# Double-hit primary lymphoma (MYC and BCL2) in the bilateral ovary: A case report

YAN ZHANG, WEI WANG and TINGTING CHEN

Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Department of Pathology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

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**Abstract.** Lymphoid neoplasm with 18q21.3/BCL2 and 8q24/MYC translocation to immunoglobulin genes as dual-hit lymphoma in female bilateral ovaries is rare and has a poor clinical outcome. The present study reported on the case of a 33-year-old female, who was admitted to the hospital due to lower abdominal distension aggravated during defecation but with no obvious inducement. The B-ultrasound revealed bilateral adnexal solid masses and the pathological examination indicated advanced B-cell lymphoma (HGBL) with MYC and BCL2 gene rearrangement. The patient then received R-CHOP treatment, but the effects were poor. Rare extranodal HGBL presentations with MYC and BCL2 rearrangement should be considered in the differential diagnosis of masses at unusual sites, such as the adnexa. Due to their aggressive nature, early and prompt recognition of these lymphomas is essential for appropriately administering therapies.

## Introduction

In 2016, the World Health Organization revised the classification of lymphoid tissue tumors, defining mature B-cell lymphoma based on the morphology into diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) as high-grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 rearrangements defined as 'double-hit' or 'triple-hit' lymphomas (DHL/THL) (1). DHL is a highly invasive mature B-cell lymphoma with rapid progression, easy recurrence, and poor prognosis (1). In addition, 70-100% of cases are diagnosed at late stages and >50% exhibit extensive infiltration, including lymph node invasion, and may also involve extranodal organs, particularly the bone marrow and the central nervous system. DHL is not sensitive to conventional treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and cannot be completely relieved after treatment or has an easy relapse after remission. Therefore, accurate diagnosis and treatment of DHL are significant to patient prognosis. Extranodal primary DHL is rare and double lymphoma originating from bilateral ovaries is even rarer, accounting for 0.5% of non-Hodgkin's lymphoma and 1.5% of all ovarian tumors (2). The current study presented a unique case of a primary DHL in the bilateral ovaries and reviewed and discussed the clinical history to provide a deeper understanding of the clinical manifestations, diagnosis and differential diagnosis of this disease, with the goals of reducing missed diagnosis and misdiagnosis, contributing to proper clinical treatment and improving the survival rate of patients.

## Case report

A 33-year-old female patient presented to the West China Second University Hospital, Sichuan University (Sichuan, China), in January 2020, with the complaint of lower abdominal distension aggravated during defecation for at least 2 months prior to admission, but with no obvious inducement of lower abdominal distension. Thus, B-ultrasound was performed locally and indicated a bilateral adnexal solid mass (Fig. 1). At 20 days prior to admission, the patient developed abdominal distension, felt abdominal skin tension, palpated an obvious abdominal mass and occasionally had severe abdominal colics. The MRI revealed two huge lobular masses in the pelvis and abdomen, mainly solid components, and focal liquefaction necrosis was detected in the mass. The diameter lines of the larger layer were ~10x17x11.8 and 10.9x9.3x8.9 cm, and a bilateral 'ovarian vascular pedicle sign' was faintly visible. Thus, the possibility of bilateral ovarian malignant tumors was considered, but the nature was undetermined (Fig. 2). In addition, the level of the tumor marker CA125 was raised to 230 U/ml (normal range, <35 U/ml). Seeking further treatment at the West China Second University Hospital in February 2020, the patient was admitted and underwent abdominal bilateral appendectomy, hysterectomy, pelvic lymph node dissection, abdominal aortic lymph node dissection, momentum resection, appendectomy, intestinal adhesion lysis and closure of great vessels.

