Case Report
Primary ovarian Burkitt lymphoma: report of a case and review of literature

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Abstract: We report a case of primary ovarian Burkitt lymphoma that occurred in a 25-year-old woman. The patient complained of a mass in the right ovary discerned by physical examination 2 months prior. Ultrasound examination indicated that the right ovary was enlarged and abundant blood flow signals were observed. Right salpingo-oophorectomy was subsequently performed. Histology was characterized by diffuse sheets of monotonous medium-sized lymphoid cells with plentiful mitotic figures and apoptosis. Numerous tingible-body macrophages were found in the ovarian tissue, presenting a starry sky pattern. The tumor cells expressed CD20, CD10, BCL6, and MYC in the absence of BCL2. Ki-67 proliferative index was very high with a proliferation rate of near 100%. MYC (8q24) rearrangement was detected by fluorescence in situ hybridization (FISH) with no BCL2 (18q21) and BCL6 (3q37) gene rearrangements. Cumulative evidence established primary ovarian Burkitt lymphoma as the final histopathologic diagnosis with clinical stage I (FIGO). The patient received HyperCVAD chemotherapy after surgery and remained complete response (CR) for 18 months. We aim to provide insight into the future treatment of this rare but lethal disease.

Keywords: Primary, ovary, Burkitt lymphoma

Introduction

Burkitt lymphoma (BL) is an aggressive B-cell lymphoma characterized by frequent presence in extranodal sites or as acute leukemia, 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 IG gene locus. Gene expression profiling has defined patterns of molecular signatures for BL [3, 4]. Mutations of TCF3(E2A) and ID3 are seen in 70% of sporadic BL cases documented [5-8]. Mutations of MYC, CCND3, TP53, RH0A, SMARCA4, AND ARID1A are present in 5-40% of BL cases [9]. About 29 cases of primary ovarian Burkitt lymphoma have been reported (Table 1) [10-38]. The present study reports the clinical data, histologic morphology, immunohistochemistry, molecular characteristics, and treatment in this case in order to provide a further reference about this tumor’s diagnosis and treatment.

Case presentation

The patient was a 25-year-old married female who complained of a mass in the right ovary detected 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 (Figure 1A). The uterus, cervix, and left ovary were normal. The endometrium measured about 7 mm in thickness. Cervical cytology was negative for intraepithelial lesion or malignancy (NILM). The patient
### Table 1. Clinical features of 26 primary ovarian Burkitt lymphoma patients

