A Rare Case Report of Primary Ovarian Burkitt Lymphoma and Review of Literature

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Case report

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Abstract

Background: Primary ovarian Burkitt lymphoma is rare, with only 26 reported cases usually with high proliferative activity and MYC translocation. A case of primary ovarian Burkitt lymphoma that occurred in a 25-year-old woman was described in the present study.

Case presentation: An ultrasound examination indicated that the right ovary was enlarged and abundant blood flow signals were observed. The right salpingo-oophorectomy was subsequently performed. Histology was characterized by diffuse sheets of monotonous medium-sized lymphoid cells with high mitotic activity and apoptosis. Numerous tangible-body macrophages were found in the ovarian tissue, presenting a starry sky pattern. The tumor cells expressed CD20, CD79-a, PAX5, CD10, BCL6, and MYC in the absence of BCL2, CD3, CD5, CD138, and TdT. A significant Ki-67 proliferation index was revealed at virtually 90%. FISH examination indicated positive MYC (8q24) rearrangement but negative, BCL2 (18q21) and BCL6 (3q37) rearrangement. Cumulative evidence indicated primary ovarian Burkitt lymphoma as the final histopathological diagnosis. The patient was treated with 8 courses of CODOX-M/IVAC combined with HyperCVAD chemotherapy after surgery.

Conclusion: By reporting the histological patterns, immunophenotypes, FISH, and successful post-surgical combined chemotherapy of this rare case of primary ovarian Burkitt lymphoma, we expected to provide insights into the future treatment of this rare but lethal disease.

1. Introduction

Burkitt lymphoma (BL) is an aggressive B-cell lymphoma characterized by the frequent presence in extranodal sites or as acute leukaemia, mostly with high proliferative activity and *MYC* translocation. All organs of the female genital tract can be involved, and ovarian involvement predominates in a majority of the cases [1; 2]. The molecular hallmark of BL is the deregulation of MYC expression due to the translocation of MYC to an Immunoglobulin (IG) gene locus. Gene expression profiling has defined the patterns of molecular signatures for BL[3; 4]. Mutations of Transcription factor 3 (TCF3) and DNA-binding protein inhibitor (ID3) are seen in 70% of sporadic BL cases documented [5–8]. Mutations of MYC, CCDN3, TP53, RHOA, SMARCA4, and ARID1A are present in 5–40% of BL cases [9]. Only 26 cases of primary ovarian Burkitt lymphoma have been reported (Table 1) [10–34]. The present study reported the clinical data, histological morphology, immunohistochemistry, molecular characteristics, and treatment of this case and expected to provide a further reference for the clinicopathological characteristics of the tumor and the basis for its treatment and diagnosis.

2. Case Presentation

The patient was a 25-year-old married female who complained of a mass in the right ovary by physical examination 2 months ago. She had regular menstruation. The preoperative transvaginal ultrasound displayed that the right ovary was enlarged approximately 93×83×74 mm. and abundant blood flow signals were also observed. The uterus, cervix, and left ovary were normal. The endometrial thickness was about 7 mm (Fig. 1, A). Cervical cytology findings revealed negative for intraepithelial lesion or malignancy (NILM). The patient denied additional aberrant symptoms or signs upon admission. The right salpingo-oophorectomy was subsequently performed.

2.1 Gross examination

The removed right ovary was measured 11×11×5 cm in size. The tumor originated from the ovary and it did not spread to the fallopian tube. The boundary was well-circumscribed, with a gray-white tender section surface. Several scattered bleeding spots were visible (Fig. 1, B). No apparent lesions were displayed in the fallopian tube.

2.2 Microscopic examination

Various morphological patterns were revealed by microscopic examination. The tumor tissue was diffusely dispersion and the ovarian structure was destroyed. The boundary between tumor tissue and ovarian was unclear (Fig. 2, A). The tumor cells were characterized by diffuse sheets of monotonous medium-sized lymphoid cells. As they had high mitotic activity and apoptosis, a pattern of the starry sky was displayed in the presence of numerous tingible-body macrophages (Fig. 2, B). The neoplastic cells presented squared-off contours, with round nuclei, finely clumped chromatin, multiple nucleoli, and basophilic cytoplasm. Numerous mitotic figures and apoptotic bodies were also revealed (Fig. 2, C and D).

