Secondary malignant transformation of testicular teratomas: Case series and literature review


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Abstract

Background: Teratomas are a spectrum of neoplasms that can undergo malignant transformation. In the World Health Organization (WHO) classification of tumors, this entity was classified as "teratoma with somatic-type malignancy", which is defined as a malignant neoplasm of non-germinal phenotype that originates in a teratoma.

Materials and methods: We present a series of nine cases of testicular teratomas with secondary malignant transformation. From January 1995 to December 2011, we found a total of 306 cases of testicular tumors. Mixed germ cell tumors were the most frequently diagnosed malignancy with 45.7%.

Results: Teratoma with secondary malignant transformation represented 2.9% of all germinal tumors. Five cases originated within a mixed germ cell tumor, two cases from mature teratomas, and two from immature teratomas. The predominant malignant somatic component was sarcomas; two cases of chondrosarcoma, one rhabdomyosarcoma, and one case showing foci of chondrosarcoma and rhabdomyosarcoma. The case of osteosarcoma is notable for its rarity. Two cases showed epithelial malignancy in the form of an adenocarcinoma, and finally, two cases were primitive neuroectodermal tumors. At the time of diagnosis, five patients had metastases.

Conclusion: The transformation of germ cell tumors to somatic type malignancies is rare. The malignant component can originate from any of the three germ lines. These tumors are resistant to standard chemotherapy for a germ cell tumor and the clinical stage is the most important prognostic factor. At our institution, the malignant component that appeared most frequently was chondrosarcoma.

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PALABRAS CLAVE
Teratoma; Testículo; Cáncer; Transformación maligna

Transformación maligna secundaria de teratomas testiculares: serie de casos y revisión de la literatura

Resumen

Antecedentes: Los teratomas son un espectro de neoplasias que pueden sufrir una transformación maligna. En la clasificación de la Organización Mundial de la Salud (OMS) de los tumores esta entidad fue clasificada como «teratoma con malignidad de tipo somático», se definió como una neoplasia maligna de fenotipo no germinal que se origina en un teratoma.

Materiales y métodos: Se presenta una serie de 9 casos de teratomas testiculares con transformación maligna secundaria. Entre enero de 1995 y diciembre de 2011 encontramos un total de 306 casos de tumores testiculares. Los tumores de células germinales mixtas fueron el tumor maligno más frecuentemente diagnosticado con un 45.7%.

Resultados: El teratoma con transformación maligna secundaria representó el 2.9% de todos los tumores germinales. Cinco casos se originaron dentro de un tumor de células germinales mixtas, 2 casos de teratomas maduros y 2 de teratomas inmaduros. El componente somático maligno predominante eran los sarcomas; 2 casos de condrosarcoma, uno de rabdomiosarcoma y un caso que muestra focos de condrosarcoma y rabdomiosarcoma. El caso de osteosarcoma se destaca por su rareza. Dos casos mostraron malignidad epitelial en la forma de un adenocarcinoma y, finalmente, 2 casos eran tumores neuroectodérmicos primitivos. En el momento del diagnóstico 5 pacientes tenían metástasis.

Conclusión: La transformación de los tumores de células germinales en tumores malignos de tipo somático es poco común. El componente maligno puede proceder de cualquiera de las 3 líneas germinales. Estos tumores son resistentes a la quimioterapia estándar para un tumor de células germinales, y el estadío clínico es el factor pronóstico más importante. En nuestra institución el componente maligno que apareció con mayor frecuencia fue el condrosarcoma.

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Introduction

Testicular tumors are the most common neoplasia in adolescents and young adult males. Over 95% of all testicular tumors are of germline origin. Teratoma is the second most frequent germ cell testicular tumor in pediatric patients (endodermal sinus tumor is the most common). In this age group it is presented as a pure neoplasm, with a median age of 13 months and it is rare in children older than 4 years. In contrast, testicular teratoma in adolescents and young adults is presented as a component of a mixed germ cell tumor found in more than half of mixed germ cell tumors. Most prepubertal teratomas contain only mature tissue elements and have a benign behavior regardless of their mature or immature components. By contrast, postpubertal teratomas are immature, and even those that are mature in adults have a high risk of metastasis; therefore, the lack of maturity of the teratoma components is not a direct indication of their biological behavior; the age of the patient is of greater importance. Teratomas are a spectrum of malignancies that may undergo malignant transformation. Friedman and Moore in 1946 reviewed 922 testicular tumors at the Institute of Pathology of the Armed Forces (IPFA) finding some cases of teratoma with malignant components such as carcinoma, rhabdomyosarcoma, and neuroblastoma, but they gave no details on the pathological findings or their clinical issues. Mostofi and Price in 1973 recognized the existence of teratomas with malignant transformation; however, the information on these cases was very scarce. In 2004, in the classification of the World Health Organization (WHO) of the tumors, this entity was classified as ‘teratoma with somatic type malignancy’ and it was defined as a neoplasm of not germinal phenotype that originates from a teratoma.