<table>
<thead>
<tr>
<th>Case number</th>
<th>1st author</th>
<th>Age</th>
<th>Nationality</th>
<th>Symptoms</th>
<th>Ovarian involvement</th>
<th>Stage</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baloglu</td>
<td>24</td>
<td>Turkey</td>
<td>Secondary amenorrhea, ascites, pleural effusion</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Chemotherapy: Cyclophosphamide, Adriamycin, Vincristine, L-asparaginase, Prednisolone, plus intrathecal Methotrexate</td>
<td>Remission; autologous bone marrow transplantation; death 35 days after transplantation</td>
</tr>
<tr>
<td>2</td>
<td>Vang</td>
<td>62</td>
<td>USA</td>
<td>Constitutional symptoms</td>
<td>Unilateral</td>
<td>I Ann Arbor</td>
<td>Chemotherapy, radiotherapy</td>
<td>Remission</td>
</tr>
<tr>
<td>3</td>
<td>Hui</td>
<td>13</td>
<td>USA</td>
<td>Abdominal pain</td>
<td>Unilateral</td>
<td>III Murphy staging</td>
<td>Surgery, chemotherapy (COPADM)</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Liang</td>
<td>38</td>
<td>Hong Kong, China</td>
<td>Abdominal pain</td>
<td>Unilateral</td>
<td>I Ann Arbor</td>
<td>Chemotherapy, radiotherapy</td>
<td>Disease-free survival (6 months)</td>
</tr>
<tr>
<td>5</td>
<td>Taylor</td>
<td>33</td>
<td>USA</td>
<td>Abdominal pain</td>
<td>Bilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy</td>
<td>Died after 171 days</td>
</tr>
<tr>
<td>6</td>
<td>Miyazaki</td>
<td>16</td>
<td>Japan</td>
<td>Abdominal pain, constipation</td>
<td>Unilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy</td>
<td>Disease-free survival (6 months)</td>
</tr>
<tr>
<td>7</td>
<td>Cyriac</td>
<td>13</td>
<td>India</td>
<td>Abdominal pain, fever</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Chemotherapy (LMB 89 protocol)</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Crawshaw</td>
<td>28</td>
<td>UK</td>
<td>Abdominal pain, pregnancy</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (CHOP)</td>
<td>Disease-free survival (30 months)</td>
</tr>
<tr>
<td>9</td>
<td>Chishima</td>
<td>25</td>
<td>Japan</td>
<td>Abdominal pain</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Chemotherapy</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Monterroso</td>
<td>21</td>
<td>USA</td>
<td>Abdominal pain</td>
<td>NA</td>
<td>NA</td>
<td>Surgery, chemotherapy</td>
<td>Died after a year</td>
</tr>
<tr>
<td>11</td>
<td>Ng</td>
<td>20</td>
<td>Malaysia</td>
<td>Abdominal pain</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (BFM regime), plus prophylactic intrathecal Methotrexate</td>
<td>Remission</td>
</tr>
<tr>
<td>12</td>
<td>Shacham-Abulafia</td>
<td>39</td>
<td>Israel</td>
<td>Night sweats, abdominal pain, dyspnea</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Chemotherapy (R-Hyper-CVAD plus GMALL-BALL/NHL 2002)</td>
<td>Disease-free survival (6 months)</td>
</tr>
<tr>
<td>13</td>
<td>Bianchi</td>
<td>57</td>
<td>Italy</td>
<td>Neurological symptoms</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (intensive G-mall protocol)</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>Danby</td>
<td>11</td>
<td>USA</td>
<td>Abdominal pain, nausea, vomiting, anorexia, and weight loss</td>
<td>Unilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy (Rituximab, Methotrexate, Cytarabine, intrathecal Hydrocortisone, Cytosine arabinoside, Methotrexate and Cyclophosphamide)</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>Etonyeaku</td>
<td>18</td>
<td>Nigeria</td>
<td>Abdominal pain, lower abdominal swelling</td>
<td>Bilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy (Cyclophosphamide, Vincristine, Methotrexate)</td>
<td>Died after second chemotherapy</td>
</tr>
<tr>
<td>16</td>
<td>Gottwald</td>
<td>27</td>
<td>Poland</td>
<td>Abdominal pain, ascites</td>
<td>Bilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy (COP followed by CODOX-M + IVAC)</td>
<td>Disease-free survival (3 years)</td>
</tr>
<tr>
<td>17</td>
<td>Gutierrez</td>
<td>34</td>
<td>Spain</td>
<td>NA</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy</td>
<td>Died after a month</td>
</tr>
<tr>
<td>18</td>
<td>Hatami</td>
<td>58</td>
<td>USA</td>
<td>Abdominal masses</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (Vincristine, Rituximab, Methotrexate with Leucovorin and intrathecal Methotrexate)</td>
<td>Disease-free survival (42 months)</td>
</tr>
<tr>
<td>19</td>
<td>Munoz</td>
<td>30</td>
<td>Spain</td>
<td>Abdominal pain</td>
<td>Bilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>Khan</td>
<td>6</td>
<td>India</td>
<td>Abdominal pain and masses</td>
<td>Bilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (CODOX-M-IVAC plus Rituximab)</td>
<td>NA</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>No</th>
<th>Name</th>
<th>Age</th>
<th>Country</th>
<th>Symptoms</th>
<th>Laterality</th>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Mondal</td>
<td>6</td>
<td>India</td>
<td>Abdominal pain, difficulties with walking</td>
<td>Bilateral</td>
<td>II R Murphy staging</td>
<td>Surgery, chemotherapy (Magrath protocol using CODOX-M regimen)</td>
<td>Remission</td>
</tr>
<tr>
<td>22</td>
<td>Gomez</td>
<td>13</td>
<td>Spain</td>
<td>Abdominal pain</td>
<td>Unilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (Doxorubicin, Vincristine, Cytarabine, Dexamethasone, Rituximab)</td>
<td>Remission</td>
</tr>
<tr>
<td>23</td>
<td>Xiao</td>
<td>19</td>
<td>China</td>
<td>Chest tightness, asthma</td>
<td>Unilateral</td>
<td>IV Ann Arbor</td>
<td>Surgery, chemotherapy (HyperCVAD, MTX plus Ara-c)</td>
<td>Deceased</td>
</tr>
<tr>
<td>24</td>
<td>Xiao</td>
<td>43</td>
<td>China</td>
<td>Fatigue, bone pain</td>
<td>Unilateral</td>
<td>I Ann Arbor</td>
<td>Surgery, chemotherapy (R-CHOP, HD-MTX plus VP)</td>
<td>Remission</td>
</tr>
<tr>
<td>25</td>
<td>Gravos</td>
<td>21</td>
<td>Greek</td>
<td>Abdominal distension</td>
<td>Unilateral</td>
<td>I Ann Arbor</td>
<td>Chemotherapy</td>
<td>Remission</td>
</tr>
<tr>
<td>26</td>
<td>Al-Maghrabi</td>
<td>42</td>
<td>Saudi Arabia</td>
<td>Abdominal pain</td>
<td>Bilateral</td>
<td>I Ann Arbor</td>
<td>Surgery, chemotherapy (R-CODOX, R-IVAC)</td>
<td>Remission</td>
</tr>
<tr>
<td>27</td>
<td>Lanjewar</td>
<td>28</td>
<td>India</td>
<td>Weight loss, distension and pain</td>
<td>Unilateral</td>
<td>NA</td>
<td>Surgery, chemotherapy, HAART</td>
<td>Died after 7 months</td>
</tr>
<tr>
<td>28</td>
<td>Sergi</td>
<td>24</td>
<td>Italy</td>
<td>Abdominal tenderess, diffuse pain</td>
<td>Unilateral</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>NA</td>
</tr>
<tr>
<td>29</td>
<td>Steininger</td>
<td>17</td>
<td>German</td>
<td>Abdominal pain</td>
<td>Unilateral</td>
<td>III Ann Arbor</td>
<td>Surgery, chemotherapy</td>
<td>Remission</td>
</tr>
</tbody>
</table>

