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LETTER TO EDITOR

Pericardial Tamponade Caused by Tumor Hemorrhage – a Rare Complication of Metastatic Testicular Choriocarcinoma

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Introduction

Testicular germ cell cancers are relatively rare with the incidence rate of 3.7 cases per 100,000 per year. Nevertheless they represent the most frequent malignant tumors in men aged 15–35 years. Pure choriocarcinoma comprises only 1 % of all testicular malignancies, but mixed germ cell cancers contain choriocarcinoma elements more frequently. Unlike other histological subtypes, choriocarcinoma metastasize early and hematogenously, so it is often diagnosed in advanced stage [1]. Metastatic, choriocarcinoma containing germ cell cancers can be complicated by serious bleeding from metastatic sites known as the choriocarcinoma syndrome [2].

Case Description

A 46 year old male patient with unremarkable medical history presented himself to a urologist because of a grossly enlarged right testis. Orchiectomy was performed. Histological examination proved pure choriocarcinoma with a tumor size of 9×7×7 cm. Grossly, the whole enlarged testis was destructed by an extensively hemorrhagic and necrotic tumor mass, which extended through the tunica albuginea. Microscopically, viable tumor cell sheets were located at the periphery of the necrotic zones, composed of predominantly cytotrophoblasts intermingled or capped with syncytiotrophoblasts (Fig. 1). The tumor cells showed strong positivity with cytokeratin 7 (CK-7) and with β-human chorionic gonadotropin (β-hCG), and scattered positivity with placental alkaline phosphatase (PLAP) antibodies. The α-fetoprotein (AFP), the octamer-binding transcription factor 4 (OCT-4) and the CD30 immunoreactions proved to be negative (Figs. 2, 3, 4, 5, 6 and 7).

Computed tomography (CT) scan of the chest showed multiple pulmonary metastases. The patient was referred to our institution for further treatment, but he didn't attend to the scheduled consultation. Two and a half months later he developed headache, nausea and confusion. CT scan of the brain demonstrated two metastases with significant perifocal edema (Fig. 8). On inspection, a skin metastasis was noted on one of the nipples. Abdominal ultrasound also showed a kidney and multiple hepatic metastases. The lungs appeared to be full of metastases and the area for ventilation seemed to be greatly reduced on chest x-ray. The β-hCG level proved to be 533,081.0 mIU/ml (normal: < 2.24 mIU/ml), the AFP level was normal and the lactate dehydrogenase (LDH) level measured to be 2,918.0 U/l (normal range: 226–451 U/l).

Due to intravenous dehydration the patient's condition improved. Chemotherapy was initiated urgently with the planned schedule of carboplatin area under the curve (AUC) 4.5 on the first day and etoposide 100 mg/m^2 for 5 days during the first cycle. On the third day following the start of treatment, febrile bronchitis occurred and the chemotherapy was interrupted.

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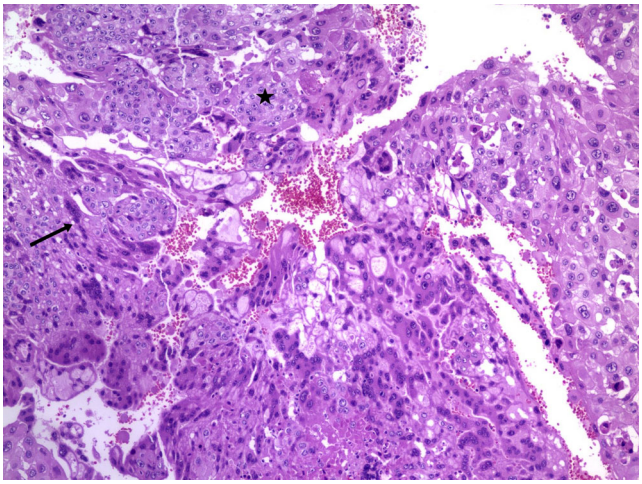