*Correspondence to:* Mrs Tingting Chen, Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Department of Pathology, West China Second University Hospital, Sichuan University, 20 Renmin Road South, Chengdu, Sichuan 610041, P.R. China
E-mail: 740095520@qq.com

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Intraoperatively, one gray and white mass (measuring 19x14x8 cm) was detected in the left adnexa, as well as a partial cytoplasmic defect. The grayish-yellow solid nature of the luminal surface was soft and the focal area was hemorrhagic. One white-gray-red nodule (measuring 15x13.5x4.5 cm) was detected in the right adnexa, appearing capsular. The section of the nodule was gray and white, solid and soft, with a focal area of hemorrhage. Grayish brown non-plastic tissue was observed in various places, including the side of the uterus serosal surface, parametrial, posterior uterine wall, the peritoneal reflection of the bladder, intestinal fat lobes. The tissue was fixed with 4% neutral formalin (for 24 h at 25˚C) and embedded in paraffin, and then 4-$\mu$m sections were prepared that were subjected to hematoxylin and eosin (H&E) staining (for 8 h at 25˚C). H&E indicated that the cell morphology was similar in all lesions. Tumor cells exhibited diffuse infiltrative growth, large areas of coagulative necrosis, cells were medium-sized and round in shape with little cytoplasm, the nuclear division was easily seen, asterisk phenomenon was observed and the interstitium had a small amount of vascular and fibrous tissue (Fig. 3). Immunohistochemical staining with the EnVision Systems method using antibodies from Fuzhou Maixin Biotechnology Co., Ltd., was performed at 37˚C for 40 min for all primary antibodies, with the following results: CD20 (+) (working liquid; cat. no. Kit-0001), CD79a (+) (working liquid; cat. no. MAB0258), CD3 (-) (working liquid; cat. no. MAB0740), CD10 (+) (working liquid; cat. no. MAB0668), Bcl6 (+) (working liquid; cat. no. MAB0746), MUM1 (-) (working liquid; cat. no. MAB0885), CyclinD1 (-) (working liquid; cat. no. RMA0541), CD5 (-) (working liquid; cat. no. MAB0827), CD30 (-) (working liquid; cat. no. MAB0868), p53 (+, 70%) (working liquid; cat. no. MAB0674), MYC (+, 80%) (working liquid; cat. no. RMA0803), Bcl2 (+, 90%) working liquid; cat. no. MAB0711) and Ki-67 (+, 80%) (1:200; cat. no. RMA0542). The results of fluorescence *in situ* hybridization (FISH) (3) analysis of the original tumor tissue were as follows: MYC and BCL2 gene translocations (Fig. 4), with no BCL6 gene translocation and no MYC/IgH fusion detected. The pathologic diagnosis was HGBL with MYC and BCL2 gene translocations.

During the postoperative follow-up, three cycles of an R-CHOP chemotherapy regimen were administered in the hospital: 600 mg rituximab on day 1 + 1 g cyclophosphamide on day 1 + 4 mg vindesine on day 1 + 110 mg epirubicin on day 1 + 100 mg prednisone on days 1-5 each week for 3 weeks, with 21 days as one cycle. The first follow-up was performed at 3 months after the surgery and suggested nodular thickening of the pericardium, pleura and possible metastases on the CT scan of the abdomen. Thereafter, the patient did not proceed with related treatments. A follow-up visit was performed every 3 months and the patient died 6 months later.

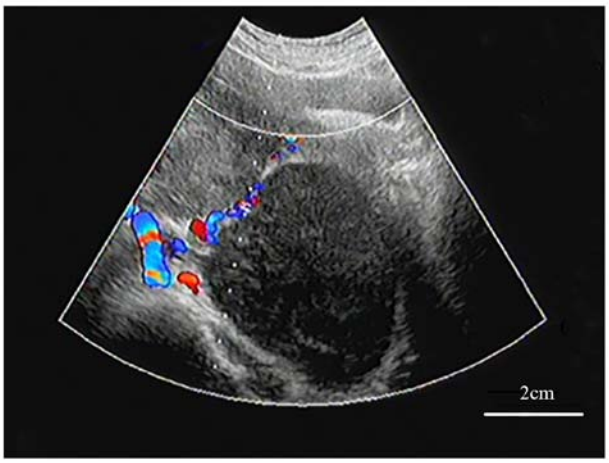


Figure 1. At the initial diagnosis (January 2020), B-ultrasound showed that there was a weak echo mass in the pelvic cavity and lower abdomen, the internal echo was uneven, and there was blood flow signal around the mass (scale bar, 2 cm).

