includes the involvement of the liver or bone marrow, lungs (other than by direct extension from elsewhere), or cerebrospinal fluid.

Valid for every stage	
A	No symptoms
B	Fever (temperature > 38.0ºC), night sweats, weight loss >10% for no apparent reason in the last 6 months.
E	Involvement of a single extranodal site adjacent to or proximal to a known nodal site.
S	*Splenic* (spleen) involvement

Treatment for advanced DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).4, 10 This patient was planned to receive the R-CHOP agent when the patient's condition was stable but the patient only had time to receive doxorubicin and then the patient's condition worsened and eventually died.

Features associated with poor outcomes in primary ovarian DLBCL include bilateral ovarian involvement, large ovarian masses, extensive disease extension at staging, and high International Prognostic Index (IPI) scores. Factors assessed in determining the IPI score included age 60 years, Eastern Cooperative Oncology Group (ECOG) performance status 2, high LDH level, Ann Arbor stage III or IV, 2 site of extranodal disease. If these factors are present, each is added 1 point then added up and put into the risk category, namely low if the score is 0 or 1, low-medium if the score is 2, moderate-high if the score is 3, high if the score is 4 or 5.6 This patient had a total IPI score of 4, thus being included in the high-risk category (poor prognosis). The patient died because his condition continued to decline due to electrolyte disturbances, hypoalbuminemia, and respiratory distress.

4.Conclusion

Primary lymphoma in the ovary is very rare, the incidence is <0.5% of all lymphomas and 1.5% of all ovarian tumors. This case reports a 31-year-old woman, complaining of abdominal pain, significant weight loss, fever, and shortness of breath. From the clinical picture, radiology, histopathology, and immunohistochemical examination, this case was concluded as diffuse large B-cell Non-Hodgkin lymphoma, anaplastic variant, stage IIIE. This patient had a total IPI score of 4, thus being included in the high-risk category (poor prognosis). The patient died because his condition continued to decline due to electrolyte disturbances, hypoalbuminemia, and respiratory distress.

Acknowledgements

The authors would like to thank all colleagues, the department of pathology anatomic of RSUP. Prof. Dr. I. G. N. G. Ngoerah Denpasar Bali, who have helped a lot in working on this case report hopefully a lot of benefit and knowledge.

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