



High Grade Malignant Germ Cell Tumor with Initial Presentation as Metastatic Liver Lesions-Case Report and Literature Review

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Abstract

Metastatic germ cell tumors are relatively uncommon, but the mediastinum is the most common extra-gonadal site. The histopathological characterization is the same as seen with the gonadal counterpart, and it is paramount to keep germ cell tumors on the list of differentials when examining a patient with metastatic hepatic lesions.

Keywords: Mediastinal germ cell tumor; Germ cell tumor; Mediastinal mass; Metastatic liver tumor; Metastatic germ cell tumor; Immunohistochemistry

Abbreviations

PMGCT: Primary Mediastinal Germ Cell Tumor; HPF: High Power Field; IHC: Immunohistochemistry

Introduction

Metastatic germ cell tumors (MGCTs) are relatively uncommon but represent 1% to 5% of all GCTs. MGCTs are found in a variety of anatomic locations, but most commonly affect the mediastinal, retroperitoneal, sacrococcygeal region, and other areas of the head and neck region. The mediastinum is the most common non-gonadal primary germ cell tumor location and account for 1-6% of all germ cell tumors [1]. Mediastinal germ cell tumors derive from germ cell crest remnants in the mediastinum [2,3]. It is relatively unlikely for germ cell tumors originating in the testicles to metastasize to the mediastinum. Metastases are most commonly found in retroperitoneal lymph nodes, often bypassing the mediastinum via the thoracic duct [2]. We report a case of mediastinal germ cell tumors with metastases to the liver.

Case Presentation

A 48-year-old male presented with generalized weakness, and yellow discoloration of his skin and eye. The patient presented with an unexplained ten-pound weight loss. Initial

imaging studies revealed multiple liver lesions and mediastinal masses. The patients did not have a prior history of malignancy or any scrotal or testicular masses. MRI showed multiple large irregular heterogeneous masses spreading throughout the liver parenchyma with the largest measuring 5.5 x 3.8 cm. The masses were predominantly hypointense on T1-weighted images with focal areas of T1 hyperintensity. The masses displayed intermediate to high signal intensity on T2 and STIR images. Mediastinal masses showed similar MRI findings. Scrotal ultrasound showed no abnormality in the testes. Fine needle aspiration biopsy (FNAB) of the liver lesion was performed. Cytology smeared slides (Figure 1A) and cell block (Figure 1B) showed a moderately cellular specimen displaying disorganized crowded groups and single-lying malignant cells with marked pleomorphism, anisonucleosis, irregular chromatin and prominent nucleoli in a background of necrotic debris. Preliminary diagnosis was high grade malignant neoplasm with prominent pleomorphic features. Additional studies were needed for a more specific diagnosis, and serum tumor markers revealed high human chorionic gonadotropin (HCG) and mildly elevated alpha-fetoprotein. Immunohistochemical studies performed on the cellblock cytology preparation revealed positive staining for AE1/AE3 (Figure 1C) b-HCG (Figure 1D) and alpha-fetoprotein; while negative for CK5/6. Scattered foci in the tumor were positive for synaptophysin, and S-100. Additional tissue sampling was obtained for definitive classification of the tumor. The tumor tissue showed evidence of mixed germ cell tumor composed of 75% choriocarcinoma component, 20% immature teratomatous component in the form of neuroepithelium, 3% embryonal carcinoma component and 2 % yolk sac tumor. Glypican 3, and alpha-feto protein highlighted the yolk sac component. CD30 was positive in the embryonal carcinoma. S100 and synaptophysin were positive in the immature neuroepithelium. Vimentin and CD34 were positive in the stroma. OCT3/4 was noncontributory. A mediastinal biopsy showed similar features as the tumor in the liver. A final diagnosis of metastatic high grade extra gonadal mixed germ cell tumor was rendered. Patient was started on 2 cycles of BEP chemotherapy. The tumor markers were normalized, repeat cross sectional scan showed variable

