Diagnostic and therapeutic challenges in extragonadal yolk sac tumor with hepatoid differentiation: A case report

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Abstract. Yolk sac tumors (YSTs) are rare aggressive tumors, arising most commonly in the gonads and occurring mainly in young adults. We herein report a case of an extragonadal YST with hepatoid differentiation localized in the brain and lung. A 41-year old man presented to our hospital with a generalized seizure. A head computed tomography and magnetic resonance imaging examination revealed a large mass in the left occipital lobe with associated edema. Following complete resection, the histopathological examination revealed that the mass was a highly malignant epithelial tumor with a hepatoid pattern. The serum lactate dehydrogenase and α-fetoprotein levels were elevated. Additional diagnostic imaging revealed a lesion in the upper lobe of the right lung, but no other tumor manifestations. Based on the clinical and immunohistochemical characteristics, hepatocellular carcinoma and hepatoid adenocarcinoma were excluded and the diagnosis of extragonadal hepatoid YST was established. A multimodal therapeutic approach (high-dose chemotherapy with autologous stem cell transplantation, radiation and surgery) was applied; however, the patient succumbed to refractory disease 10 months after the diagnosis. Therefore, the diagnosis and treatment of hepatoid YST is an interdisciplinary challenge.

Introduction

Germ cell tumors (GCTs) are the most common malignancies in males aged 15-35 years, whereas only 2-5% of these tumors arise in extragonadal sites (1). The most common extragonadal localization is the mediastinum, followed by the retroperitoneum, pineal gland and suprasellar region (2,3). GCTs comprise a variety of histologically different types that carry different prognoses. The presence of yolk sac elements is associated with a dismal prognosis (4-6) and is found in 30-40% of GCTs (1,7). Yet pure yolk sac tumors (YSTs) in adult males are rare. We herein report a case of an extragonadal YST with hepatoid differentiation (hepYST), primary localized in the brain and lung.

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restaging revealed an increase in the serum AFP and LDH levels, as well as an increase in the size of the intracranial lesion; the lung lesion remained stable. Given the refractory disease and unfavorable prognostic characteristics (8), a decision was made to treat the patient with a high-dose salvage chemotherapy protocol according to Kondagunta et al [two courses of paclitaxel and ifosfamide (TI regimen) followed by three courses of high-dose carboplatin and etoposide (CE regimen) plus peripheral blood stem cell support] (9). However, after the first high-dose chemotherapy course, the patient developed hemiparesis. The serum AFP and LDH levels increased and the head CT revealed marked tumor progression. In order to achieve a fast tumor mass reduction, cranial irradiation and surgical removal of the lung tumor were performed. The histopathological examination was consistent with hepYST. High-dose chemotherapy (two remaining high-dose CE courses) was resumed as ultima ratio for disease control.

Unfortunately, despite therapy, subsequent restaging showed an increase in tumor markers, as well as new and multiple lung and liver metastases. Palliative therapy with oral etoposide was administered and the patient succumbed to refractory disease 10 months after the initial diagnosis.

Discussion

YSTs are rare, aggressive tumors, occurring mainly in young adults, with a peak incidence at 21 years (10,11). YSTs arise most commonly in the gonads, but extragonadal sites of origin are reported in 24% of the cases (11). The most common localization of YST is the anterior mediastinum, followed by the retroperitoneum and cranium (2,3); exceedingly rare sites, such as the lungs, pancreas, kidney and spinal cord, have also been reported (12-15). Regarding the intracranial manifestations, YSTs are typically located midline in the pineal region or the suprasellar region (3). One case of mixed GCT with extensive yolk sac elements outside the midline (in the frontal lobe) in an adult was also reported (16).

Intracranial YSTs present a unique entity. They may disseminate along the neuroaxis, at the time of diagnosis or early during the course of the disease. However, to the best of our knowledge, a case of intracranial YST with concomitant extracranial manifestation has not been reported thus far. In the case presented herein, the tumor was located in the occipital lobe and lungs. Due to its atypical location and the radiological findings (absence of necrosis, hemorrhage, cysts) (17), the suspected preoperative diagnosis was primary brain tumor rather than GCT. However, the histological examination did not support this diagnosis. Immunohistochemically, the tumor cells expressed Hep Par-1, glypican 3 and AFP; this immunoprofile is compatible with hepatocellular carcinoma (HCC), hepatoid adenocarcinoma (HAC), as well as hepYST (Table II) (10). Hep Par-1 is expressed in normal and neoplastic hepatocytes and has been used to confirm hepatoid differentiation. The degree of staining may correlate with hepatoid differentiation, and a strong Hep Par-1 positivity favors HCC diagnosis, but is found only in a minority of hepYST (18). Glypican 3 and AFP are also quite specific for hepatocellular differentiation and are typically expressed in HCC, HAC and hepYST (18).

