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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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Case report

A 41-year old man was admitted to our emergency department with a generalized seizure. No motor or sensory symptoms were present, but there was retrograde amnesia and altered mental status. The physical examination was unremarkable. The patient's past medical history included orchidopexy in childhood.

A head computed tomography (CT) and magnetic resonance imaging (MRI) examination revealed a large mass (5x3 cm) in the left occipital lobe with associated edema (Fig. 1). The patient underwent total tumor removal via left occipital craniotomy. The postoperative course was complicated by severe transitional hemiparesis.

The histopathological examination of the resected tumor revealed large, eosinophilic cells with round, centrally located nuclei, arranged in cords or trabeculae. The tumor cells focally contained PAS-positive intracytoplasmic and extracytoplasmic hyaline bodies. Immunohistochemically, the tumor cells were diffusely positive for Hep Par-1, glypican-3 and cytokeratin (CK) 8; α-fetoprotein (AFP) was focally expressed and Ki-67 staining revealed 80% positive tumor cell nuclei, indicating a very high proliferation activity (Fig. 2). By contrast, the tumor cells were negative for placental alkaline phosphatase, octamer-binding transcription factor 3/4, CK20, CD30 and c-kit. The immunohistochemical findings were thus consistent with malignant epithelial GCT with a hepatoid pattern.

The serum lactate dehydrogenase (LDH) and AFP levels were markedly elevated (Table I). The serum human chorionic gonadotropin level was within the normal range. Chest CT revealed a lesion sized 2x1 cm in the upper lobe of the right lung. No other lesions were identified using testicular ultrasound, abdominal CT, liver MRI and gastroscopy.

Taking all laboratory findings into account, the diagnosis of an extragonadal hepYST was considered to be likely.

Initially, the patient underwent two courses of cisplatin, etoposide and ifosfamide (PEI regimen). However, subsequent

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.

Table I. Tumor marker levels during the course of the disease.

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

[a]AFP reference value, <7 ng/ml; [b]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.

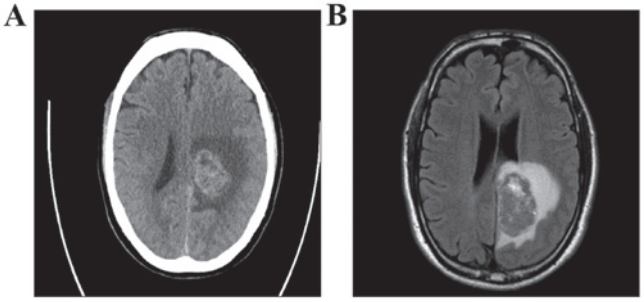

Figure 1. Radiological examination. Preoperative (A) Computed tomography and (B) magnetic resonance imaging with contrast enhancement of the brain, showing a lesion sized 5x3 cm in the left occipital lobe, with associated edema.

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 (2,24). In our case, due to tumor location in the brain and lung, PEI was selected. Unfortunately, the patient had already experienced progression during therapy.

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

Staining	HCC	HAC	hepYST
AFP	+	+	+
pCEA	+ Canalicular pattern	+ Diffuse membranous or canalicular patterns	+
Glypican 3	+	++	+
SALL4	+ (Cut-off: 7% in 25% of cells)	+	++ (Cut-off: 100% in 25% of cells)
Hep Parl	+	+	-
CK7/CK20	-/-	+ or -/+ or -	-

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.

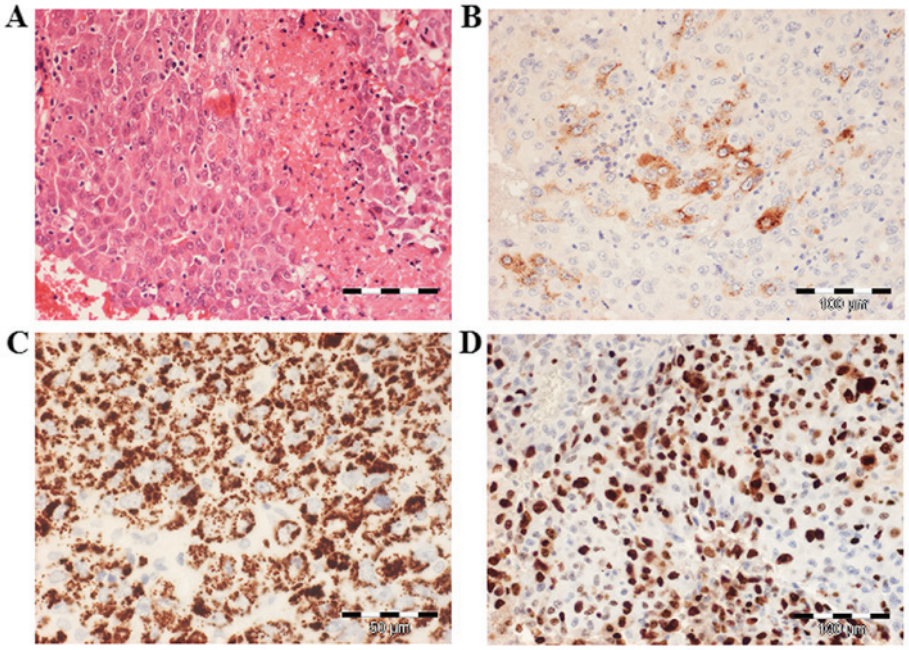

Figure 2. Histopathological examination. (A) Hematoxylin and eosin staining demonstrated a cellular tumor with polygonal cells and tumor necrosis. (B) Focal expression of α-fetoprotein. (C) Diffuse and strong immunopositivity for Hep Par-1. (D) Ki-67 staining revealed an extremely high proliferation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

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.

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