Fig. 1 Choriocarcinoma consists of two distinct cell populations, the multinucleated syncytiotrophoblasts (*arrow*) with purple cytoplasm are intermingled with the mononuclear cytotrophoblasts (*asterisk*) with eosinophilic cytoplasm (hematoxylin and eosin, 10×)

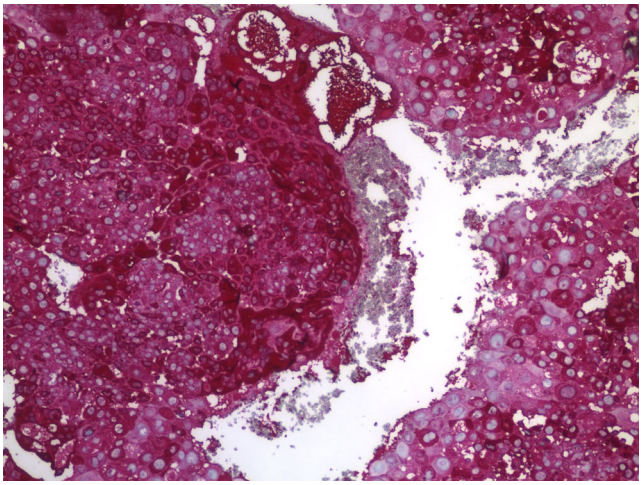

Fig. 3 An immunostain for β-hCG shows strong cytoplasmic staining in all of the tumor cells (10×)

Despite antibiotic and expectorant treatment the patient developed shortness of breath, his sputum became slightly bloody and the oxygen saturation dropped to 78 %, but he remained hemodinamically stable without decrease in the hemoglobin level. He was transferred to the intensive care unit and mechanical ventilation was started. With continuation of the antibiotic and supportive treatment, his sputum cleared of blood and diminished. By prophylactic filgrastim administration significant neutropenia could be prevented and although grade 3 thrombocytopenia occurred, it resolved quickly, so the decision was made to complete the first cycle of chemotherapy. Subsequently the patient improved further and after two weeks it became possible to take him off the ventilator.

Although there was no significant change on chest x-ray, the LDH level decreased to 851.0 U/L after four weeks, a control brain CT scan showed regression of the brain metastases (Fig. 8) and also the size of the skin metastasis on the nipple diminished. Nevertheless four weeks after the start of chemotherapy, the patient was found dead in his room at night without any preceding signs.

During autopsy hemorrhage was discovered in the pericardial cavity, which originated from a small subepicardial choriocarcinoma metastasis (Fig. 9) and caused fatal pericardial tamponade. In addition to the

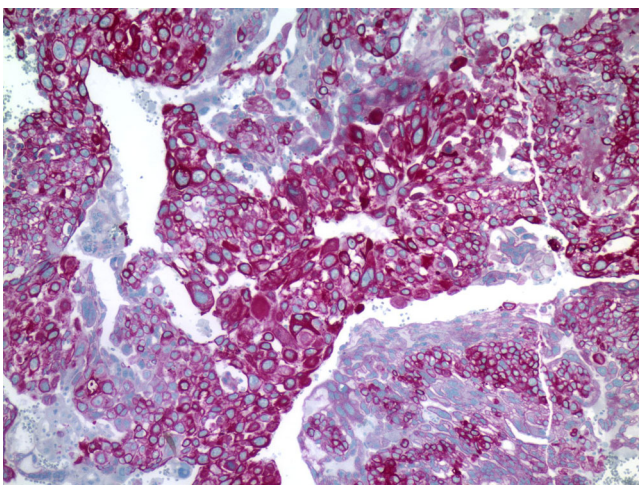

Fig. 2 There is moderate to strong staining of tumor cell cytoplasms with an immunostain for CK-7 (10×)