Materials and methods

Subjects and study design

This is a retrospective descriptive study. We report a series of 9 cases of testicular teratomas with secondary malignant transformation, diagnosed at the Department of Pathology and Cytopathology of Dr. José E. González of the University Hospital of Monterrey, Mexico, reviewing the final diagnoses of all the testicular samples sent to our laboratory during the period between January 1995 and December 2011.

Histopathology

All cases correspond to radical orchietomy specimens that were reviewed by a pathologist with expertise in uropathology. All specimens were fixed in 10% formaldehyde. In each case, a section for each centimeter of tumor size was included, with an average of 10 sections of different areas of the tumor, including sections of the tumor and the adjacent testicular parenchyma and epididymis. The specimens were processed and embedded in paraffin, paraffin blocks were formed, and 5-micrometer-thick histological sections were prepared, undergoing the histological technique, and they were stained with hematoxylin and eosin. Additional
clinical data were also collected in the medical history of each patient.

Results

We found a total of 306 cases of testicular tumors, which were classified as shown in Table 1. A total of 9 cases were secondary teratoma with malignant transformation, representing 2.9% of all germ cell tumors. The clinico-pathologic characteristics of each case are summarized in Table 2. Among the cases, 5 (56%) originated from a mixed germ cell tumor, 2 (22.2%) of the cases originated from mature teratomas, and 2 (22.2%) from immature teratomas.

Table 1 Testicular tumors, January 1995 to December 2011.

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Number</th>
<th>Cases with malignant transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal mixed</td>
<td>140</td>
<td>5</td>
</tr>
<tr>
<td>Seminoma</td>
<td>95</td>
<td>0</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Coriocarcinoma</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mature teratoma</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Intratubular germ cell neoplasia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Leydig cell tumor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma involvement</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Leukemia involvement</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>306</td>
<td>9</td>
</tr>
</tbody>
</table>

Intratubular germ cell neoplasia (IGCN) was found in 55.5% of the cases, of which 4 were undifferentiated, and one patient had a seminoma in situ. With respect to a malignant somatic component, in this case series we found predominantly sarcomas: 2 cases of chondrosarcoma, one rhabdomyosarcoma, and one case showing foci of chondrosarcoma and rhabdomyosarcoma. In order to demonstrate myogenic differentiation, immunohistochemical stains for desmin were performed. In this group of sarcomas, a case of osteosarcoma stands out for its rarity. Two cases showed epithelial neoplasia in the form of an adenocarcinoma, and finally, the remaining 2 cases were primary neuroectodermal tumors (Fig. 1). At the time of diagnosis, 5 patients had metastases in the lung, liver, mediastinum, and retroperitoneal lymph nodes.

Discussion

Testicular teratomas with secondary malignant transformation are a relatively rare entity. They are estimated to represent approximately 3–6% of all tumors of metastatic testicular germ cells. Most somatic malignancies derived from a testicular germ cell tumor, as demonstrated in this series of 9 cases, originate within the teratomatous component of a mixed germ cell tumor, although they can occasionally arise from an endodermal sinus tumor. Some sarcomas may also develop from undifferentiated spermatocytic seminomas.

Malignant teratomas with somatic components occur mainly in young men (20–40 year olds), but some cases have also been reported in pediatric patients with clinico-pathological features similar to those of adults. Most cases present as a testicular mass; postpubertal patients may have symptoms secondary to metastasis. The

Table 2 Clinico-pathological characteristics of patients.

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Age</th>
<th>Type of germ cell tumor</th>
<th>Malignant somatic component</th>
<th>Associated with IGCN</th>
<th>Presentation with metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>Mixed germ cell (EC 40%, TI 60%)</td>
<td>Chondrosarcoma</td>
<td>No</td>
<td>Lung</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>Mixed germ cell (EC 10%, IT 40%, SE 50%)</td>
<td>Osteosarcoma</td>
<td>Yes</td>
<td>Mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>Mixed germ cell (IT 70%, SE 30%)</td>
<td>Chondrosarcoma</td>
<td>No</td>
<td>Liver</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>Mature teratoma</td>
<td>Adenocarcinoma</td>
<td>No</td>
<td>Retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>Mixed germ cell (IT 90%, SE 10%)</td>
<td>Primitive neuroectodermal tumor</td>
<td>Yes</td>
<td>Retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>Immature teratoma</td>
<td>Chondrosarcoma and rhabdomyosarcoma</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Immature teratoma</td>
<td>Adenocarcinoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>Mixed germ cell (IT 80%, SE 10%, 5% EC, 5% EST)</td>
<td>Primitive neuroectodermal tumor</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>Mature teratoma</td>
<td>Rhabdomyosarcoma</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

EC, embryonal carcinoma; IT, immature teratoma; SE, seminoma; EST, endodermal sinus tumor.
Secondary malignant transformation of testicular teratomas