Primary ovarian Burkitt lymphoma

Figure 1. Ultrasound image and gross features of the case. A. Preoperative transvaginal ultrasound showed that the right ovary was enlarged, with abundant blood flow signals in the ovarian tissue (marked by red arrow). B. The tumor originated from the ovary and was well-circumscribed. A gray-white tender cut surface and scattered hemorrhage was visible.

Denied additional aberrant symptoms or signs upon admission. A right salpingo-oophorectomy was subsequently performed.

Gross examination

The removed right ovary measured 11 × 11 × 5 cm in size. The tumor originated from the ovary and it did not spread to the fallopian tube. It was well-circumscribed with a gray-white tender cut surface and scattered hemorrhage was visible (Figure 1B). The ipsilateral fallopian tube was grossly unremarkable.

Microscopic examination

Microscopically, the tumor obliterated normal ovarian parenchyma. The involved ovarian tissue was diffusely infiltrated by sheets of monotonous medium-sized neoplastic lymphoid cells and the boundary between the tumor tissue and ovary was unclear (Figure 2A). Innumerable neoplastic cells interspersed with scattered reactive tangible-body macrophages engulfing nuclear debris, creating a prominent “starry sky” pattern (Figure 2B). When examined at high magnification, the neoplastic cells showed molding and squaring-off of the nuclear membrane and cell membrane, with relatively uniform round or oval nuclei, coarse chromatin, multiple small nucleoli, and an appreciable rim of basophilic cytoplasm. Mitotic figures were numerous as well as a high rate of apoptosis (Figure 2C and 2D).

Immunohistochemical findings

Immunohistochemically, tumor cells expressed pan-B-cell antigens (CD20, CD79-a, and PAX5), germinal center markers (CD1 and BCL6), and MYC. BCL2, CD3, CD5, CD138, and TdT were negative. EBV was negative. The proliferation fraction (Ki67 index) was very high, approaching 100% (Figure 3A-C).

FISH examination

The t (8;14) (q24; q32)/IGH-MYC was detected by fluorescence in situ hybridization (FISH) (break-apart probes) (Figure 3D) whereas BCL2 (18q21) and BCL6 (3q37) rearrangements were absent.

The patient underwent bone marrow aspirate evaluation for hematological immunotyping and chromosomes analysis. The results were negative for malignancy and atypical chromosomes. The subsequent PET-CT showed no lesions on other organs. Combined with the clinical visualization, histologic features, immunohistochemical results, cytogenetics, and molecular test, the diagnosis was ascertained as primary ovarian Burkitt lymphoma. The patient received the treatment protocol of HyperCVAD chemotherapy after surgery.

