



Case report

Case Report: Treatment of primary pulmonary choriocarcinoma with lung lobectomy and adjuvant chemotherapy

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1. Introduction

Choriocarcinoma is a germ cell tumor characterized by presence of syncytiotrophoblasts, cytotrophoblasts and production of β -human chorionic gonadotropin (β -hCG) (Jonathan and Berek, 2021). Choriocarcinoma of the gonads is known to exhibit rapid hematogenous spread, commonly to the lungs, but also to bone, liver, brain, and spleen. However, primary pulmonary choriocarcinoma (PPC) is very rare. More commonly, extragonadal primary choriocarcinomas occur in the retroperitoneum, mediastinum, or cranium (Wu, 2020).

Primary pulmonary choriocarcinoma is a particularly grave diagnosis that is commonly fatal. Its rarity results in a lack of standard therapy and late diagnosis. Its anaplastic nature makes PPC recalcitrant to treatment, which also contributes to the high mortality rate (Snoj et al., 2017). We report a patient who was diagnosed with PPC and was cured with surgical resection and adjuvant chemotherapy. We also provide a review of the PPC literature.

Case. A 37-year-old female presented to the emergency department for evaluation of recurrent syncopal episodes over two months. She had no significant medical or surgical history, was taking no medications, and denied smoking. She had one previous full-term pregnancy with an uncomplicated vaginal delivery 6 years prior. Vital signs on presentation were normal. Cardiac work-up, including echocardiogram, Holter monitoring, and chest x-ray were normal. Neurologic work-up, including electroencephalogram and brain magnetic resonance imaging (MRI), was also normal. Labs were significant only for a quantitative β -hCG of 160 mIU/mL. The patient was observed overnight in the hospital but ultimately discharged with suspected diagnosis of vasovagal episodes due to stress and pregnancy.

One week later the patient presented for a new obstetric visit, reporting uterine cramping and bleeding. β -hCG had increased to only 170 mIU/mL, and ultrasound showed no intrauterine gestational sac and

no ectopic pregnancy. One week later, β -hCG had increased to 226 mIU/mL, despite continued vaginal bleeding. Suction dilation and curettage was performed, with surgical pathology showing no products of conception. The patient received 3 doses of intramuscular methotrexate 50 mg/m² for suspected ectopic pregnancy. β -hCG continued to increase to 443 mIU/mL and remained elevated (213–413 mIU/mL) for 2 weeks despite methotrexate therapy. She underwent diagnostic laparoscopy and bilateral salpingectomy with surgical pathology showing no products of conception again.

The patient's β -hCG continued to be elevated at 278 mIU/mL 4 weeks later. Heterophilic antibody testing was negative. The patient was referred to gynecologic oncology, and computed tomography (CT) of her chest, abdomen, pelvis was notable for 1.5 cm \times 1.6 cm nodule in the left lung at the level of the left subclavian artery which was thought to be a benign hamartoma. Positron emission tomography (PET) showed no hypermetabolic activity of the left lung nodule, and no additional lesions. After extensive discussions with the patient, gynecologic oncology colleagues, and national gestational trophoblastic neoplasia experts, the decision was made to continue β -hCG and imaging surveillance without immediate treatment. β -hCG remained relatively stable for 2 weeks (704–715 mIU/mL), then increased to 930 mIU/mL. A blood sample was sent to an outside laboratory (Quest Diagnostics) for evaluation of hyperglycosylated hCG (hCG-H) (Cole, 2007). The β -hCG to hCG-H ratio was noted to be 42.6%, which was consistent with active neoplasia.

While waiting for the hCG-H results, the patient also had repeat chest, abdomen, and pelvis CT which showed an increase in the size of the left lung lesion to 1.9 cm \times 1.9 cm (Fig. 1). A CT-guided biopsy showed a poorly differentiated carcinoma containing few viable, malignant cells associated with extensive tumor necrosis. The tumor cells exhibited strong expression of pan-cytokeratin (AE1/AE3) and were moderately positive for β -hCG and negative for TTF-1 immunostain. The immunoprofile and histology including a rare syncytiotrophoblast along with the clinical history raised the possibility of choriocarcinoma

