Anaplastic Large Cell Lymphoma of the Ovary in a Pediatric Patient

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Summary: Lymphoma can rarely present as an ovarian tumor in children. We describe the unusual case of a 14-year-old adolescent with a locally disseminated ovarian anaplastic large-cell lymphoma, treated with surgery followed by chemotherapy, and who remains disease free at 2 years after diagnosis.

Key Words: pediatric, lymphoma, ovary (J Pediatr Hematol Oncol 2009;31:702–704)

Anaplastic large-cell lymphoma (ALCL) accounts for approximately 10% to 15% of pediatric non-Hodgkin lymphoma, and is clinically characterized by the frequent presence of B symptoms and involvement of extranodal sites such as skin, lung, bone, and soft tissue.1 Histologically, ALCL is characterized by large anaplastic cells of T-cell or null-cell phenotype expressing CD30 (Ki-1 antigen).2 Up to 80% of childhood ALCL, versus 30% in adults, have a characteristic cytogenetic translocation t(2;5) leading to the expression of the fusion-protein nucleolar protein nucleophosmin-anaplastic lymphoma kinase (ALK) and reactivity to the ALK-1 antibody. Secondary lymphomatous involvement of the gynecologic tract is common, but a true primary ovarian lymphoma is rare.3 Ovarian ALCL is extremely rare and all cases reported so far in the literature involved adult patients.

CASE REPORT

A 14-year-old adolescent presented with a 5-day history of vomiting, lower back pain, shortness of breath, and fever. She denied weight loss, night sweats, or bony pain. Physical examination revealed a tender distended abdomen with a palpable mass in the right lower quadrant. Past medical history was unremarkable. Abdominal ultrasound and computed tomography (Fig. 1) showed an enhancing noncalcified pelvic mass (8.1 × 7.6 × 9.8 cm), generalized lymphadenopathy, multiple peritoneal nodes, moderate ascites, and bilateral pleural effusions. A gallium scan showed numerous peritoneal and right pleural metastases with focal uptake in the left proximal femoral diaphysis. Blood work revealed mild anemia (hemoglobin 116 g/L), normal lactate dehydrogenase, uric acid, β-human chorionic gonadotropin, α-fetoprotein, carcino-embryonic antigen, and an elevated cancer antigen-125 (224 U/mL). A right salpingo-oophorectomy with inferior omentectomy and iliac lymph node sampling was performed. Histology was consistent with ALCL with a t(2;5) fusion gene. Bone marrow aspirate/biopsy and cerebrospinal fluid were negative. She was considered as stage III in view of her extensive intra-abdominal disease. Repeat abdominal imaging before chemotherapy showed residual perihepatic and pelvic disease. She was treated with the Children’s Oncology Group-ANHL0131 protocol for 1 year. Induction (wk 1 to 5) chemotherapy included: doxorubicin (75 mg/m² on days 1 and 22), vincristine (1.5 mg/m² weekly × 5), prednisone (40 mg/m² orally for 28 d), and intrathecal methotrexate (weekly × 3); and consolidation (wk 6 to 52) 1 cycle every 3 weeks: doxorubicin (30 mg/m² intravenously × 1 d), 6-mercaptopurine (225 mg/m² orally × 5 d), and prednisone (120 mg/m² orally × 5 d) with intravenous methotrexate (60 mg/m²) replacing doxorubicin when a cumulative dose of 300 mg/m² is reached. The first cycle was complicated by sepsis, severe tumor lysis syndrome, prolonged QT intervals, and posterior reversible encephalopathy syndrome. Follow-up imaging after 2 cycles of chemotherapy showed complete resolution of her lymphoma. She remains in complete remission at 12 months after the end of therapy and at 2 years of diagnosis.

PATHOLOGY

Intraoperative snap frozen tissue sections of the tumor showed replacement of ovarian stroma by a diffuse medium sized lymphoid infiltrate with marked proliferation of reactive histiocytes. As a result, the tissue section had a starry sky appearance that is most commonly seen in Burkitt lymphoma. A preliminary diagnosis of Burkitt

FIGURE 1. Initial abdominal computed tomography showing a large noncalcified pelvic mass with ascites and generalized lymphadenopathy.
lymphoma was made. The salpingo-oophorectomy specimen consisted of a markedly enlarged homogeneous soft ovarian mass with a pale grey fish-flesh-like appearance. Patchy hemorrhages were present in the stroma (Fig. 2). Thickened and distorted fimbriae and Fallopian tube were adhered to the external surface of the ovarian mass. These tissues were heavily infiltrated by lymphoma cells. There were also disseminated lymphoma nodules in portions of omentum removed. Hematoxylin and eosin stained, formalin fixed, and paraffin embedded tissue sections showed a monomorphic population of medium to large lymphoma cells (Fig. 3). Immunohistologic stains with T-cell antibodies revealed T-cell lineage. The lymphoma cells were also positive for CD30, ALK-1, and epithelial membrane antigen. Polymerase chain reaction analysis revealed T-cell clonality and a t(2;5)/nucleolar protein nucleophosmin-ALK fusion transcript was detected. Cytogenetic analysis by fluorescence in situ hybridization also detected an ALK gene translocation, thus confirming the diagnosis of ALCL of the ovary.