The clinical characteristics of our patient made the diagnosis of HCC and HAC highly unlikely, as both those tumors predominantly affect older males (19,20). Brain metastases at the time of diagnosis are extremely rare (<1% in HCC and not reported in HAC) (19,20). Most importantly, the absence of a primary tumor in the liver or other gastrointestinal organs on initial presentation strongly argued against HCC or HAC. Based on all the characteristics mentioned and discussed above, hepYST was the most likely diagnosis.

hepYSTs are exceedingly rare, with only 32 reported cases in the English medical literature to date (10). The majority of these tumors arise from the ovary, whereas only single cases with an extraovarian origin are described. In adult males, cases of sole mediastinal and testicular hepYSTs are reported (21,22).

The treatment of YSTs may be challenging. Standard care is similar to that for other types of non-germinoma GCT and includes platinum-based chemotherapy protocols, followed by surgical resection of the residual tumor or radiation (23). The most widely adopted regimens are PEI and bleomycin, etoposide and cisplatin; PEI, cisplatin/etoposide/ifosfamide; TI, paclitaxel/ifosfamide; CE, carboplatin/etoposide; autoTx, autologous stem cell transplantation.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AFP (ng/ml)</th>
<th>LDH (µmol/sec/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative/naïve</td>
<td>n/a</td>
<td>7.53</td>
</tr>
<tr>
<td>Postoperative</td>
<td>265</td>
<td>3.40</td>
</tr>
<tr>
<td>After 1 PEI</td>
<td>230</td>
<td>3.48</td>
</tr>
<tr>
<td>After 2 PEI</td>
<td>410</td>
<td>4.53</td>
</tr>
<tr>
<td>After 1 TI</td>
<td>332</td>
<td>12.76</td>
</tr>
<tr>
<td>After 2 TI</td>
<td>262</td>
<td>3.37</td>
</tr>
<tr>
<td>After 1 CE + autoTx</td>
<td>614</td>
<td>4.08</td>
</tr>
<tr>
<td>After radiation and lung resection</td>
<td>397</td>
<td>6.43</td>
</tr>
<tr>
<td>After 2 CE + autoTx</td>
<td>559</td>
<td>8.62</td>
</tr>
</tbody>
</table>

*AFP reference value, <7 ng/ml; †LDH reference value, 2.25-3.75 µmol/sec/l. AFP, α-fetoprotein; LDH, lactate dehydrogenase; n/a, not available; PEI, cisplatin/etoposide/ifosfamide; TI, paclitaxel/ifosfamide; CE, carboplatin/etoposide; autoTx, autologous stem cell transplantation.

Figure 1. Radiological examination. Preoperative (A) Computed tomography and (B) magnetic resonance imaging with contrast enhancement of the brain, showing a lesion sized 5x3 cm in the left occipital lobe, with associated edema.
Subsequent salvage high-dose chemotherapy, including tumor resection and radiation, did not achieve disease control and the patient succumbed to the disease 10 months after diagnosis. Similar survival rates were reported by Moran et al (21). In a case series of 4 patients with mediastinal hepYST, 3 patients succumbed to the disease within 1 year after the initial diagnosis. A large series with 788 YST patients reported sustainably better survival rates: The 5-year overall survival was 55% (54% for mediastinal and 60% for retroperitoneal YSTs) (11). Unfortunately, survival rates according to histological YST subtypes are not available, which poses the question whether histological YST subtype, i.e., hepatoid differentiation, affects survival. Goebel et al (Proc ASCO 22: abs. 1842, 2003) reported an association of hepYST with a higher risk of relapse following initial treatment, as supported by our case.

In conclusion, hepYST is a rare differential diagnosis in the spectrum of brain tumors, including metastases, with poor prognosis. Due to the rarity of these tumors, clear therapeutic recommendations and survival data are currently not available. Thus, treatment of hepYST is considered to be an interdisciplinary challenge.

Acknowledgements

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Table II. Characteristics of immunohistochemical staining of hepatocellular carcinoma, hepatoid adenocarcinoma and hepatoid yolk sac tumor.

<table>
<thead>
<tr>
<th>Staining</th>
<th>HCC</th>
<th>HAC</th>
<th>hepYST</th>
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<tbody>
<tr>
<td>AFP</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pCEA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glypican 3</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>SALL4</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Glypican</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep Par1</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CK7/CK20</td>
<td>+/-</td>
<td>+ or -/+ or -</td>
<td>-</td>
</tr>
</tbody>
</table>

HCC, hepatocellular carcinoma; HAC, hepatoid adenocarcinoma; hepYST, hepatoid yolk sac tumor; AFP, α-fetoprotein; pCEA, polyclonal carcinoembryonic antigen; SALL4, SAL-like protein 4; Hep Par-1, hepatocyte paraffin 1; CK, cytokeratin.

Figure 2. Histopathological examination. (A) Hematoxylin and eosin staining demonstrated a cellular tumor with polygonal cells and tumor necrosis. (B) Focal expression of α-fetoprotein. (C) Diffuse and strong immunopositivity for Hep Par-1. (D) Ki-67 staining revealed an extremely high proliferation rate. Magnification, x200 in all panels.
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References