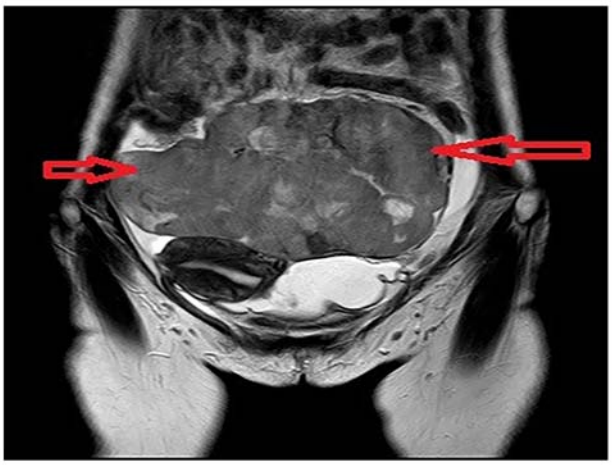

Figure 2. Plain MRI scan (February 2020) in which the red arrows indicate the huge pelvic mass at diagnosis before treatment, ~10x17x11.8 cm in size.

## Discussion

Primary lymphomas of the female genital tract account for 0.2-1.1% of all extranodal lymphomas and most cases are due to secondary disease involvement (4,5). The ovary is usually involved in 7-30% of secondary disseminated lymphomas. Primary ovarian lymphoma has a 5-year survival rate of 80%, while it is only 33% for secondary ovarian lymphoma (6). Hence, clarifying the origin of the lymphoma is crucial. The following diagnostic criteria were proposed for primary ovarian non-Hodgkin lymphoma: i) At diagnosis, the lymphoma is clinically confined to the ovary with no evidence of lymphoma in other tissues but may still be considered primary if the ovarian lymphoma has spread to immediately adjacent lymph nodes or has directly invaded adjacent structures; ii) peripheral blood and bone marrow should not contain any abnormal cells; iii) if other lymphomatous lesions developed at sites distant from the ovary, at least a few months would have elapsed between the appearance of the ovarian and extraovarian lesions (7,8). A previous study reported lymphoma originating in one ovary (9), but DHL originating in the bilateral ovaries is rare.

Currently, the main aspect of clinical DHL diagnosis is based on hematopathological examinations, requiring combined tissue and cell morphology, immunohistochemistry, genetics and molecular biology. DHL gene abnormalities detected by FISH are classified into the MYC