**DISCUSSION**

Ovarian tumors are extremely rare in childhood and the differential diagnosis includes rhabdomyosarcomas, germ cell tumors (teratomas, sex cord, and stromal tumors), granulosa cell tumors, and embryonal carcinomas. Malignant lymphomas may also occur in the ovary either as a primary tumor or more frequently as a manifestation of a disseminated systemic lymphoma. Strict criteria defining primary ovarian lymphoma (POL) were proposed by Fox and Langley in 1976, who limited this diagnosis to patients with Murphy stage-I E and omitted those who subsequently disseminate from this primary site. Our patient’s lymphoma does not meet the criteria of POL because of local dissemination of her disease. The origin of these lymphoma cells even in stage I E-POL is not clear, as the presence of normal lymphoid tissue in the ovaries is controversial; however, both B-cell and T-cell population have been identified. It has been proposed that these lymphoid aggregates develop in the ovarian lumen because of chronic inflammation, such as pelvic inflammatory disease, and later can undergo malignant changes.

Ovarian lymphoma has been described predominantly in adults and has been associated with poor prognosis. In children, most of the reported cases have been of the small, noncleaved cell type (Burkitt or non-Burkitt category), although T-cell non-Hodgkin lymphoma has also been reported. Ovarian ALCL is very rare, with only 3 adult cases reported so far (Table 1). Our patient had classic ALCL with some unusual histologic features such as the abundance of reactive histiocytes (that mimicked Burkitt lymphoma) and increased phagocytic activities; however, the clinical symptoms of ALCL-induced hemophagocytic lymphohistiocytosis were absent.

Typical prognostic factors for ALCL are extrapolated from adult studies and do not have the same impact in children. ALK positivity is the most important prognostic indicator in adult series, but it is not clear whether it affects clinical course or response to therapy in pediatric ALCL. Recent data showed that the biologic features of childhood ALCL are quite different from its adult counterpart. For example, cytoplasmic localization of survivin

### TABLE 1. Cases of Ovarian ALCL Reported in the Literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (y)</th>
<th>Sites of Involvement</th>
<th>Staging*</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azizoglu et al15</td>
<td>60</td>
<td>Bilateral ovaries, mesentery of ileum</td>
<td>4</td>
<td>ND</td>
<td>NED after 2mo</td>
</tr>
<tr>
<td>Vang et al9,14</td>
<td>39</td>
<td>Right ovary</td>
<td>I E</td>
<td>TAH + BSO</td>
<td>NED after 4 y</td>
</tr>
<tr>
<td>Monterroso et al6</td>
<td>35</td>
<td>Bilateral ovaries, omentum, serosa of rectum, mesoappendix, iliac, and inguinal lymph nodes</td>
<td>ND</td>
<td>TAH + BSO, chemotherapy</td>
<td>NED after 6 y</td>
</tr>
</tbody>
</table>

*Ann Arbor classification.
ND indicates not documented; NED, no evidence of disease; TAH + BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.
tissue inhibitor of metalloprotease-1 (inhibitors of apoptosis and poor prognostic factors) is not frequent even in advanced-stage pediatric ALCL. This may help, in part, explaining the relatively good prognosis of ALCL in children. The presence of B symptoms, visceral organ involvement, mediastinal mass, advanced stage, atypical histologic subtype, and extent of circulating tumor cells in the peripheral blood and bone marrow have been associated with the increased risk of relapse in childhood ALCL. The presence of complex secondary chromosome abnormalities like 1q21 (MCL 1) and 10q24 (HOX11/TCL3) may also contribute to a worse prognosis in pediatric advanced-stage disease. Recent pediatric trials have shown disease-free survivals for advanced-stage ALCL in the range of 50% to 80% using chemotherapy protocols varying in duration and intensity.

Although we cannot rule out the possibility that the case reported by Turken et al could be an ALCL, to the best of our knowledge, our patient is the first reported case of anaplastic large T-cell lymphoma arising from the ovary in a child. The patient had a good response to surgery and chemotherapy even in the presence of advanced-stage disease. As the follow-up time is too short, it is difficult to predict her long-term outcome at this time.

REFERENCES