2.3 Immunohistochemical findings

Immunohistochemical studies revealed that tumor cells express B-cell antigens (CD20, CD79-a, and PAX5), germinal-center markers (CD1 and BCL6), and MYC except for BCL2, CD3, CD5, CD138, and TdT. The proliferation index of Ki-67 was virtually 90% (Fig. 3).

2.4 FISH examination

The technique of fluorescence in situ hybridization (FISH) was employed and the molecular pathology examination results indicated that MYC (8q24) rearrangement was positive whereas BCL2 (18q21) and BCL6 (3q37) rearrangement was negative (Fig. 4).

The patient underwent bone marrow aspirate evaluation for hematological immunotyping and karyotype analysis. The results were negative for malignancy and atypical chromosomes. The subsequent Positron emission tomography–computed tomography (PET-CT) showed no lesions on other organs. Combined with the clinical visualization, histological features, immunohistochemical results, and FISH results, the patient was confirmed the diagnosis as primary ovarian Burkitt lymphoma and introduced the treatment protocol of eight cycles of CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate / ifosfamide, etoposide, high-dose cytarabine) combined with HyperCVAD (Course A: cyclophosphamide, vincristine, doxorubicin and dexamethasone. Course B: methotrexate and cytarabine) chemotherapy after surgery.

3. Discussion

Despite primary extranodal invasive lymphoma of the ovary is a rare disease, ovarian lymphoma is typically secondary to diffuse systemic disorder. In extranodal lymphoma, primary ovarian lymphoma accounts for 0.5% of extranodal non-Hodgkin's lymphoma and 1% of all ovarian tumors [35]. Several perspectives regarding the origin of primary ovarian lymphoma have been documented currently as the following: 1. Primary ovarian lymphoma originates from the lymphoid tissues that already exist in the ovary[23]; 2. The blood vessels around the hilum of the ovary or the corpus luteum cells may be tumor-derived cells[10]; 3. Reactive lymphocytes may be secondary to ovarian inflammation (pelvic inflammatory disease and endometriosis) or autoimmune diseases, and following processes of malignant transformation into ovarian primary lymphoma [37].

L.R. Weekes first discovered primary bilateral ovarian Burkitt lymphoma in a 15-year-old girl from Guatemala in 1986[36]. To our knowledge, only 26 cases of primary ovarian Burkitt lymphoma have been reported in the literature. Among the described cases, 15 of them were bilateral and 10 were unilateral (1 unavailable). The age of the patients ranged from 6 to 62 years (average, 27 years old). The clinical manifestations of ovarian primary Burkitt lymphoma are unique from one another [38]. Most patients complained of abnormal pain accompanied by additional symptoms included fever, abnormal mass, lower abdominal swelling, ascites, and vaginal bleeding [39; 40]. As for our patient, the young married woman was diagnosed with a mass in the right ovary by physical examination due to infertility. The grossly ovarian mass was well-circumscribed and encapsulated. The tumor was measured at approximately 11×11×5 cm in size. The section surface of the tumor presented tender, gray-white in color with some scattered bleeding spots. The histological findings of the present case were identical to Burkitt's lymphoma that occurred in other organs, which were characterized by diffuse growth of medium-sized lymphoid cells with round nuclei and agglomerated chromatin [41]. Necrotic debris could be seen in the background, which was swallowed by many tissue cells, forming a typical pattern of the "starry sky". Among the reported cases, 6 were FIGO (International Federation of Gynecology and Obstetrics) staging 1A, 1 was FIGO staging 1B, 2 were FIGO staging 2A, and 11 were FIGO staging 4A (6 unavailable). This case presented a primary ovarian Burkitt lymphoma of FIGO staging 1A.

Primary ovarian Burkitt lymphoma originates from B cells and expresses B cell markers such as CD20, CD22, CD19, and CD10. Cytokeratin and T cell markers are negative. MYC represents a family of regulator gene and proto-oncogene that codes for transcription factors. The MYC family consists of three related human genes c-myc (MYC), l-myc (MYCL), and n-myc (MYCN). c-myc (also sometimes referred to as MYC) is the first gene discovered in this family due to its homology with a viral gene v-myc. In cancer, c-myc is often expressed constitutively (persistently), which leads to an increase in the expression of multiple genes. Additionally, some of them are even involved in cell proliferation and contribute to the formation of cancer cells. Common human translocations involving c-myc are critical to the development of most Burkitt lymphomas [13; 42], and the mutation is usually t (8;14) (q24; q32) translocation. In this case, CD20 was strongly positive, the result of fluorescence in situ hybridization (FISH) was MYC (8q24) rearrangement, and the morphology combined with immunohistochemical results and molecular pathological features were consistent with the diagnosis of Burkitt lymphoma.