Discussion

Although primary extranodal invasive lymphoma of the ovary is a rare disease, ovarian lym-
Primary ovarian Burkitt lymphoma

Figure 2. Histology of the ovarian tumor. A. The involved ovarian tissue was diffusely infiltrated by sheets of monotonous medium-sized neoplastic lymphoid cells and the boundary between the tumor tissue and ovary was unclear (magnification: × 40). B. Innumerable neoplastic cells interspersed with scattered reactive tangible-body macrophages engulfing nuclear debris, creating a prominent “starry sky” pattern (magnification: × 100). C and D. The neoplastic cells showed molding and squaring-off of the nuclear membrane and cell membrane, with relatively uniform round or oval nuclei, coarse chromatin, multiple small nucleoli, and an appreciable rim of basophilic cytoplasm. Mitotic figures were numerous as well as a high rate of apoptosis (marked by red arrows). C. Magnification: × 400; D. Magnification: × 1000.

Burkitt 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 [39]. Several perspectives regarding the origin of primary ovarian lymphoma have been documented: 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 [40]. No specific association was described with EBV. Sporadic BL may coexist with EBV infection [41]. However, tests for EBV infections are also recommended. As reported in this case, the patient has no EBV infection.

Weekes first discovered primary bilateral ovarian Burkitt lymphoma in a 15-year-old girl from Guatemala in 1986 [42]. To our knowledge, about 29 cases of primary ovarian Burkitt lymphoma have been reported in the literature. Among the described cases, 15 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 [43]. Most patients complained of abnormal pain accompanied by additional symptoms including fever, abnormal mass, lower abdominal swelling, ascites, and vaginal bleeding [44, 45]. As for our patient, the young married woman was diagnosed with a mass in the right ovary by physical examination due to infertility. Staging plays an important role in accessing disease progression and determine the individualized treatment of patients. Ann Arbor classification is mostly used in adult BL pa-
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tients, while St. Jude/Murphy applies to pediatric patients. Seven of them are stage I (1 stage 1B, FIGO), 2 are stage II, 11 are stage IV, 6 unavailable. This case presented a primary ovarian Burkitt lymphoma of FIGO staging 1A. The histologic findings of the present case were identical to Burkitt’s lymphoma that occurred in other organs, which are characterized by diffuse growth of medium-sized lymphoid cells with round nuclei and agglomerated chromatin [46]. Necrotic debris could be seen in the background, which was swallowed by many tissue cells, forming a typical pattern of the “starry sky”.

Primary ovarian Burkitt lymphoma originates from B cells and expresses B cell markers such as CD20, CD79a, PAX5. Cytokeratin and T cell markers are negative. MYC represents a family of regulator genes and proto-oncogenes 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, 47], 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, the morphology combined with immunohistochemical results and molecular pathologic features were consistent with the diagnosis of Burkitt lymphoma.

The differential diagnosis of primary ovarian Burkitt lymphoma includes secondary ovarian lymphoma, High-grade B-cell lymphoma with double-hit or triple-hit, adult granular cell tumor of the ovary, and small cell neuroendocrine carcinoma (SCNEC). Fox et al. proposed the diagnostic criteria for primary ovarian lym-
Primary ovarian Burkitt lymphoma

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 an optimal treatment protocol for patients with Burkitt lymphoma [49, 50]. The 29 cases previously reported were mostly (20/29) treated with surgery followed by chemotherapy. Surgical treatment plays an important role in providing clinical information, staging, and diagnosis, and patients with 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 (average 1.6 years). Four deaths were reported, giving an overall survival rate of 15/19 (78.95%) (7 unavailable). In our case, the patient underwent right salpingo-oophorectomy and accepted HyperCVAD chemotherapy after surgery. The patient developed complete response (CR) 18 months following the completion of the therapy.

Conclusion

We report a case of a primary ovarian Burkitt lymphoma that occurred in a young woman, confirmed by histological morphology, immunohistochemistry, and FISH. Further studies are of great significance to characterize clinical features of this rare disease, for differential diagnosis and effective therapy.

The reporting of this study conforms to CARE guidelines [51].

Acknowledgements

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Informed consent has been obtained from patients included in this study.

Disclosure of conflict of interest

None.

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References


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