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CASE REPORT

Atypical Presentation of Advanced Diffuse Large B Cell Lymphoma of Germinal Center Subtype in a Young Woman: A Case Report.

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype and is known to be an aggressive type of non-Hodgkin lymphoma that develops from the B cells of the lymphatic system. DLBCL may occur at all ages but is more common in the elderly. Extranodal manifestation is common in non- Hodgkin lymphoma. DLBCL commonly incidentally diagnosed in patients of otherwise healthy or with atypical clinical manifestations. The prognosis of DLBCL is found to be better in young age patients.
We report a young woman who presented with acute gastroenteritis symptoms, advanced stage of DLBCL diagnosed from incidental findings. She responded to R-CHOP chemotherapy regime followed by autologous hematopoietic stem cell transplantation (ASCT) and remained in remission for a year before she developed relapse and succumbed to the illness.

Keywords: Lymphoma, DLBCL, advanced stage, extranodal, young woman, incidental, R-CHOP, ASCT.

Introduction

DLBCL, arising from B cell of lymphatic system, is the most common high-grade and aggressive type of non-Hodgkin lymphoma with a prevalence of 40%-50% of all new cases of lymphomas [1, 2]. It has multiple subtypes with heterogeneous in clinical phenotyping [3]. Extranodal manifestation is common in non-Hodgkin lymphomas (25-30%) with less than 40% originated in extranodal sites [4-6]. Common primary extranodal DLBCL involvement sites are the gastrointestinal (GI) tract, including tissues such as lymph node, spleen, Waldeyer's ring, and the thymus and relatively uncommon in the skin, bone, and the central nervous system [7-10]. Ovarian involvement is rare (< 1%) of which it can be primary or secondary [11-13]. We report a young woman of otherwise perfectly well presented with acute gastroenteritis symptoms. Advance DLBCL was diagnosed from histopathological and immunohistochemical findings.

Case report

A 23-year-old Malay woman, previously well, presented with three days of diarrhea, vomiting and mild abdominal pain. She had no fever, loss of appetite and no other family members had similar symptoms. She denies eating outside food and no history of similar episode. Her menstrual cycle has been regular as usual and no episode of heavy menses.

Clinically she was overweight, not toxic looking, afebrile with stable hemodynamically. There were no signs or stigmata of liver disease and peripheral lymphadenopathy. Neither there was hepatosplenomegaly, nor could ascites be appreciated. The bowel sound was normal. Other systems were unremarkable.

Initial laboratory investigations showed hypochromic microcytic anemia : Haemoglobin (Hb) 10.0 g/dL (12 – 16 g/dL), MCV 67 fL (76 – 96 fL), MCH 22 pg (28 – 34), marked thrombocytosis, platelet 906 x 10^9/L (150 – 400 x 10^9/L), leukocytosis (25.1 x 10^9/L, Neutrophil 81.7%), alkaline phosphatase 275 U/L (38 – 124 U/L), aspartate transaminase (AST) 139 U/L (< 34 U/L), gamma-glutamyl transpeptidase (GGT) 343 U/L (4 – 47 U/L), serum albumin 29 g/L (normal, 34 – 50 g/L), serum uric acid 0.53 mmol/L (0.16 – 0.36 mmol/L) and normal renal function. The lactate dehydrogenase (LDH) was markedly raised, 1193 U/L (100 – 190 U/L). The cancer antigen (CA) 125, 388.7 U/mL (< 46 U/L) was raised. Septic workout and stool for ova and cysts were negative.

She was treated as acute infective gastroenteritis until ultrasonography, and computed tomography (CT) scan of the abdomen reveals multiple lobulated lesions in the liver and the adnexal of the right ovary with multiple para-aortic and paracaval lymphadenopathy suggestive of metastases (Figure 1). The bone marrow and trephine biopsy revealed no lymphoma cell infiltration.

Exploratory laparotomy reveals a two lobulated firm solid right and left ovarian tumor measuring 10 cm x 8 cm x 7.5 cm and 7cm x 4 cm x 3 cm weighing 350 gm and 43 gm, respectively. (Figure 2) The right tumor was found adhered to the anterior rectum and pouch of Douglas. There were solid nodules over the whole length of the small bowel and the omentum was thickened. The histopathological examination (HPE) of the ovary shows moderate to large size of malignant lymphoid cells with pleomorphic, hyperchromatic nuclei and frequent mitoses, which was diffusely distributed with patchy necrosis. The capsular invasion was noted with the presence of angiolymphatic infiltration. The tumor cell was expressing strong and diffuse leukocyte common antigen (LCA), CD20 (CD; cluster of differentiation), CD79a, CD10, BCL6 (BCL; B-cell lymphoma) and negative for MUM1 (MUM; Multiple myeloma oncogene), BCL2, terminal deoxynucleotidyl transferase