The differential diagnosis of primary ovarian Burkitt lymphoma includes secondary ovarian lymphoma, adult granular cell tumor of the ovary, and small cell neuroendocrine carcinoma (SCNEC). Fox et al. proposed the diagnostic criteria for primary ovarian lymphoma in

1988 included 1. Lymphoma should be confined to the ovary or adjacent lymph nodes or structures at the time of diagnosis; 2. There is no evidence showing the presence of blood or bone marrow disease; 3. Distal involvement should occur at least a few months after ovarian involvement [43]. Adult granular cell tumor of the ovary is frequently encountered in postmenopausal women, with the peak age of onset at 50–55 years old, which represents the most typical clinical ovarian tumor-related to estrogen secretion. The nucleus is round, oval, or polygonal, lightly stained, less cytoplasm, and the nuclear groove is visible. Immunohistochemical expression of sex cord-stromal markers such as α-inhibin, calretinin, FOXL2, and CD99. The epithelium marker is negative. Differential diagnosis of the disease also requires an accurate determination of SCNEC. SCNEC is a high-grade carcinoma composed of small to medium-sized cells with scant cytoplasm and neuroendocrine differentiation. The cytoplasm of the tumor is sparse with a small cell nucleus. Single small nucleolus can be visible and mitotic images are common. Tumor cells can be a nested pattern, string-shaped and irregular cell clusters, and express neuroendocrine markers such as CgA, Syn, and CD56.

As Burkitt lymphoma is an aggressive B-cell non-Hodgkin's lymphoma with a short and active proliferation cycle, multi-drug combination chemotherapy is considered as an optimal treatment protocol for patients with Burkitt lymphoma [44]. The 26 cases previously reported were mostly treated with surgery followed by chemotherapy (17/26). Surgical treatment plays an important role in providing clinical information, staging, and diagnosis, and patients who confirmed diagnosis should start chemotherapy as early as possible. Although Burkitt lymphoma is highly malignant, combined treatment with multiple chemotherapy regimens can substantially improve the survival rate of Burkitt lymphoma patients [13]. The follow-ups ranged from 0.5 to 3.5 years (average1.6 years). Four death cases were reported at an overall survival rate of 15/19 (78.95%) (7 unavailable). In our case, the patient underwent right salpingo-oophorectomy and accepted eight cycles of CODOX-M/IVAC combined with HyperCVAD chemotherapy after surgery. The patient developed no relevant disease 10 months following the completion of the therapy.

4. Conclusion

We report a rare case of a primary ovarian Burkitt lymphoma that occurred in a young woman. The histological morphology demonstrated diffuse sheets of monotonous medium-sized lymphoid cells with high mitotic activity and apoptosis, presenting a pattern of the starry sky due to the presence of numerous tangible-body macrophages. Immunohistochemistry staining was used to identify the specific orientation. FISH results demonstrated MYC gene arrangement. Combination chemotherapy after surgery demonstrated a satisfactory therapeutic efficacy using the treatment protocol. Further studies are of great significance to characterize clinical features of this rare disease, to assist differential diagnosis, and to develop effective therapeutic regimens.

Abbreviations

BL：Burkitt lymphoma

IG: Immunoglobulin

TCF3: Transcription factor 3

ID3: DNA-binding protein inhibitor

NILM: negative for intraepithelial lesion or malignancy

FISH: fluorescence in situ hybridization

PET-CT: Positron emission tomography–computed tomography

CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate / ifosfamide, etoposide, high-dose cytarabine

HyperCVAD: Course A: cyclophosphamide, vincristine, doxorubicin and dexamethasone. Course B: methotrexate and cytarabine

FIGO: International Federation of Gynecology and Obstetrics

SCNEC: small cell neuroendocrine carcinoma

Declarations

Ethics approval and consent to participate

The research related to human use has been complied with all the relevant national regulations, institutional policies and follows the tenets of the Helsinki Declaration, and has been approved by the Anhui Province Maternal and Child Health Hospital review board or equivalent committee (No.2021467).