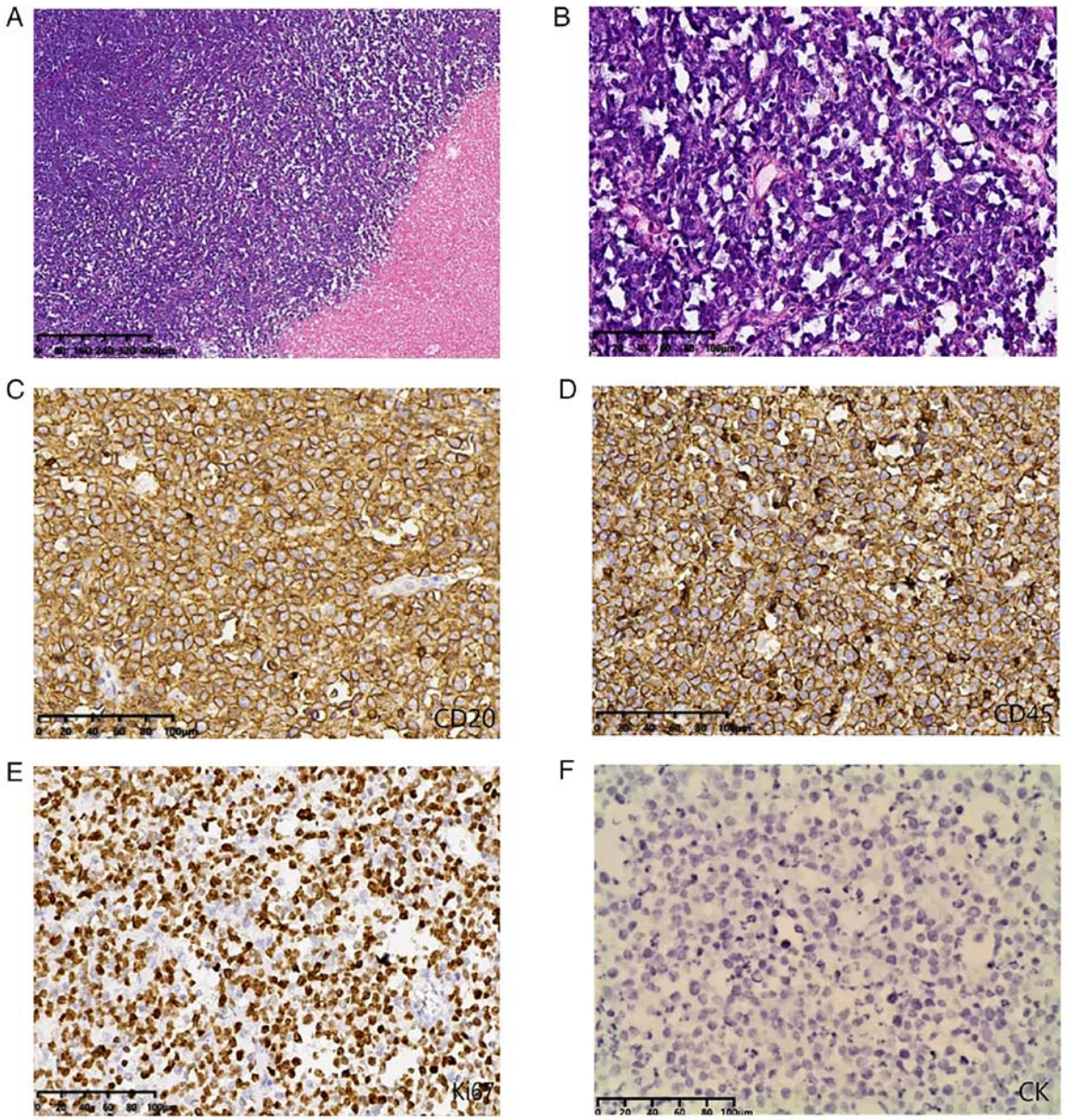


Figure 3. Histology and immunohistochemical images. (A) Histological analysis indicated that the tumor cells exhibited diffuse infiltrative growth, large areas of coagulative necrosis (magnification, x10; scale bar, 400 $\mu$m; H&E); (B) cells were medium-sized and round in shape with little cytoplasm, nuclear division was easily observed, asterisk phenomenon was present and the interstitium had a small amount of vascular and fibrous tissue (magnification, x100; scale bar, 100 $\mu$m; H&E). (C) Tumor cells were positive for CD20 and (D) CD45. (E) The Ki67 labeling index was 80%. (F) Tumor cells were negative for CK. [(C-F) magnification, x200; scale bar, 100 $\mu$m]. CK, cytokeratin.

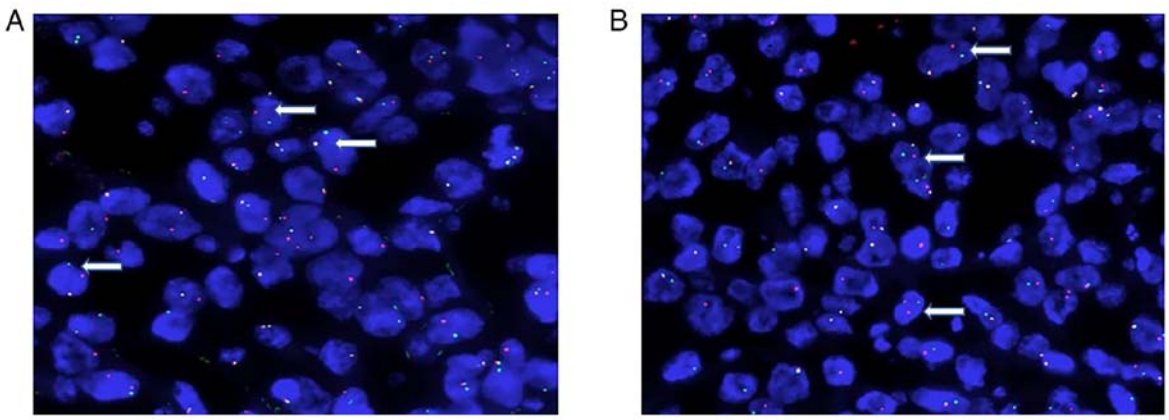


Figure 4. Fluorescence *in situ* hybridization analysis. (A) BCL2 translocation and (B) MYC translocation. White arrows show BCL2 and MYC translocation: One orange, one green and one fusion signal (magnification, x100).