(TdT), CD5, CYCLIN D1, cytokeratin AE1/AE3, Vimentin and CD21. The Ki 67 proliferative index was about 90%. The HPE finding was consistent with DLBCL germinal center subtype involving right fallopian tube, right and left ovaries. (Figure 3)

Based on the HPE results, she was treated with rituximab, cyclophosphamide, adriamycin, vincristine, prednisolone (R-CHOP) regimen, of which she completed six cycles. She responded with the treatment. However, due to her advance stage with high possibility of refractory-relapse (RR) to the initial regimen, she was eligible and subjected for autologous hematopoietic stem cell transplantation (ASCT) and was performed successfully. Repeated PET scan showing no evidence of active fluorodeoxyglucose (FDG) avid lymphomatous disease seen which suggestive of complete metabolic response to the therapy. She remained in remission for one year before developed relapse. Unfortunately, she succumbed to the illness as she refused all treatment.

Discussion

The initial presentation of this patient was misleading as acute gastroenteritis is a common diagnosis made in this region. However, despite clinically 'stable' with unremarkable physical findings, with microcytic anemia without history of bleeding including menorrhagia, marked thrombocytosis and leukocytosis, lead to diagnosis uncertainty. The imaging findings of solid ovarian mass with evidence of metastases followed by operative finding further complicates the clinical conundrum until the HPE studies halt the diagnostic cascades.

As suggested by Suh-Burgmann and Kinney that adnexal masses such as ovarian tumor should be assessed by its symptoms, signs of malignancy such as elevated cancer antigen 125(CA125) levels significantly in a postmenopausal patient, and presence of ascites, women at high genetic risk for ovarian cancer and large masses (>10 cm) with symptoms and inconclusive on ultrasound imaging [14]. Our patient is very young, asymptomatic despite elevated CA125 and unexpected incidental imaging findings. Nonetheless, both prominent nor subtle symptoms and clinical signs of these tumors illustrated in this patient. Definitive HPE and immunohistochemical staining usually help in revealing the diagnosis. In this patient the immunohistochemical staining showed positivity of almost all related antibody specifically CD20 with highly active index (Ki67).

Based on the finding in this patient, it is difficult to arbitrate the origin of the tumor, primary or secondary. However, it has been shown that secondary dissemination with nodal involvement is much more common than primary ovarian lymphoma. The intriguing clinical presentation often led to incidental finding during examination and evaluation pelvic or abdominal symptoms [15-18].

Nevertheless, secondary tumor of the ovary such as the Krukenburg tumor may present with similar manifestation which is usually asymptomatic. It is commonly arising from gastrointestinal tract with non-specific symptoms and patient may present with hormonal irregularities and menstrual disturbances [19] which did not occur in this patient. The prevalence of Krukenburg tumor estimated between 1% - 2% of all ovarian tumours[19]. Mixed pathways (lymphatic, haematogenous and transcoelomic) has been found to be common mode of metastasize of Krukenburg tumor [20]. However, the distinct HPE of Krukenburg is distinguishable from that of ovarian lymphoma in addition of positivity of immunohistochemistry findings in the latter as well illustrated in this patient.

Lymphoma involving the female reproductive organs is rare and in case series lymphoma originated from the ovary was 59% [21]. The incidence of primary ovarian lymphomas is 0.5%

of all non-Hodgkin's lymphomas (NHLs) and 1.5% of all ovarian malignancies [22] and commonly occurs in women in their 40s. Diagnostic criteria of primary ovarian lymphoma has been suggested by *Fox et al*.: (1) tumor has confined to the ovary regional lymph nodes or adjunctive organs at the time of the diagnosis, (2) no infiltration of lymphoma cell in the bone marrow and peripheral blood and (3) there will be few months lapsed between the time of ovarian and extra-ovarian lesions [23].

Although it is not uncommon, based on these criteria, we believe that the ovarian lymphoma is the primary origin with secondary extranodal infiltration of the lymphoma cells in the liver and lymph nodes in this patient.

DLBCL may occur at all ages, but commonly among elderly in their sixth decades. The atypical presentation in this very young patient with diagnostic uncertainty, in the beginning, is consistent with previous established studies emphasizing the heterogeneous phenotyping with unknown risk factors [10].

