Angiosarcoma Masquerading as Embryonal Carcinoma in the Metastasis From a Mature Testicular Teratoma

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- Sarcoma can arise within a germ cell tumor (GCT) from a malignant transformation of teratomaous elements or as late sequelae to radiation therapy. Angiosarcoma as a malignant component in testicular GCTs has rarely been reported and is often misdiagnosed as embryonal carcinoma. We report the case of a 23-year-old man with mature teratoma of the testis and retroperitoneal metastasis exhibiting components of mature teratoma intermingled with high-grade angiosarcoma. It is important to recognize the presence of a high-grade sarcomatous component within a GCT because of its aggressive clinical behavior and different response to therapy. (Arch Pathol Lab Med. 2003;127:360–363)

Teratoma accounts for about 7% of testicular germ cell tumors (GCTs) and often occurs during infancy and childhood. Occurrence in children older than 4 years is unusual. In postpubertal patients, testicular teratoma is usually present as a component of a mixed GCT. Teratoma with malignant transformation (TMT) is rare and is most commonly encountered in adult patients with GCT. The most frequent malignant components associated with testicular GCT are sarcomas of which rhabdomyosarcoma is the most common subtype. The presence of angiosarcoma as a component of teratoma is extremely rare and has been reported following treatment for other GCTs. We describe a rare association of angiosarcoma with teratoma in a patient who had received no treatment prior to surgery and discuss the various clinical scenarios in which angiosarcoma is found in patients with testicular GCT.

REPORT OF A CASE

A 23-year-old man presented with severe intermittent pain in the right flank and back that had persisted for several days in November 2000. Work-up showed a right testicular mass as well as a right retroperitoneal mass. Serum tumor markers were within normal limits. The patient underwent right orchiectomy, which revealed a mature teratoma. One month later, he underwent excision of the retroperitoneal mass and retroperitoneal lymphadenectomy that confirmed metastatic tumor. In April 2001, the patient developed pleuritic chest pain and right-sided abdominal pain. A computed tomography scan showed multiple nodules in the liver and bilateral pulmonary metastasis. A percutaneous needle biopsy of the liver confirmed metastatic tumor. Four weeks later, a computed tomography scan showed spontaneous regression of some of the metastatic lesions. The patient was treated with thalidomide 400 mg daily for 10 weeks.

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Figure 1. Testicular tumor. A, Mature teratoma exhibiting cystic spaces lined by intestinal type epithelium surrounded by smooth muscle bundles (hematoxylin-eosin, original magnification ×200); B, Seminiferous tubules lined by large cells with clear cytoplasm consistent with intratubular germ cell neoplasia (hematoxylin-eosin, original magnification ×400).
metastatic retroperitoneal tumor. A, Mature intestinal type epithelium surrounded by vascular channels, spindle cell proliferation, and hemosiderin-laden macrophages (hematoxylin-eosin, original magnification ×200). B, Immunoperoxidase staining for CD31 demonstrates positive reactivity in the endothelial and spindle cells (immunoperoxidase, original magnification ×200). C, Areas of high-grade malignant component characterized by nests of epithelioid cells with occasional lumen formation (hematoxylin-eosin, original magnification ×200). D, Immunoperoxidase staining for CD31 demonstrates positive reactivity in the tumor cells (immunoperoxidase, original magnification ×200).

Figure 2. Metastatic retroperitoneal tumor. A, Mature intestinal type epithelium surrounded by vascular channels, spindle cell proliferation, and hemosiderin-laden macrophages (hematoxylin-eosin, original magnification ×200). B, Immunoperoxidase staining for CD31 demonstrates positive reactivity in the endothelial and spindle cells (immunoperoxidase, original magnification ×200). C, Areas of high-grade malignant component characterized by nests of epithelioid cells with occasional lumen formation (hematoxylin-eosin, original magnification ×200). D, Immunoperoxidase staining for CD31 demonstrates positive reactivity in the tumor cells (immunoperoxidase, original magnification ×200).

PATHOLOGIC FINDINGS

The gross examination of the orchiectomy specimen revealed a 6.5 × 6.0 × 5.5-cm multiloculated cystic tumor within the testis. The cysts measured from 0.3 to 3.0 cm. Histopathology of the extensively sampled testicular tumor (11 sections) showed only components of mature teratoma (Figure 1, A) and intratubular germ cell neoplasia (Figure 1, B). The retroperitoneal mass consisted of a 10.0 × 6.0 × 5.0-cm solid and cystic tumor and enlarged retroperitoneal lymph nodes. The initial pathologic examination of the retroperitoneal mass was interpreted as metastatic mature teratomatous components mixed with areas of embryonal carcinoma. A reevaluation of the initial pathology material at our institution showed mature teratomatous components and hemorrhagic areas consisting of thin anastomosing vascular channels lined by prominent endothelial cells with hyperchromatic nuclei and aggregates of spindle cells reminiscent of well-differentiated angiosarcoma (Figure 2, A). Immunoperoxidase studies using antibodies to vascular markers showed positive staining with CD31 (Figure 2, B) and CD34 in the tumor cells. In other areas, solid nests of large polygonal cells resembled embryonal carcinoma (Figure 2, C), were positive for vascular markers CD31 (Figure 2, D) and CD34 and negative for keratins (AE1/AE3 and CAM 5.2) and germ cell markers (PLAP), consistent with high-grade epithelioid angiosarcoma. On the basis of histologic and immunohistochemical findings, a diagnosis of metastatic teratoma with high-grade angiosarcoma was made. One of the enlarged retroperitoneal lymph nodes was invaded by angiosarcoma. The needle biopsy of the liver and pleural
nodules showed metastatic high-grade angiosarcoma of similar histology, which was confirmed by positive immunoreactivity for vascular markers.