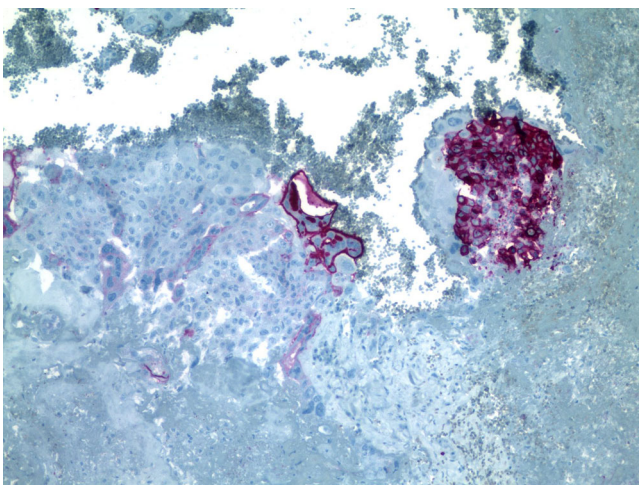

Fig. 4 Staining for PLAP varies in intensity and not all tumor cells stain (10×)

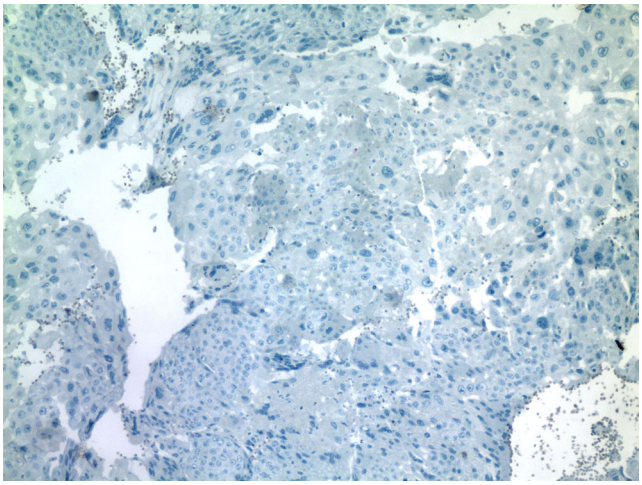

Fig. 5 There is no staining with AFP (10×)

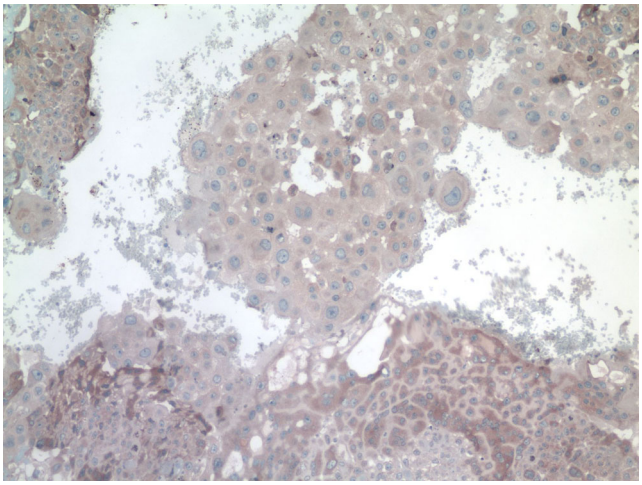

Fig. 7 There is no membrane staining with CD30, only non-specific background staining is visible (10×)

previously known metastatic sites, peritoneal carcinomatosis was revealed. By histological examination most of the metastases found to be extensively necrotic with intralesional bleeding.