This patient presented with advanced DLBCL with International Prognostic Index (IPI) [24] score of 3 which categorized her in the high-intermediate risk group before the commencement of recommended up-front chemo-immunotherapy i.e., the R-CHOP regime. There is various salvage chemotherapy regimen available and the additional of rituximab in the regime had shown improved in the outcome of DLBCL [25, 26]. R-CHOP chemo-immunotherapy regimen has been shown to induce remission in > 60% patient with DLBCL with good prognosis in germinal center subtype [27]. In RR cases with initial regime, consolidative ASCT is effective in DLBCL patient [28]. This patient should be carefully monitored for any signs and symptoms of relapse post ASCT of which may result in a poorer prognosis.

Conclusion

DLBCL may present with unusual, atypical symptoms and commonly in advanced stage at the onset of diagnosis. Primary ovarian lymphoma is rare, and immunohistochemistry is of diagnostic value and distinct. Critically appraised the unexplained laboratory abnormality supported by imaging evidence inconsistent with clinical presentation should raise the suspicion of this condition. Germinal center subtypes show better prognosis in young patient < 60 years treated with an aggressive chemo-immunotherapy combination of R-CHOP regimen and ASCT.

Conflict of Interest and financial disclosures
None

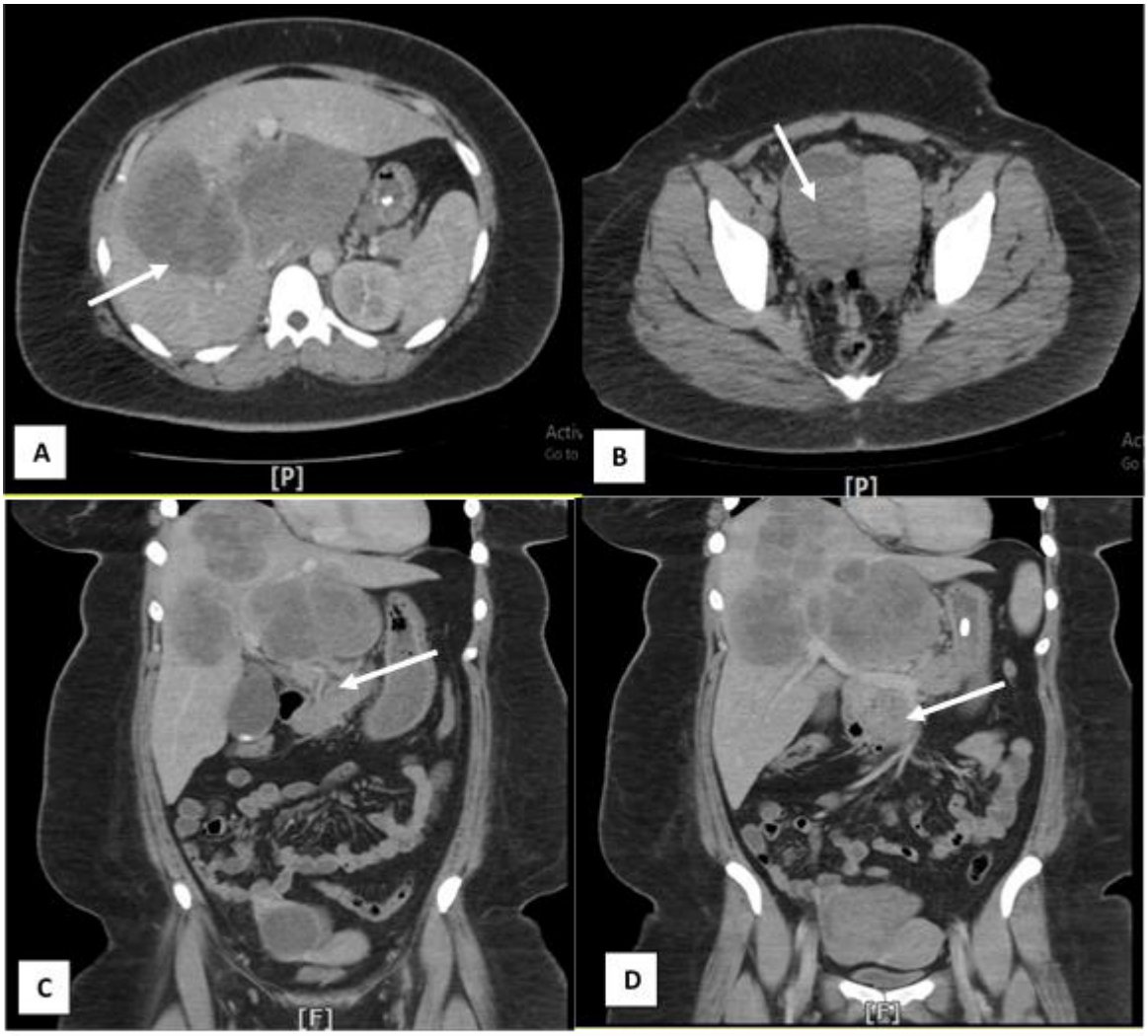

Figure 1. Computed tomography scan transverse section of the abdomen showing multi-lobulated hypodense area in the right lobe of the liver (**A**) and heterogenous enhancing lesion in the right adnexal suggesting ovarian mass (**B**)(Arrow). Coronal section of the abdomen showing multiple small paraaortic and paracaval lymph node enlargement (**C** and **D**) (Arrows).

Figure 2. Resected right and left ovarian mass.

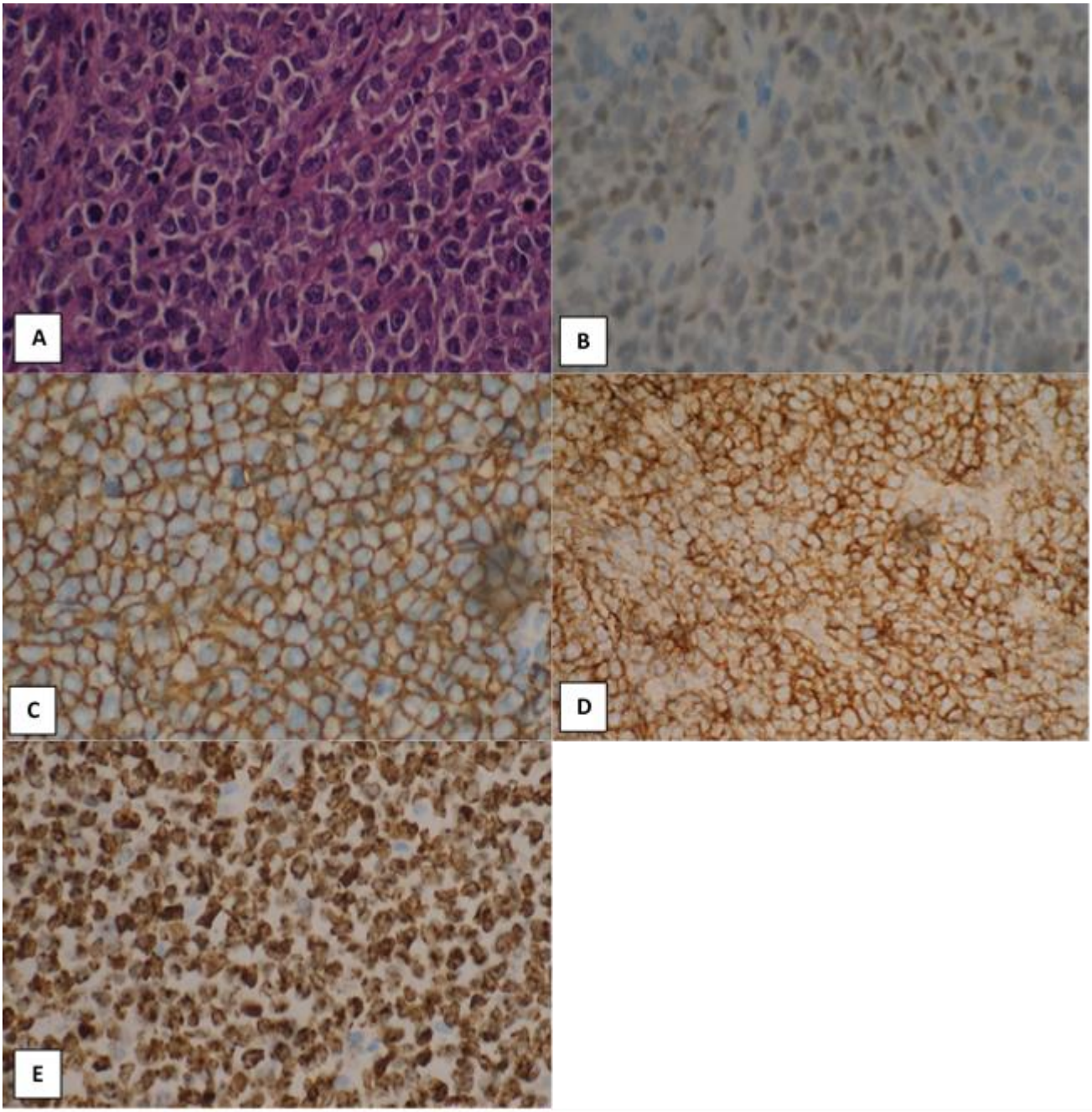

Figure 3. HPE from ovarian tissue. Hematoxylin and eosin stain showing malignant lymphoid cells in the ovary. (x40)(**A**). Different types of immunohistochemical staining showing diffusely positive for BCL6 (**B**), CD20 (**C**), CD79a (**D**) and Ki67 (**E**).

