Case report

A presumed extragonadal germ cell tumor that turned out to be a gastric cancer—a case report

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Abstract: A solely retroperitoneal mass in males in combination with elevated serum Alpha-Fetoprotein (AFP) and beta-human choriogonadotropin (β-HCG) levels is highly indicative of a metastatic testicular cancer. Although testicular cancers are rare, they represent the most common diagnosed cancer in males between 14 and 40 years. However, in cases without evidence of a primary testicular tumor, the rare diagnosis of a retroperitoneal extragonadal germ cell tumor (EGCT) must be assumed. Here, we describe the first published case of a 66-year-old man presenting with this typical clinical picture and the diagnosis of an AFP and β-HCG producing advanced gastric cancer with retroperitoneal lymph node metastases mimicking a primary retroperitoneal EGCT. The final diagnosis was only made by gastroscopy performed after a CT-guided retroperitoneal lymph node biopsy revealed an adenocarcinoma, suggesting an upper gastrointestinal tract primary origin. However, a specific initial anamnesis and also in the primary staging, including a full-body CT-scan there was no hint for another primary tumor. Only the slightly unusual extension of the retroperitoneal mass up to the ligamentum hepatoduodenale and the pylorus, as well as the atypical age made us question our initial diagnosis. This extraordinary case is of special clinical interest to all practising physicians and once again highlights the importance of keeping rare differential diagnosis such as AFP-producing gastrointestinal tumors in mind.

Keywords: Germ cell tumor; gastric cancer; Alpha-Fetoprotein (AFP); beta-human choriogonadotropin (β-HCG)

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Introduction

Testicular cancer is a rare neoplasm and represents only 1% of all malignancies occurring in males, yet is the most commonly diagnosed cancer in males aged 15 to 40 years (1). Peak incidences for diagnosis of a testicular cancer are the third decade of life with mainly non-seminoma or mixed germ-cell-tumors and around the fourth decade with generally pure seminomas (2). Usually, unilateral scrotal mass is the typical symptom of testicular cancer detected mostly by self-examination, or as an incidental ultrasound finding. Whereas more than 70% of patients with a non-seminomatous germ cell tumor (NSGCT) present with elevated serum tumor markers of either Alpha-Fetoprotein (AFP) or beta-human choriogonadotropin (β-HCG), only 30% of pure seminomas are β-HCG positive (3,4). The retroperitoneal region is the typical primary stage of metastasis hence a contrast enhanced whole-body computed tomography (CT) scan is the gold standard imaging tool for staging (2).

Primary extragonadal germ cell tumors (EGCTs) are a rarity and only seen in 2–5% of all testicular cancer patients (5). Trama *et al.* recently conducted a large retrospective analysis evaluating the current incidence of

Table 1 Differential diagnosis: Differential diagnosis of disease associated with elevated AFP and beta-HCG serum markers

Diagnosis	AFP↑	Beta-HCG↑
Malignant	Hepatocellular carcinoma	Germ cell cancers
	Germ cell cancers	Gestational trophoblastic disease
	Ovarian cancers	Rarely gastrointestinal cancers
	Gastric cancers	
	Biliary cancers	
	Pancreatic cancers	
Benign	Liver cirrhosis	Hypogonadal states
	Hepatitis	Marijuana use
	Pregnancy	Pregnancy

AFP, Alpha-Fetoprotein; β-HCG, beta-human choriogonadotropin.

EGCTs in Europe and found an annual incidence rate of only 1.27/1,000,000 with a 5-year survival rate of 71% (6). EGCTs originate from neoplastic germ cells in extragonadal localisations and represent without evidence of a primary testicular cancer (5). Although the clear pathophysiological mechanism behind the development of EGCT is not fully understood yet, the two most widely accepted hypotheses are a malignant transformation of (I) displaced primordial germ cells during midline migration of the body and (II) persisting pluripotent cells in various organs (7). The question whether this special tumor is "truly" extragonadal or may present a secondary EGCT following a burned-out testicular tumor is difficult to answer. However, EGCTs with retroperitoneal localization are more often associated with a burned-out tumor compared to mediastinal EGCTs (8,9). In cases with fibrous testicular scarring seen on ultrasound, the possibility of a burned-out tumor should always be considered (10).