Discussion

Choriocarcinoma is an aggressive tumor with rapid proliferation, so in spite of its high vascularity it often outgrows it's blood supply which results in intratumoral necrosis. As a consequence ulceration or structure perforation can occur with bleeding [3]. The choriocarcinoma syndrome usually occurs in patients with β-hCG level above 50,000 mIU/ml, which indicates high-volume choriocarcinoma. The most common site of hemorrhage is the lung, but bleeding complications has been reported to originate from metastatic mediastinal and retroperitoneal lymph nodes, and from liver, bowel, and kidney metastases [2, 4–9]. Choriocarcinoma syndrome can occur spontaneously, or more often shortly after the initiation of chemotherapy [3]. As the hemorrhage is frequently serious or even life-threatening, choriocarcinoma syndrome requires multimodality management, which usually includes medical and supportive treatment in the intensive care unit and embolization or surgery to control bleeding, when appropriate. Additionally successful use of recombinant factor VII was reported in the setting of diffuse pulmonary hemorrhage [10]. Choriocarcinoma syndrome has high lethality. In an autopsy series hemorrhage has been implicated as the cause of death in 44 % of patients with choriocarcinoma containing testicular tumor [11].

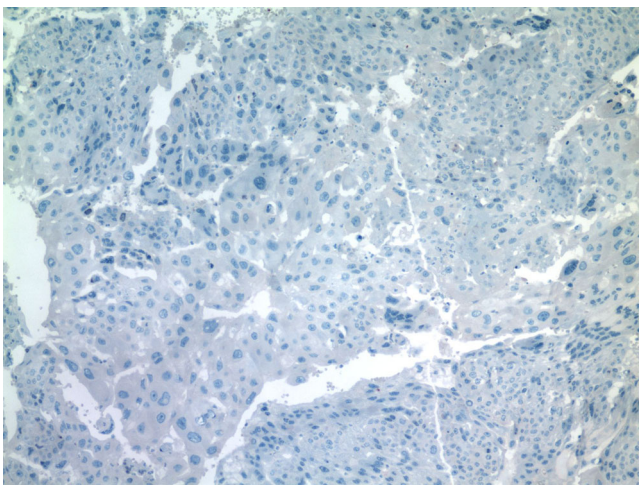

Fig. 6 Staining with OCT-4 is completely missing (10×)

The primary chemotherapy of advanced germ cell cancers, including choriocarcinoma, is a platinum containing regimen, usually the BEP (bleomycin, etoposide, cisplatin) protocol. Very advanced choriocarcinoma containing germ cell cancer patients frequently experience significant complications after the initiation of chemotherapy, like choriocarcinoma syndrome, tumor lysis syndrome, cytopenias, infections and respiratory insufficiency partly because of the high sensitivity of germ cell cancers to platinum based regimens. So to reduce the risk of such side effects in this setting we usually start with only a short course of chemotherapy (usually the first 2 days of the first cycle) as a cytoreductive treatment. After that we observe the patient for several days. If there is no complication, the rest of the first cycle is given. Bleomycin has a