gene and the BCL2 or BCL6 gene. MYC gene rearrangement accompanied by BCL2 or BCL6 gene rearrangement is required for DHL diagnoses or THL if the MYC gene rearrangement is accompanied by both BCL2 and BCL6 gene rearrangements. Given the relatively low incidence of DHL and the high cost of FISH to complete the examination of three gene rearrangements (MYC, BCL2 and BCL6), immunohistochemistry should be performed in patients with DLBCL with high MYC and BCL2 protein levels, germinal center subtype origin and Ki-67 >90%. However, it has been indicated that this practice may miss certain cases (10). For instance, the Ki-67 was ~80% in the current case. Of the 108 patients with DHL studied by Li *et al* (11), ~84% presented with Ki-67 >70%, and the distribution of its expression level was 20-100%. Therefore, there are numerous patients with DHL with Ki-67 <90%. Thus, the Ki-67 index is only one reference and the most reliable diagnostic basis is genetic testing. The histologic support of the present case was a small round cell malignant tumor, and CD20 (+), CD79a (+), CD3 (-), CD10 (+), Bcl6 (+), MUM1 (-), CyclinD1 (-), CD5 (-), CD30 (-), P53 (+, 70%), MYC (+, 80%) and Bcl2 (+, 90%), suggesting the germinal center-like source, and DLBCL with double MYC and BCL2 expression. The gene test results detected the MYC and BCL2 gene translocations, which may be diagnosed as DHL.

Since DHL occurring in the ovary is not common in the clinic, it should be distinguished from the following common ovarian lesions: i) Undifferentiated carcinoma-the tumor is mostly solid, large in size and frequently accompanied by bleeding and necrosis. Under the microscope, the tumor cells have a solid nest-shaped distribution, obvious cell atypia, the nuclear division is common, a spindle cell area may be seen and immunohistochemical expression of epithelial markers cytokeratin (CK) and epithelial membrane antigen (EMA); ii) juvenile granulosa cell tumor-it usually occurs in adolescent females. It is a cystic, solid mass; the solid area is gray and yellow. Under the microscope, it is typically characterized by a diffuse or nodular distribution of tumor cells, interspersed with follicles of different sizes and shapes or round, oval shape. Immunohistochemical staining indicates that the tumor cells express inhibin, calrentin, SF-1, CD99, CD56 and, in certain cases, CK8 or CK18; iii) hypercalcemia small cell carcinoma-it frequently occurs in young females and may be accompanied by hypercalcemia. The tumor is large, solid, gray and yellow in section, and immunohistochemical CK, vimentin, neuron-specific enolase and EMA are frequently positive; iv) HGBL, non-specific, with a morphology between DLBCL and BL, high Ki index, positive CD45 and CD20 on immunohistochemistry, but no rearrangement of MYC and BCL-2/BCL-6-related genes; v) metastatic tumors, combined with CT, B-ultrasound and MRI imaging results, no space-occupying lesions in other systems.

Furthermore, patients with DHL generally have high LDH levels, late clinical stages, rapid development, high cell proliferation indexes and are prone to extranodal invasion, particularly bone marrow and central nervous system involvement. The international prognostic index score is usually medium or high risk, the treatment effect is poor and the survival time is ~0.2-1.5 years (1). R-CHOP is a classic treatment for DLBCL, but its therapeutic effects on DHL are not ideal, which cannot be completely relieved or relapse occurs soon after treatment. The patient of the present study did not undergo gene testing in time after the operation and the effect of the treatment, according to DLBCL, was poor. However, there is no unified standard for DHL treatment. R-Hyper-CVAD, R-CODOX-M/IVAC and R-ECHOP are the most widely used treatments in clinical practice (12). Studies have supported using more intensive regimens to treat patients with DHL; for instance, R-DA-EPOCH rather than R-CHOP (12,13). However, a retrospective multicenter study of 90 patients with double expressor lymphoma indicated that DA-EPOCH-R provided no survival benefit compared to R-CHOP (14). These conflicting results indicate the requirement for prospective studies. The effects are still controversial for other treatments, such as autologous hematopoietic stem cell transplantation. Given the presence of MYC/BCL-2 and/or BCL6 gene rearrangements in DHL, specific inhibitors targeting MYC, BCL-2 and BCL-6 have attracted increasing attention, and immunotherapy and targeted drugs are promising therapeutic directions (13,15).