Consent for publication

Written informed consent for publication of the clinical details and/or clinical images was obtained from the parents of the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

All data generated or analyzed during this case are included within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Hongliang Xu: Project development, Data Collection, Manuscript writing. Caixia Zhao: Data collection. Qing Wang: Data collection. Yong Chen: Data collection. Weiqin Zhang: Data collection. Heping Zhang: Data Collection, Manuscript editing.

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Tables

Table 1 The clinical features of 26 primary ovarian Burkitt lymphoma patients.

Case number	1st author	Age	Nationality	Symptoms	Ovarian involvement	Stage	Treatment	Follow-up
1	Baloglu[10]	24	Turkey	Secondary amenorrhea, ascites, pleural effusion	Bilateral	IV Ann Arbor	Chemotherapy: Cyclophosphamide, Adriamycin, Vincristine, L-asparaginase, Prednisolone, plus intrathecal Methotrexate	Remission; autologous bone marrow transplantation; death 35 days after transplantation
2	Vang[11]	62	USA	Constitutional symptoms	Unilateral	I Ann Arbor	Chemotherapy, radiotherapy	Remission
3	Linden[12]	24	USA	Abdominal pain	Unilateral	II Ann Arbor	Surgery, Chemotherapy	NA
4	Liang[13]	38	Hong Kong, China	Abdominal pain	Unilateral	I Ann Arbor	Chemotherapy, radiotherapy	Disease-free survival (0.5 year)
5	Mitra[14]	23	India	Abdominal pain	Unilateral	I Ann Arbor	Radiotherapy	Disease-free survival (0.5 year)
6	Miyazaki[15]	16	Japan	Abdominal pain, constipation	Unilateral	NA	Surgery, chemotherapy	Died after 171 days
7	Cyriac[16]	13	India	Abdominal pain, fever	Bilateral	IV Ann Arbor	Chemotherapy (LMB 89 protocol)	Disease-free survival (0.5 year)
8	Crawshaw[17]	28	UK	Abdominal pain, pregnancy	Bilateral	IV Ann Arbor	Chemotherapy	NA
9	Chishima[18]	25	Japan	Abdominal pain	Bilateral	IV Ann Arbor	Surgery, chemotherapy (CHOP)	Disease-free survival (2.5 years)
10	Monterroso[19]	21	USA	Abdominal pain	NA	NA	Surgery, chemotherapy	Died after a year
11	Ng[20]	20	Malaysia	Abdominal pain	Bilateral	1B FIGO	Surgery, chemotherapy (BFM regime), plus prophylactic intrathecal Methotrexate	Remission
12	Shacham-Abulafia[21]	39	Isreal	Night sweats, abdominal pain, dyspnea	Bilateral	IV Ann Arbor	Chemotherapy (R-Hyper-CVAD plus GMALL-BALL/NHL 2002)	Disease-free survival (0.5 year)
13	Bianchi[22]	57	Italy	Neurological symptoms	Bilateral	IV Ann Arbor	Surgery, chemotherapy (intensive G-mall protocol)	NA