EGCTs show a typical clinical presentation as masses localized along the midline of the body, predominantly in the anterior mediastinum (50-70%) or the retroperitoneum (30–40%) (11,12). As EGCTs demonstrate the same histopathological subtypes as gonadal germ cell neoplasms, AFP and β-HCG are the tumor markers of interest (10,13). Consequently, an isolated retroperitoneal mass in males with negative testicular ultrasound is highly suspicious for an EGCT also based on the small number of potential differential diagnosis, such as lymphomas or retroperitoneal soft-tissue sarcomas (14). In case with further elevated tumor markers, the diagnosis of an EGCT seems to be obvious. However, extremely rare subtypes of gastrointestinal tumors also produces AFP and can mimic an EGCT (*Table 1*) (15). These AFP-secreting gastrointestinal tumors are characterized by an aggressive biological behaviour, high metastatic potential and poor prognosis (16,17).

We present the first report describing an AFP- and HCG producing, retroperitoneally metastasized gastric adenocarcinoma mimicking a primary retroperitoneal EGCT. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/tau-21-150).

Case presentation

A 66-year-old man presented with enlarged retroperitoneal lymph nodes (up to 2.4 cm of short axis diameter) and elevated AFP (42.2 µG/L), β-HCG (167.6 U/L) and normal value of lactatdehydrogenase (LDH 168 U/L). Detailed anamnesis yield a negative family history for tumors, no pre-existing conditions or previous medical interventions. As no abnormalities were found on testicular ultrasound, an EGCT was assumed. However, patient`s age and the distribution of the lymphadenopathy atypical for a testicular cancer with significant non-midline affection (up to the ligamentum hepatoduodenale and the pylorus) made us question the initial diagnosis (*Figure 1*). Therefore, a CT-guided retroperitoneal lymph node as well as a testicular biopsy were performed.

The histological result of the testicular biopsy was inconspicuous. Interestingly, the final pathological report on the retroperitoneal lymph nodes revealed metastasis