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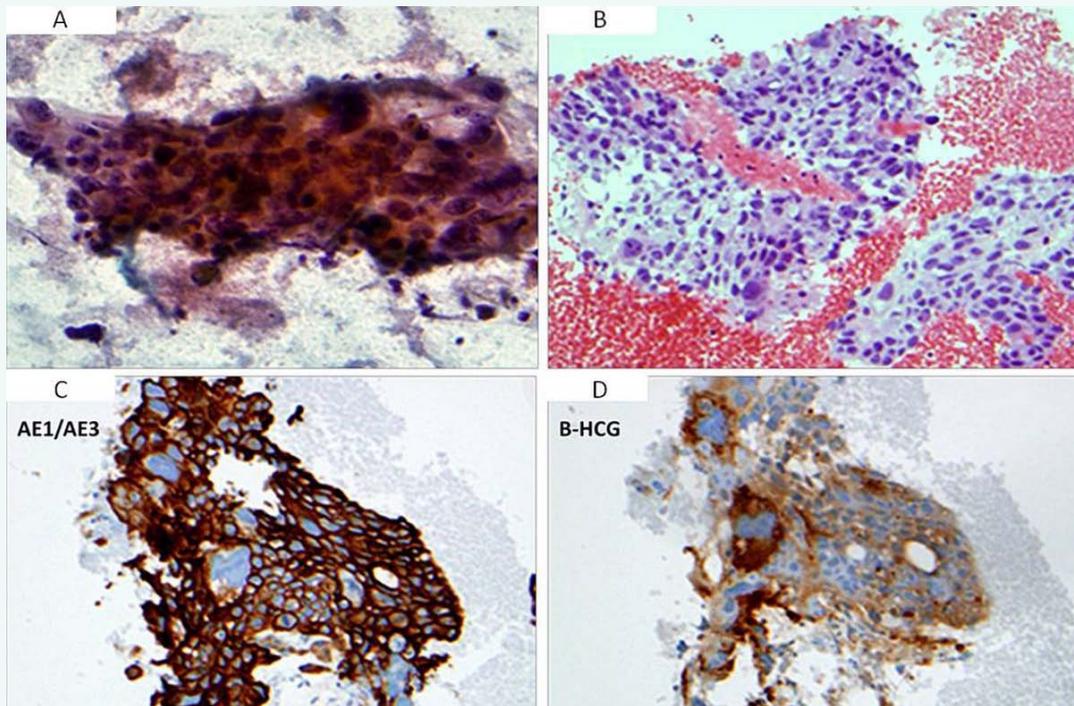


Figure 1

- Smears cytology shows moderately cellular specimen displaying disorganized crowded groups and single-lying malignant cells showing marked pleomorphism H&E stain X 40
- Cell block cytology showing moderately cellular and hyperchromatic cells displaying pleomorphism, anisonucleosis, irregular chromatin, and prominent nucleoli in a background of necrotic debris H&E stain X 20
- Immunohistochemical study revealing positive staining for Cytokeratin AE1/AE3
- Immunohistochemical study revealing positive staining for b-HCG (Beta- Human Chorionic Gonadotropin).

response in the liver lesions and stable mediastinal lesions. Five months later, lung metastases were identified. The patient was started on 2nd line chemotherapy but after two more cycles of chemotherapy, he received palliative care after which the patient was lost to follow up.

Discussion

Presentations can be similar amongst tumors typically found in the same location as germ cell tumors. These include seminomas, spermatocytic seminoma, embryonal carcinoma, yolk sac tumor, trophoblastic tumor, and teratoma. Pure gonadal tumors are rare and only represent roughly 40% of all gonadal tumors. The more frequent majority (60%) are of a mixed histologic type [3,4]. Important distinctions should be made between the differential diagnoses. FNAB cytology, together with clinical history, imaging studies, and specific tumor markers, are crucial to the early diagnosis and subsequent management of patients with MGCTs.

Current morphologic, cytogenetic, and DNA-ploidy data support the theory that seminomas may be the precursor for non-seminoma germ cell tumors. It has been recognized that seminoma cells may have early carcinomatous transformation, which is difficult to identify based solely on hematoxylin-and-eosin-stained sections. In these cases, immunohistochemistry is complementary and advantageous [5]. Seminomas are distinctly

recognized based on their sheet-like arrangement of clear cells with well-defined cytoplasmic borders and flattened, 'squared-off' nuclear membranes. These can be subdivided into variably sized, smaller groups of cells, lymphocyte-bearing, and fibrovascular septa [5]. Seminomas stain positively for OCT3/4 but negatively for AE1/AE3 and AFP. OCT3/4 is a nuclear transcription factor that is expressed in human embryonic and stem cells and has been found to mark the nuclei of germinomas and embryonal carcinomas with very high sensitivity and specificity [5].