Case number	1st author	Age	Nationality	Symptoms	Ovarian involvement	Stage	Treatment	Follow-up
14	Danby[23]	11	USA	Abdominal pain, nausea, vomiting, anorexia, and weight loss	Unilateral	NA	Surgery, chemotherapy (Rituximab, Methotrexate, Cytarabine, intrathecal Hydrocortisone, Cytosine arabinoside, Methotrexate and Cyclophosphamide)	NA
15	Etonyeaku[24]	18	Nigeria	Abdominal pain, lower abdominal swelli	Bilateral	NA	Surgery, chemotherapy (Cyclophosphamide, Vincristine, Methotrexate)	Died after second chemotherapy
16	Gottwald[25]	27	Poland	Abdominal pain, ascites	Bilateral	NA	Surgery, chemotherapy (COP followed by CODOXM + IVAC)	Disease-free survival (3 years)
17	Gutierrez[26]	34	Spain	NA	Bilateral	IV Ann Arbor, 3 FIGO	NA	NA
18	Hatami[27]	58	USA	Abdominal masses	Bilateral	IV Ann Arbor	Surgery, chemotherapy (Vincristine, Rituximab, Methotrexate with Leucovorin and intrathecal Methotrexate)	Disease-free survival (3.5 years)
19	Munoz[28]	30	Spain	Abdominal pain	Bilateral	NA	Surgery, chemotherapy (CODOX-M-IVAC plus Rituximab)	NA
20	Khan[29]	6	India	Abdominal pain and masses	Bilateral	IV Ann Arbor	Surgery, chemotherapy (MCP-842 protocol)	NA
21	Mondal[30]	6	India	Abdominal pain, difficulties with walking	Bilateral	II R Murphy staging	Surgery, chemotherapy (Magrath protocol using CODOX-M regimen)	Remission
22	Ana Gómez Alarcón[31]	13	Spain	Abdominal pain	Unilateral	IV Ann Arbor	Surgery, chemotherapy (Doxorubicin, Vincristine, Cytarabine, Dexamethasone, Rituximab)	Remission

Case number	1st author	Age	Nationality	Symptoms	Ovarian involvement	Stage	Treatment	Follow-up
23	Xiao[32]	19	China	Chest tightness, asthma	Unilateral	IV Ann Arbor	Surgery, chemotherapy (HyperCVAD, MTX plus Ara-c)	Deceased
24	Xiao[32]	43	China	Fatigue, bone pain	Unilateral	I Ann Arbor	Surgery, chemotherapy (R-CHOP, HD-MTX plus VP)	Remission
25	Gravos[33]	21	Greek	Abdominal distension	Unilateral	I Ann Arbor	Chemotherapy	Remission
26	Al-Maghrabi[34]	42	Saudi Arabia	Abdominal pain	Bilateral	I Ann Arbor	Surgery, chemotherapy (R-CODOX, R-IVAC)	Remission