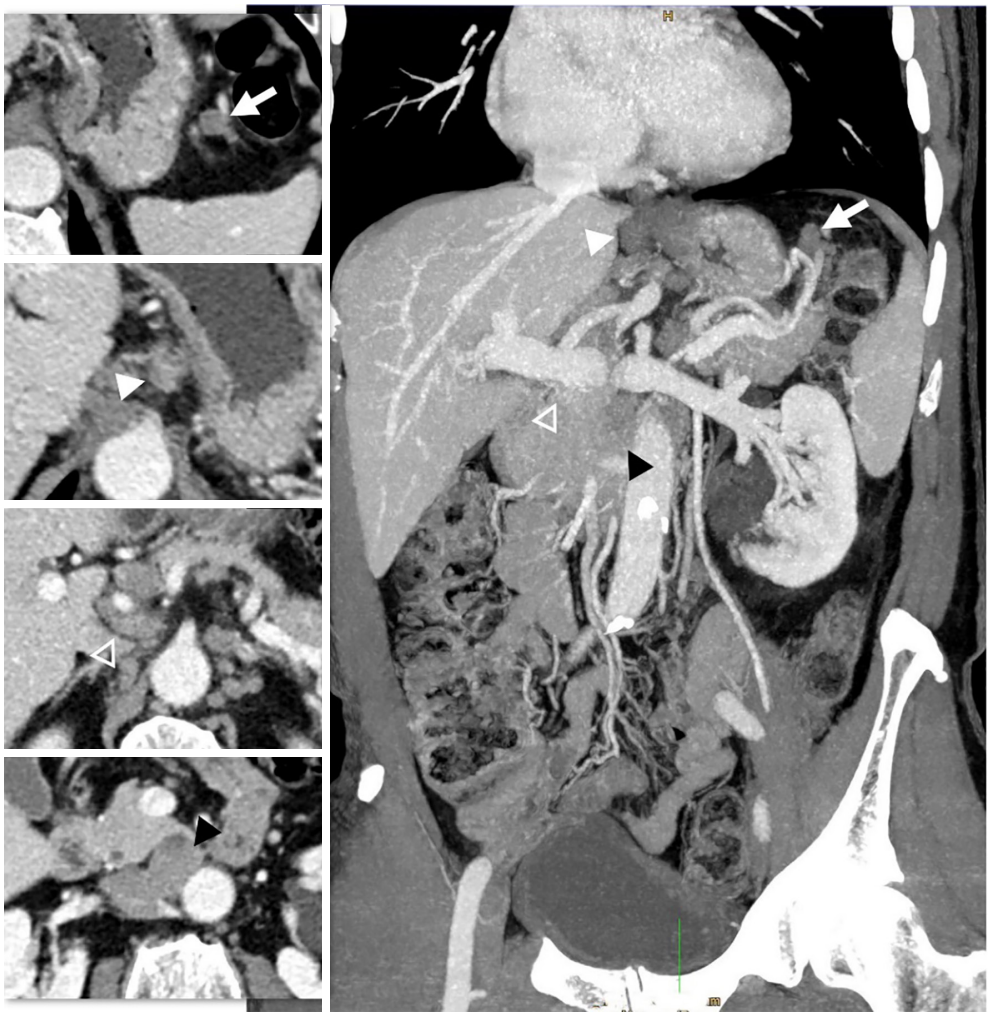

Figure 1 Representative CT-images of the metastatic expansion. Illustration of lymph node metastases distribution in computed tomography in coronal plane (maximum intensity projection reformatted main image, right) and corresponding axial planes (left): along the greater (white arrows) and lesser gastric curvature (white arrowheads), portal vein (empty arrowheads) and aorta (black arrowheads).

of a poorly differentiated adenocarcinoma with an immunohistochemical marker profile (TTF-1$^-$CK7$^+$CK20$^+$) suspicious for gastrointestinal cancer. Notably, there was no hint for a gastrointestinal cancer in the initial staging including a full-body CT-scan. Still, as the patient retrospectively reported he had suffered from epigastric pain with weight loss of 6 kg during the last 5 months, a gastroscopy was performed, revealing a locally advanced gastric cancer (*Figure 2*).

Histopathology confirmed a poorly differentiated mixed type gastric adenocarcinoma with trophoblastic tumor cell proliferations and the expression of β-HCG and HER2/Neu (*Figure 3*). Subsequently, systemic therapy of the metastasized tumor with a triple combination using Capecitabine (1,000 mg/m^2), Oxaliplatin (85 mg/m^2) combined with Trastuzumab (6 mg/kg) was initiated. The first re-staging CT-scan after 3 cycles of treatment confirmed stable disease. Currently, the fifth chemotherapy cycle (of 6 planned) is ongoing. After the sixth cycle of chemotherapy, gastroscopy control with CT scan is scheduled followed by Trastuzumab maintenance. Up to now, no serious treatment-related adverse events occurred and the patient tolerates chemotherapy very well. This Case report was prepared in accordance to the Helsinki Declaration (as revised in 2013) and a written consent form was obtained by the patient and a positive ethical vote was

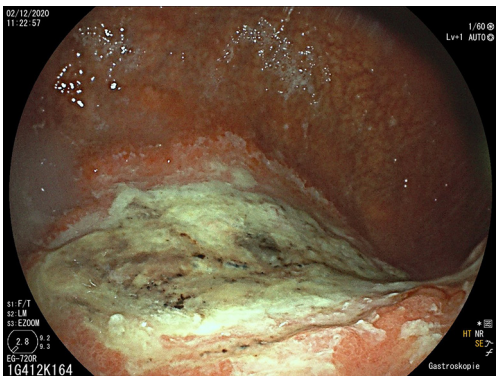

Figure 2 Endoscopic image. Representative endoscopic image of the gastroscopy confirming locally advanced gastric cancer.

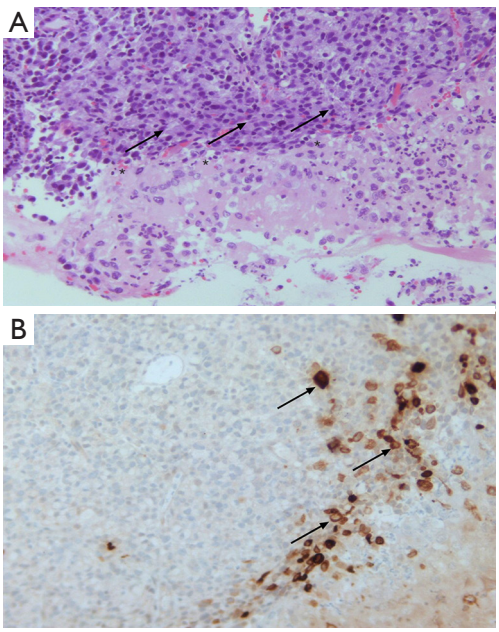

Figure 3 Histopathological picture. (A) Hematoxylin and eosin (HE) staining image demonstrating the gastric adenocarcinoma formation exhibiting high cellularity and densely packed, hyperchromatic nuclei (arrows), whereas the trophoblastic tumor cell component shows extensive cytoplasmatic staining with strong nuclear chromatin inhomogeneity (*). (B) Strong beta-human choriogonadotropin staining is observed in the trophoblastic tumor component (arrows) in contrast to conventional gastric adenocarcinomatoid tissue. The images are represented in a magnification level of ×200.

already approved (Ethical vote Number: 1017/2021).