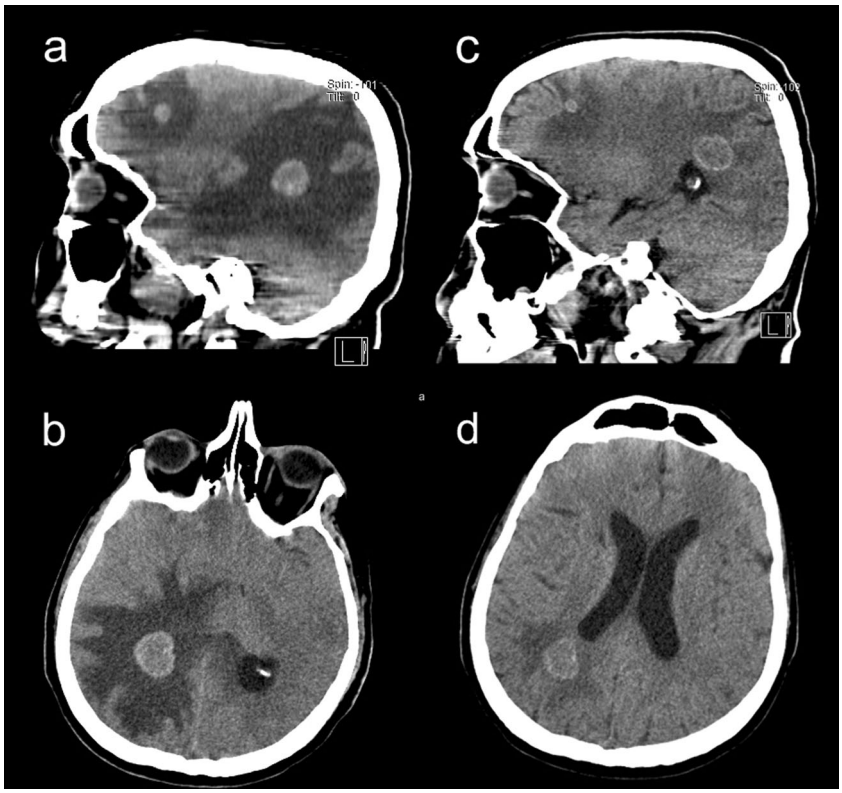

Fig. 8 **a**–**b** CT scan of the brain before treatment demonstrated one metastasis in the right frontal and one other in the right parietal lobe with significant perifocal edema (**a** - sagittal section, **b** – transverse section). **c**–**d** Control CT scan after the first cycle of chemotherapy. The size of the metastases slightly, the amount of the edema greatly decreased (**c** - sagittal section, **d** – transverse section). The patient holds his head in different angles during the two examinations

potential for producing pulmonary damage, attributed in part to its free radical promoting ability. Pulmonary toxicity occurs in 6–10 % of patients and can progress to life-threatening pulmonary fibrosis. The risk of bleomycin-induced pulmonary injury increases with exposure to high concentration oxygen [12]. So, as an institutional practice we don't administer bleomycin during the first cycle of chemotherapy to those germ-cell cancer patients, who present with widespread pulmonary involvement and therefore are susceptible to pulmonary insufficiency eventually requiring mechanical ventilation and oxygen therapy.

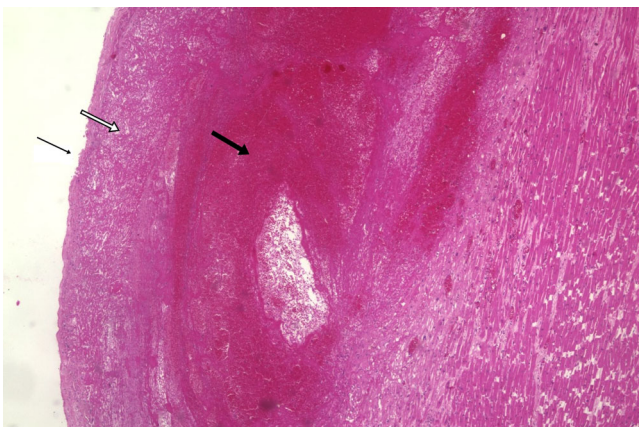

Fig. 9 Necrotic, hemorrhaged choriocarcinoma metastasis in the posterior wall of the left ventricle (*black arrow*) surrounded by loosely deposited fibrin (*white arrow*), which disrupts the subepicardial connective tissue (*thin arrow*). The mesothelial layer cannot be seen on the surface, because it disintegrated during the processing of the specimen

Cardiac metastases are generally uncommon. In case of a testicular primary they are usually localized intracavitary and can cause obstruction of the blood flow occasionally requiring surgery [13]. To our knowledge the case of our patient represents the first report of a subepicardial choriocarcinoma metastasis accompanied by pericardial hemorrhage and tamponade. This case also shows that life-threatening hemorrhage can still occur weeks after the initiation of chemotherapy. Finally we would like to emphasize that for all germ cell cancer patients, including cases with very advanced disease, the goal of treatment is cure and to achieve that, patients in this setting should be referred to comprehensive cancer centers experienced in the treatment of advanced germ cell malignancies.

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