Figures

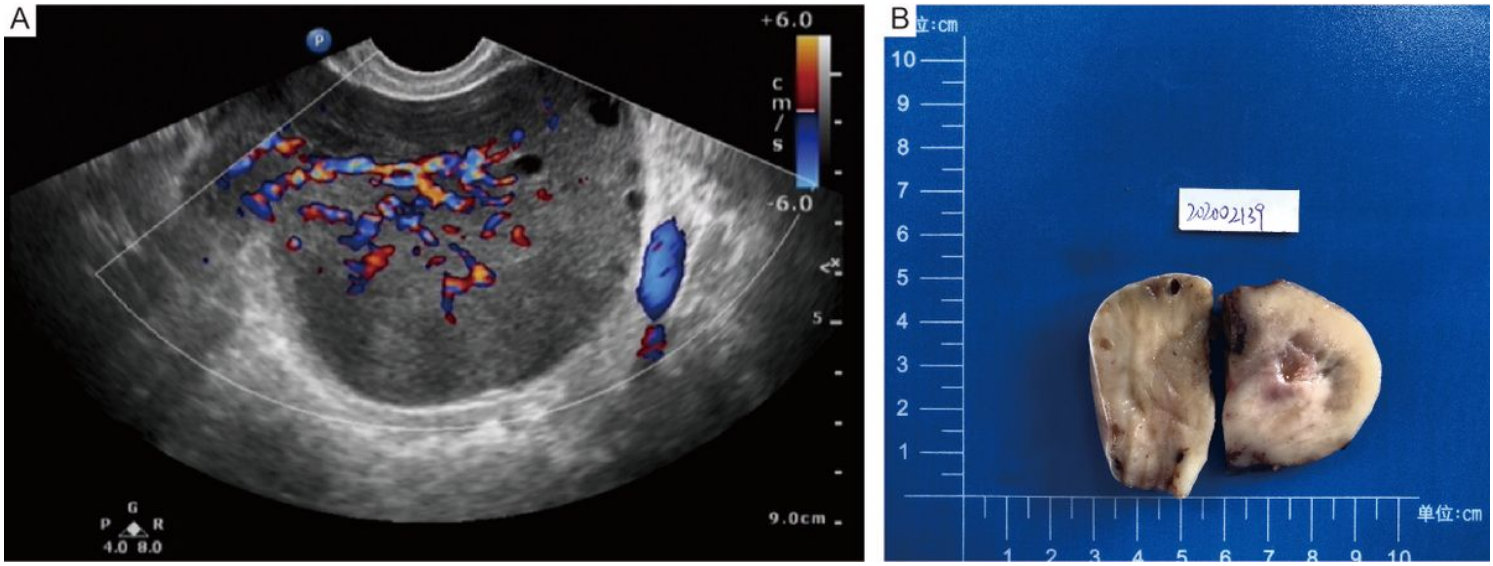

Figure 1

Imaging and gross feature of the case. A) Preoperative transvaginal ultrasound showed that the right ovary was enlarged, with abundant blood flow signals in the ovarian tissue. B) The tumor originated from the ovary, well-circumscribed, with gray-white tender section surface and visible scattered bleeding spots.