**COMMENT**

A GCT is characterized by its capacity to differentiate from pluripotential precursor stem cells to embryonal cell carcinoma, extraembryonic cell types (yolk sac tumor, choriocarcinoma), or somatic cell types (teratoma). Teratoma with malignant transformation (TMT) refers to a form of GCT in which a somatic teratomatous component becomes morphologically malignant and develops aggressive growth patterns. It is postulated that TMT originates either from the malignant transformation of preexisting teratomatous elements or from the differentiation of totipotential germ cells with concomitant malignant transformation. This hypothesis is supported by the almost universal coexistence of GCT elements, mainly teratoma or yolk sac tumors, within the GCT containing the transformed elements. Of the various malignant tumors that occur in TMT, sarcomatous differentiation predominates over carcinomatous differentiation. Among the sarcomas reported, rhabdomyosarcoma is the most common subtype, followed by sarcomas not otherwise specified. Tumors containing a solid tumor histology other than sarcomas previously mentioned were noted in 37% of the cases (17 of 46), with adenocarcinoma and primitive neuroectodermal tumors being the most common types.

Two cases of teratoma with primary angiosarcoma as a malignant component within the testis or in the metastasis have been reported in patients who had received no radiotherapy or chemotherapy at the time of diagnosis (Table). The former case reported by Steele et al was a mature testicular teratoma (40% of the tumor mass) admixed with high-grade epithelioid angiosarcoma (60% of the tumor mass) that was initially interpreted as embryonal carcinoma. In the current case, although the primary testicular tumor was adequately sampled, the possibility of a small unsampled focus of angiosarcoma can not be entirely excluded. Three instances of therapy-related angiosarcoma of the retroperitoneum and gut have been documented in patients who were treated with radiotherapy with or without chemotherapy for testicular teratoma or seminoma (Table).

Several explanations have been offered for the appearance of second malignancies. Among treatment-related causes, radiation-induced carcinogenesis has been well recognized for nearly a century. Sarcomas, in particular, are typical of being causally related to ionizing radiation. Although angiosarcoma is not commonly encountered among such sarcomas, its occurrence after radiotherapy is well documented, especially in the treatment of breast and cervical carcinomas. However, in some cases of GCT, it is unclear whether the mechanism of malignant transformation is de novo or therapeutically induced. Potentially, genetic analysis may be helpful if a specific chromosomal abnormality is demonstrated in the malignant component. Indeed, Motzer et al analyzed a series of TMT and were able to demonstrate chromosomal abnormality (11p), a specific marker of germ cell tumors, among non-GCT components of TMT, in addition to other chromosomal abnormalities associated with the transformed histology. The prognosis of GCTs has greatly improved with combined surgery, radiotherapy, and cisplatin-based chemotherapy. The combined therapy has resulted in curative treatment for more than 90% of all diagnosed patients, including 70% to 80% of those with metastatic disease at initial presentation. The prognosis of patients with TMT, however, is poorer than that of patients without malignant non–germ cell elements, with an overall survival rate ranging from 56% to 65%. Unlike GCT, TMT does not respond to the standard cisplatin-based chemotherapy regimens. Reischling et al in a recent study of TMT suggested that the prognosis of patients with TMT may be improved with chemotherapy regimes directed at the transformed histology, which, in the case of sarcoma, may best be treated with an anthracycline combined with ifosfamide. Therefore, correct classification of the malignant component in GCT is crucial for the management of these patients.

**References**


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**Previously Reported Angiosarcoma in Association With Testicular Germ Cell Tumor**

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Age, y</th>
<th>Primary Diagnosis (Testicular Tumor)</th>
<th>Metastatic Sites</th>
<th>Treatment</th>
<th>Time Interval†</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Current case</td>
<td>23</td>
<td>Mature teratoma</td>
<td>Retroperitoneum, liver, and pleura</td>
<td>Surgery and CT</td>
<td>0</td>
<td>Alive 22 mo after diagnosis</td>
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<td>Hughes et al, 1991</td>
<td>16</td>
<td>Mature teratoma and well-differentiated angiosarcoma</td>
<td>None</td>
<td>Surgery</td>
<td>0</td>
<td>Alive 9 mo after surgery</td>
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<tr>
<td>Steele et al, 2000</td>
<td>24</td>
<td>Mature teratoma and high-grade angiosarcoma</td>
<td>Lung and renal hilar lymph node</td>
<td>None</td>
<td>0</td>
<td>Multiple recurrences despite aggressive chemotherapy</td>
</tr>
</tbody>
</table>

* RT indicates radiotherapy; CT, chemotherapy; DOD, died of disease; and NA, not available.
† Time interval between primary diagnosis and detection of metastasis.