Discussion

The clinical constellation of a men presenting with a retroperitoneal mass combined with elevated AFP and β-HCG is highly indicative of a metastatic testicular GCT. In light of missing evidence for a primary testicular cancer, the hypothesis of a primary EGCT was presumed. This was strengthened by the absence of clinical symptoms for another malignancy and only retroperitoneal lymphadenopathy on the initial whole-body CT-scan. Still, a somewhat peculiar lymph node localization deviating significantly from the midline, together with the presentation at a quite atypical age (66 years) for testicular cancer, made us question our initial diagnosis. Although it is known that gastric cancers tend to present with histological heterogeneous differentiations, this clinical picture represents an exceptional case (17,18). AFP-secreting gastric cancer is an extremely rare subtype with unique clinicopathological features, high rates of lymphatic and liver metastasis with poor prognosis (18). The worldwide incidence of AFP-positive gastric cancer ranges only between 1.3% and 15% of all gastric cancers (19). AFP-positive gastric cancers can be classified into four subtypes including the hepatoid, yolk sac tumor, fetal gastrointestinal and mixed type (20). Currently, there is no specific treatment for these special subtype, thus following treatment concepts of common gastric cancer (21). However, preliminary data suggest that patients with AFP-producing gastric cancer and hepatoid adenocarcinoma of the stomach may benefit from PD-1 checkpoint inhibitor combined with chemotherapy (21). In our case, systemic therapy with Capecitabine, Oxaliplatin and Trastuzumab was initiated based on positive IHC expression of HER2/Neu and β-HCG. A similar case with a HER2 and β-HCG producing poorly differentiated gastric adenocarcinoma was described by Eivaz-Mohammadi *et al.* (22). Concerning β-HCG, elevated serum levels are much less frequently compared to AFP in gastric cancer, although a positive IHC staining of β-HCG can be found in up to 50% of patients with gastric cancer (23). Actually, measurable β-HCG serum level were only found in few individual cases, despite confirmed positive IHC staining for β-HCG (23-25). Knowledge on the exact pathophysiological mechanism of β-HCG

production in gastric cancer is still lacking. However, in our case it might be assumed that β-HCG secretion originates through the presence of trophoblastic cells. In cases without trophoblastic cells the hypothesis of dedifferentiation of the tumor leading to the secretion of β-HCG is described in the literature (26). These findings show that β-HCG is not a typical paraneoplastic hormone in gastric cancer with a large discrepancy of β-HCG analysis on tumor tissue and serum levels, thus being less suitable as biomarker in gastric cancer compared to AFP, CEA and CA19-9 (27). Moreover, the prognostic role of β-HCG positivity on IHC in gastric cancer remains still unclear (26,28).

We highlight the first case of a gastric cancer with trophoblastic differentiation producing both AFP and β-HCG with distinct retroperitoneal lymphadenopathy. The described clinical presentation nearly lead us to the initial misdiagnosis of a retroperitoneal EGCT. Therefore, this extraordinary case is of special clinical interest to demonstrate the importance of a precise diagnostic evaluation and to include rare differential diagnosis. Without histological verification, an unsuitable treatment strategy and a consequent poor clinical course may have resulted.

Conclusions

To our best knowledge, this is the first case of a gastric cancer secreting both AFP and β-HCG mimicking a testicular tumor. The clinical picture of a retroperitoneal mass combined with a negative testicular ultrasound and elevated testicular tumor markers is highly indicative of an EGCT. According to the current EAU guidelines (2), this constellation of findings alone would already justify the decision for chemotherapy according to the PEB (cisplatin, etoposide, bleomycin) regimen. Clearly, this extraordinary case is of special interest for all practicing physicians and highlights the importance of keeping rare differential diagnoses in mind.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/tau-21-150

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This Case report was prepared in accordance to the Helsinki Declaration (as revised in 2013) and a written consent form was obtained by the patient and a positive ethical vote was already approved (Ethical vote Number: 1017/2021).

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