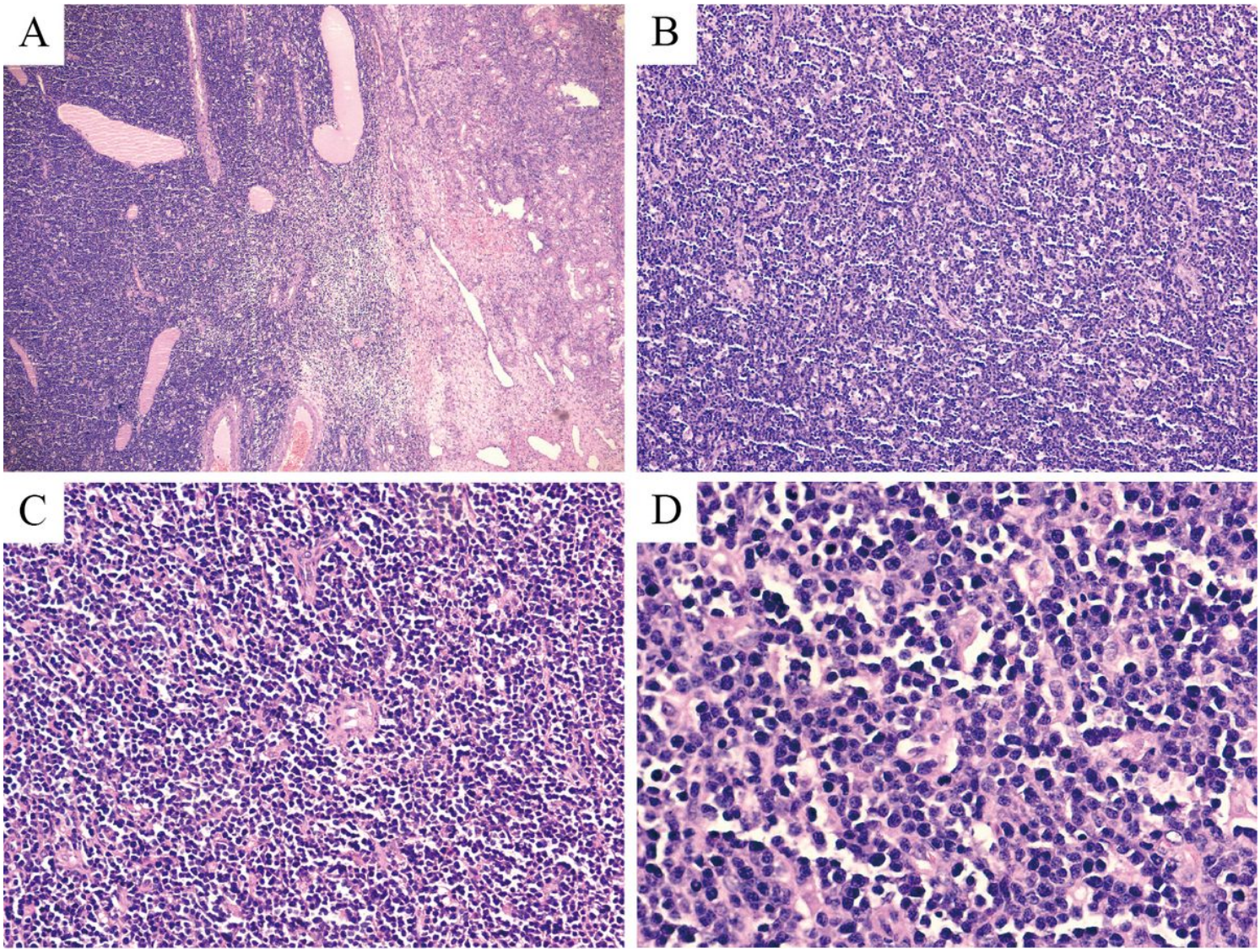

Figure 2

Histology of the ovary tumor. A) The tumor tissue was diffusely invasive and the ovarian structure was destroyed. Residual ovarian tissue was displayed. The boundary between tumor tissue and ovarian was unclear (magnification: ×40). B) The tumor cells were medium-sized with high mitotic activity and apoptosis, presenting a pattern of a starry sky due to the presence of numerous tangible-body macrophages (magnification: ×100). C) and D) The tumor cells were squared-off contours, with round nuclei, finely clumped chromatin, multiple nucleoli, and basophilic cytoplasm. Numerous mitotic figures and apoptotic bodies were revealed (C, magnification: ×200; D, magnification: ×400)