One limitation of the present study is that no further information is available on the patient, as they did not consent to any further relevant tests, such as fluorodeoxyglucose positron emission tomography-CT scanning and gene expression profiling or gene sequencing, which may have been due to economic or other reasons.

To the best of our knowledge, this rare HGBL presentation with MYC and BCL2 translocations and unusual extranodal locations has been reported less frequently in the ovary. In addition, the case of the present study had involvement of the bilateral ovaries. Hence, clinicians require awareness of these aggressive lymphomas that frequently involve extranodal sites to provide early diagnoses, and the correct multi-agent chemotherapy may be initiated promptly.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors' contributions**

YZ and TC drafted the manuscript and conceived the study. WW and YZ were responsible for the collection and analysis of case data and literature. TC and WW revised the manuscript and interpreted the data. WW provided financial support. YZ, TC and WW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images.

## Competing interests

The authors declare that they have no competing interests.

## References


1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD and Jaffe ES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127: 2375-2390, 2016.
2. Elharroudi T, Ismaili N, Errihani H and Jalil A: Primary lymphoma of the ovary. J Cancer Res Ther 4: 195-196, 2008.
3. Salam DSDA, Thit EE, Teoh SH, Tan SY, Peh SC and Cheah SC: C-MYC, BCL2 and BCL6 translocation in B-cell non-Hodgkin lymphoma cases. J Cancer 11: 190-198, 2020.
4. Nasioudis D, Kampaktsis PN, Frey M, Witkin SS and Holcomb K: Primary lymphoma of the female genital tract: An analysis of 697 cases. Gynecol Oncol 145: 305-309, 2017.
5. Ng SP, Leong CF, Nurismah MI, Shahila T and Jamil MA: Primary Burkitt lymphoma of the ovary. Med J Malaysia 61: 363-365, 2006.
6. Crasta JA and Vallikad E: Ovarian lymphoma. Indian J Med Paediatr Oncol 30: 28-30, 2009.
7. Zhang H, Lui F and Chen Y: A case of primary ovary non-Hodgkin's malignant lymphoma. Hunan Yi Ke Da Xue Xue Bao 23: 516, 1998 (In Chinese).
8. Fox H, Langley FA, Govan AD, Hill AS and Bennett MH: Malignant lymphoma presenting as an ovarian tumour: A clinicopathological analysis of 34 cases. Br J Obstet Gynaecol 95: 386-390, 1988.
9. Sarina SJ and Song J: A case report and literature review of 'double strike' ovarian diffuse large b-fine. Gold lymphoma. Chin J PractGynecol Obstet 38: 247-249, 2022.
10. Wei XX, Zhao Q, Li DP and Huang YH: Recent advances in diagnosis and treatment of double strike lymphoma. J Exp Hematol 27: 1311-1315, 2019.
11. Li S, Saksena A, Desai P, Xu J, Zuo Z, Lin P, Tang G, Yin CC, Seegmiller A, Jorgensen JL, *et al*: Prognostic impact of history of follicular lymphoma, induction regimen and stem cell transplant in patients with MYC/BCL2 double hit lymphoma. Oncotarget 7: 38122-38132, 2016.
12. Sehn LH and Salles G: Diffuse large B-cell lymphoma. N Engl J Med 384: 842-858, 2021.
13. Zhuang Y, Che J, Wu M, Guo Y, Xu Y, Dong X and Yang H: Altered pathways and targeted therapy in double hit lymphoma. J Hematol Oncol 15: 26, 2022.
14. D'Angelo CR, Hanel W, Chen Y, Yu M, Yang D, Guo L, Karmali R, Burkart M, Ciccosanti C, David K, *et al*: Impact of initial chemotherapy regimen on outcomes for patients with double-expressor lymphoma: A multi-center analysis. Hematol Oncol 39: 473-482, 2021.
15. Savage KJ, Johnson NA, Ben-Neriah S, Connors JM, Sehn LH, Farinha P, Horsman DE and Gascoyne RD: MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 114: 3533-3537, 2009.