Figure 1  I. Primitive neuroectodermal tumor from a mixed germ cell tumor. (A) Gross anatomy. (B) Microscopic view showing diffuse neuroepithelial overgrowth changing the testicular parenchyma (10×). C. Higher magnification (40×) reveals a proliferation of monotonous round cells with prominent rosette formation. II. A. Gross appearance of an osteosarcoma from a mixed germ cell tumor, which shows a typical heterogeneous mixed germ cell tumor. B and C. Photomicrograph showing a spindle cell proliferation with a deposit of osteoid matrix with malignant characteristics (40×). III. (A) Macroscopic sample of an intestinal-type adenocarcinoma from a mixed germ cell tumor. (B) Panoramic photomicrograph showing the haphazard proliferation of glands (5×). (C) Intestinal type glands with desmoplastic reaction (10×). IV. (A) Gross appearance of a teratoma with malignant transformation to rhabdomyosarcoma and chondrosarcoma. (B) Malignant cartilaginous component is observed, with increased cellularity and atypia; besides this there is a sarcomatoid appearance with muscle differentiation (10×). (C) Cells with muscle differentiation strongly positive for desmin (40×). (D) The higher the magnification (40×), the cartilaginous component highlights the presence of atypia and mitosis. (E) Rhabdomyosarcoma component (40×), spindle cell proliferation, atypia, and hyperchromatic nuclei, abundant eosinophilic cytoplasm with displacement of the core, which were strongly positive for desmin.
malignant component may originate in any of the 3 germ lines. Ulbright proposed that the malignant component must take up at least one low-power field. 11 The most common histological types reported in the literature are sarcomas: in this group rhabdomyosarcoma predominates, followed by chondrosarcoma, leiomyosarcoma, myxoid liposarcoma, angiosarcoma, and malignant tumors of the peripheral nerve sheath. 14,21-24 Squamous cell or adenocarcinomas have also been reported. 25 Other reported tumors are carcinoid, 26 primitive neuroectodermal tumor, 27-30 nephroblastoma, 31 and osteosarcoma. 32

There are reported cases of germ cell tumors in combination with sarcomatous elements that are diagnosed as primary sarcomas, in which the germ component was demonstrated in metastasis. In a retrospective review of cases, there are areas of fibrosis, hemosiderophages, chronic inflammatory cells, and often microcalcifications associated with IGCN. 33 Chromosomal abnormalities typically associated with germ cell tumors have been identified in the teratomas with secondary malignant transformation, although the phenotype of these neoplasms is completely different from the germ cell line. Motzer performed cytogenetic studies in somatic tumors arising in germ cell tumors and found isochromosome 12p in 10 cases and deletion of chromosome 12p in one case. 11 Korski also showed that this change is also found in metastases, finding isochromosome 12p in metastatic rhabdomyosarcoma tumors arising from testicular germ cell tumors. 34 The mechanism by which these malignant tumors develop is still a matter of debate. Ulbright et al. have postulated 2 possible mechanisms 35: de-differentiation of totipotential germ cells with concomitant malignant transformation or it is a de novo neoplasm that originates from an undifferentiated teratomatous element. 14,35,36 The morphology of the teratoma (mature vs. immature) has no impact as a risk factor for the development of a somatic malignant tumor. 37 The conventional germ cell tumors show an excellent response to platinum-based chemotherapy, with an estimated 90% survival 11; however, those with malignant transformation show an aggressive behavior and propensity to systemic progression. In a study, Comiter et al. reported an 81% range of recurrence in patients treated with surgical resection and platinum-based chemotherapy, with a median time to recurrence of 6 months. 36 On the other hand, Guo et al. 38 showed in a series of 33 cases that the malignant somatic component increases mortality only when there is metastasis; 50% of the patients presenting with metastasis with malignant somatic components died from this disease. However, only 15% of patients with a malignant somatic component confined to the testicle died. Spiess et al. 12 concluded that the clinical stage is the most important prognostic factor, since all stage I patients remained free of disease, whereas all patients with stage III died from this neoplasia. Surgical resection combined with chemotherapy appears to be the therapy of choice. 13 Chemotherapy primarily oriented toward a specific type of somatic neoplasm may also be useful. 39 Finally, with respect to metastasis, in a study conducted at the University of Indiana, the authors recommend resection of metastases whenever possible; 89% of patients who underwent retroperitoneal lymphadenectomy remained free of the disease, with the average life free of disease declining by 50% if metastases are not resected. In conclusion, patients with radical resection of the metastases show better survival. 17

Conclusions

The transformation of germ cell tumors to somatic malignant tumors is rare. A malignant tumor of somatic type may appear in both mature and immature teratomas. The malignant component can come from any of the 3 germ lines. In order to establish an appropriate therapeutic approach, a correct diagnosis of the malignant somatic component is very important, both in the primary tumor and in the metastases. Secondary malignant transformation of teratomas is resistant to standard chemotherapy for a germ cell tumor, and the clinical stage is the most important prognostic factor. At our institution, the malignant component that appeared most frequently was chondrosarcoma, and 2 patients had metastatic disease at diagnosis.

Funding

The work was carried out using resources provided by each of the participating departments.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors acknowledge the critical reading of the manuscript by Dr. Sergio Lozano.

References