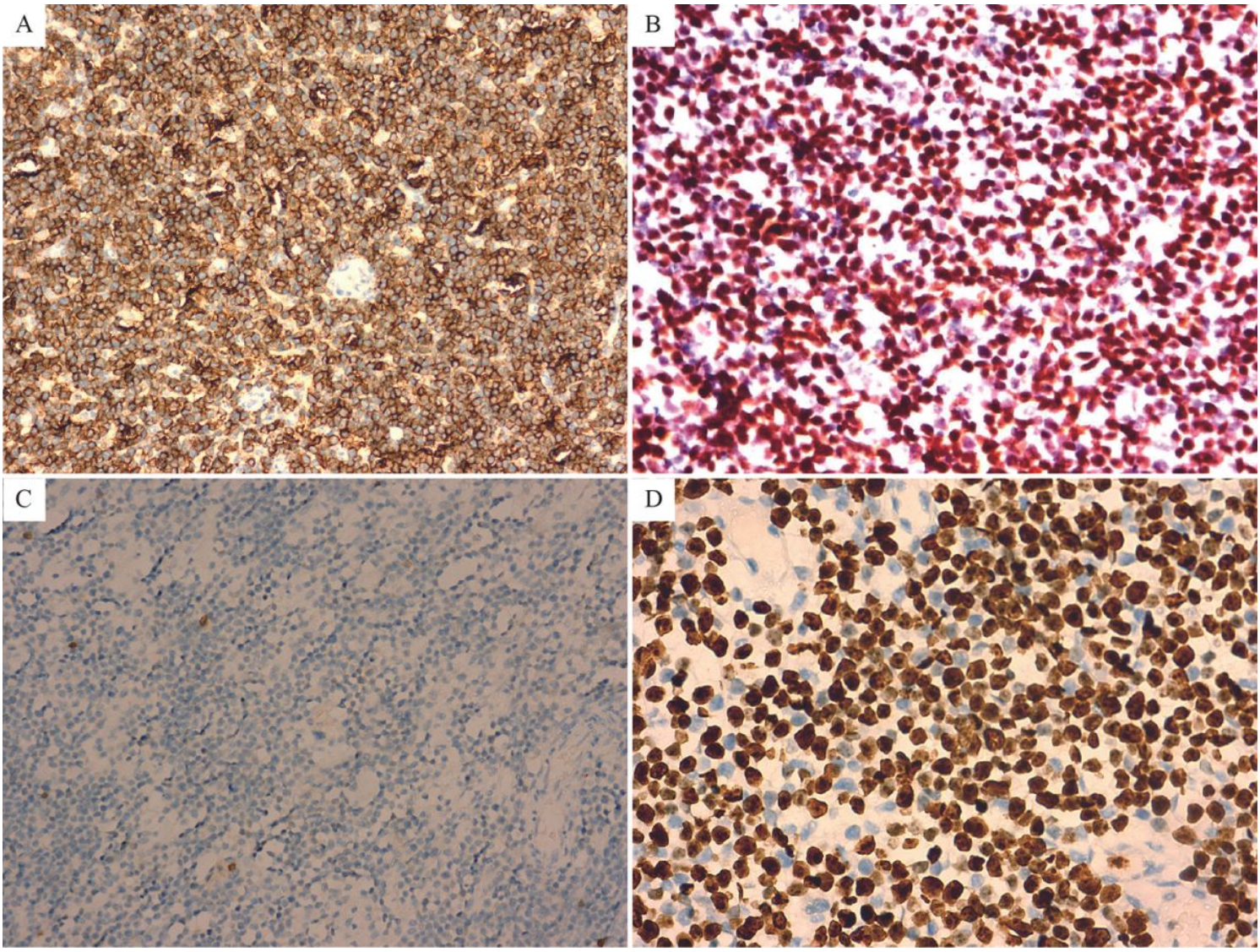

Figure 3

Immunophenotypes of the ovary tumor. A) Immunohistochemical images indicated that tumor cells were positive after staining with monoclonal anti-CD20 antibody (magnification: ×200). B) Immunohistochemical examination revealed that tumor cells were positive for monoclonal anti-MYC antibody ((magnification: ×200). C) Immunohistochemical examination revealed that tumor cells were negative for monoclonal anti-CD3 antibody ((magnification: ×100). D) Immunohistochemical examination revealed that tumor cells were positive for monoclonal anti-Ki-67 antibody ((magnification: ×400).

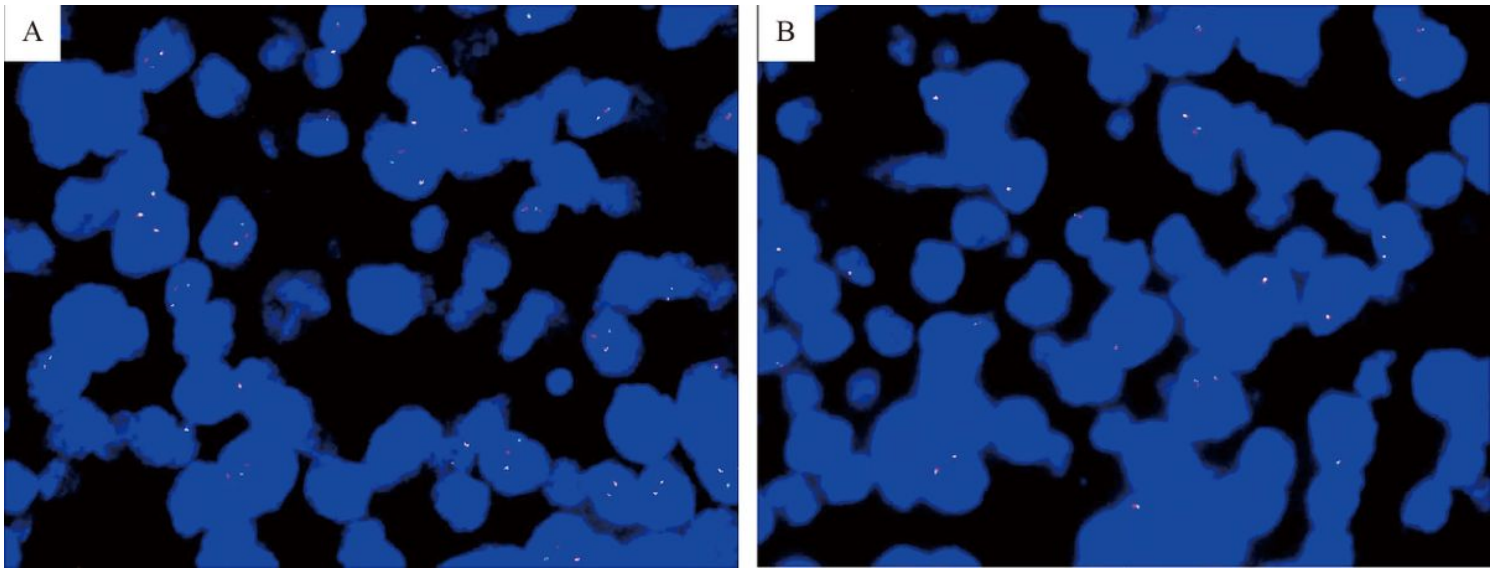

Figure 4

FISH examination of the tumor cells. A). MYC (8q24) rearrangement was positive. B) BCL2 (18q21) rearrangement was negative.