Spermatocytic seminomas should be distinguished from GCTs and seminomas as their clinical courses differ. Spermatocytic seminomas very rarely metastasize and do not require treatment apart from tumor extraction [5]. Grossly, spermatocytic seminoma is typically more gelatinous than the fleshy appearance of "usual" seminomas [5]. Spermatocytic seminomas are arranged sheet-like with a paucity of lymphocytes containing round nuclei and variable cell size [5]. Immunostains for placental alkaline phosphatase and OCT3/4, positive in similar tumors (seminoma and embryonal carcinoma), are negative in spermatocytic seminoma. CD30 and AE1/AE3 are negative in these tumors [5].

Embryonal carcinomas typically affect a younger patient population and are relatively common GCTs, most cases of embryonal carcinomas are a component of a mixed germ cell tumor, but only 10% are pure embryonal carcinomas. These



tumors can be distinguished by their sheets, glands, and papillary structures composed of primitive epithelial cells with crowded, pleomorphic nuclei, and are usually distinctive among the germ cell tumors. An immunochemistry panel of CD30, EMA, and OCT3/4 can also help obtain a diagnosis. Embryonal carcinomas will stain positively for both CD30 and OCT3/4, but will stain negatively for EMA [5].

Pure yolk sac tumors are rare in adults but are the most common testicular germ cell tumor in children. Representing about 70% of pediatric testicular germ cell tumors, with a peak age of 1.5 years [5]. Yolk sac tumors present with a sheet-like arrangement of lightly staining cells and well-defined borders, a high degree of nuclear variability, and lack lymphocytes [5]. Occasional occurrences of intracytoplasmic hyaline globules and extracellular basement membrane deposits are useful in helping distinguish them from germinomas. Immunostaining consists of positive (AE1/AE3) and AFP, but negative for OCT3/4 [5].

Trophoblastic tumors, microscopically, are composed of relatively uniform populations of mononucleate intermediate trophoblastic cells forming nests and solid masses. Islands of trophoblastic cells are surrounded by extensive necrosis and are associated with hyaline-like matrix creating a “geographic” pattern, which is a notable characteristic [6]. These tumors are diffusely positive for inhibin-alpha, (AE1/AE3), epithelial membrane antigen, E-cadherin, Prolyl 4-hydroxylase, and epidermal growth factor receptor [6]. Furthermore, focal reactivity can occur with human placental lactogen, human chorionic gonadotropin, PIAP, and Mel-CAM [6].

Teratomas represent about 4% of germ cell tumors [3,7]. Most instances are associated with mixed germ cell tumors, containing teratoma in roughly 50% of cases. Testicular teratomas have a disordered arrangement, frequently showing significant cytological atypia, and may have widespread mitotic activity. According to Ulbright, the seminiferous tubules adjacent to these tumors show intratubular germ cell neoplasia of the unclassified type in approximately 90% of cases, and there is also widespread testicular atrophy with impaired or absent spermatogenesis. Unlike their ovarian counterpart, testicular teratomas very rarely display other tissues on microscopy [3,8,9].

According to the risk classification of the International Germ Cell Cancer Collaborative Group (IGCCCG), mediastinal NSGCTs are classified as poor risk, with a 5-year relapse-free chance of survival of 40 percent [10]. Regardless of the presence or absence of metastasis, or of levels of the serum tumor markers, lactate dehydrogenase (LDH), α -fetoprotein (AFP), and human chorionic gonadotropin (hCG) the survival rate is unchanged. The current standard of care for non-seminoma germ cell tumors (NSGCTs) is combination chemotherapy with bleomycin, etoposide, and cisplatin and resection of residual tumor [11,12]. Serum levels of LDH, AFP, and hCG levels should be measured to monitor the response to treatment. A decrease in these markers is consistent with predicting a good treatment outcome [13].

We bring this case forward to shed light on the importance of including germ cell tumors in your differential of a patient with multiple liver lesions. Current available knowledge of this tumor indicates that Metastatic germ cell tumors resemble their gonadal counterparts on immunochemistry and biopsy.

It is our hope that this report raises awareness of what remains an unmet need in the diagnosis and management of MGCT, and continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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