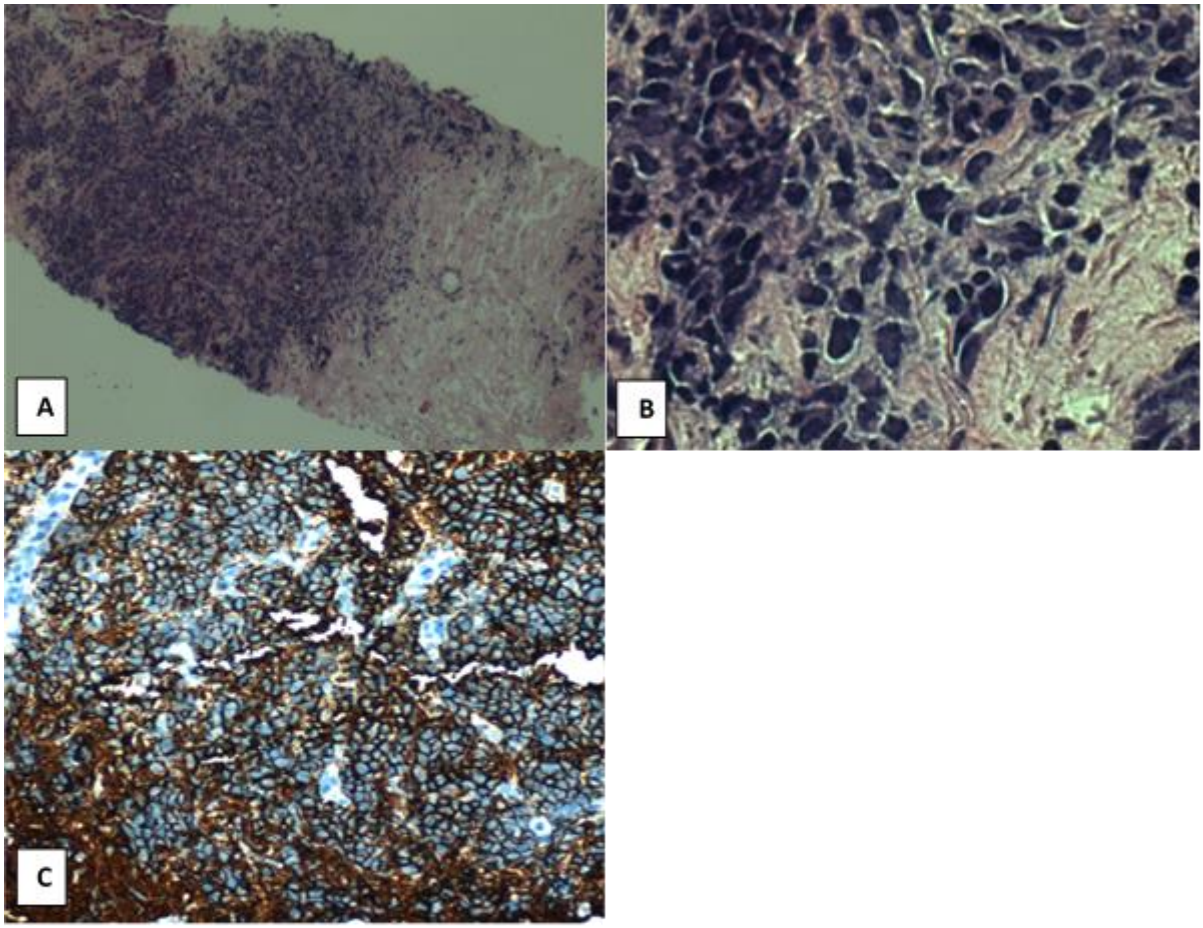

Figure 4. HPE of liver tissue. **A.** Tumor tissue with adjacent area of necrosis. Liver tissue infiltrated by malignant lymphoid cells with extensive areas of necrosis. **B.** Hematoxylin and eosin stain showing the large lymphoid cells arranged in diffuse pattern with hyperchromatic nuclei and irregular nuclear membrane. **C.** Immuno-histochemical staining showing the tumour composed of large B cell diffusely positive for CD20.

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