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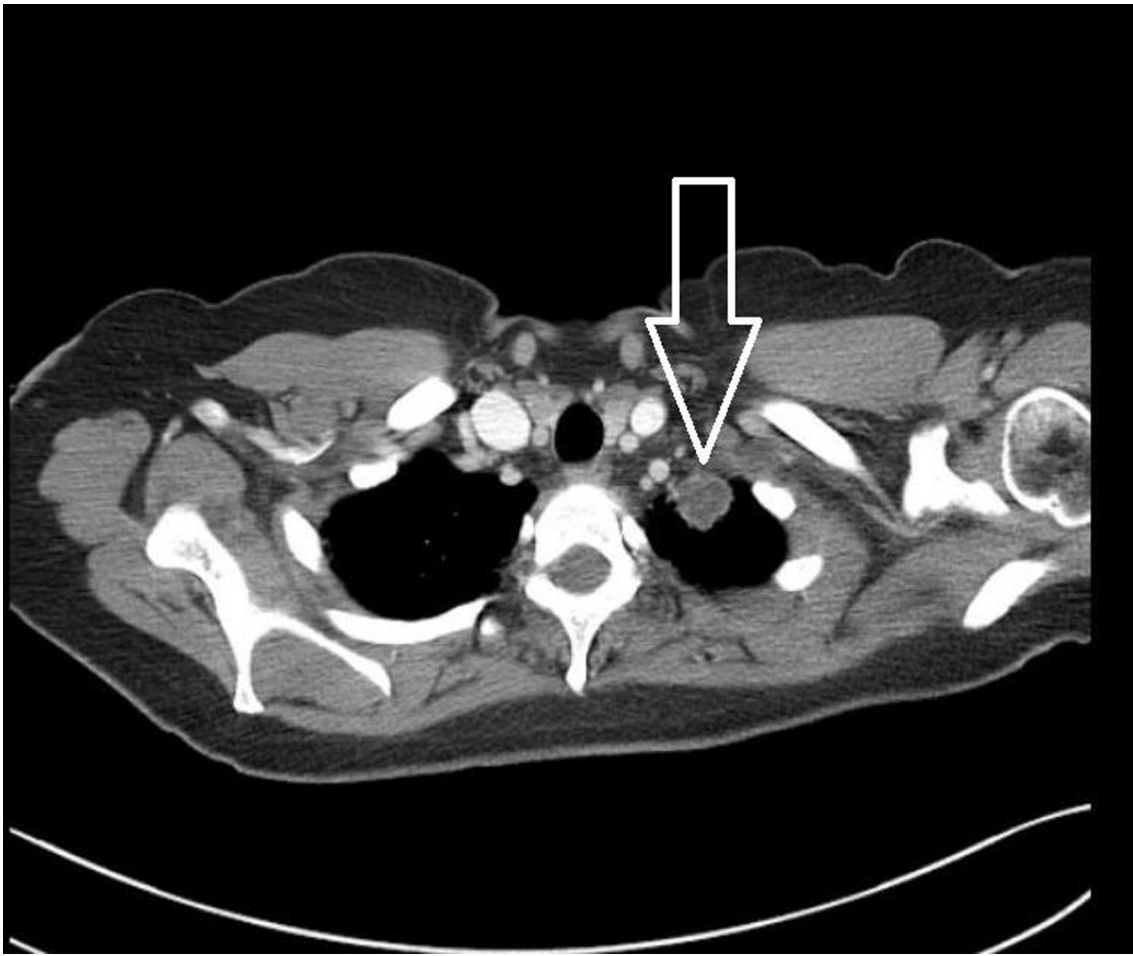


Fig. 1. Chest CT with left apical lung nodule.

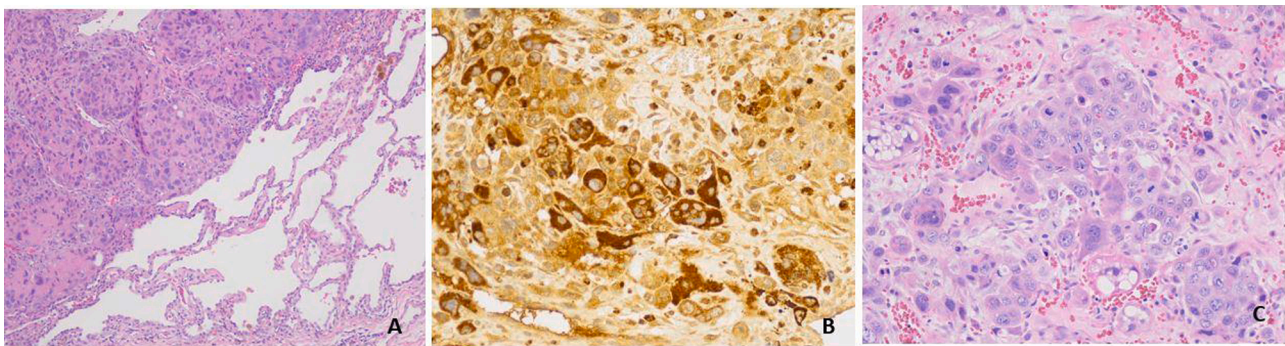


Fig. 2. Choriocarcinoma of lung – histologic and immunohistochemistry findings. (A) Sheets of mononuclear cytotrophoblastic cells on left with adjacent alveolar lung tissue on right (hematoxylin and eosin, magnification 100 \times). (B) Immunohistochemistry for β -hCG is positive in the tumor cells (magnification 200 \times). (C) Cytotrophoblasts with elevated mitotic activity and scattered multinucleate syncytiotrophoblastic cells (magnification 200 \times).

(Fig. 2). Follow-up chest CT 1 week later showed increase in the size of the lung lesion to >2 cm.

The patient underwent a left upper lobectomy with mediastinal lymph node dissection with cardiothoracic surgery. Surgical pathology was consistent with biopsy diagnosis of PPC. Preoperative β -hCG was 371 mIU/mL, and 1 day postoperatively the β -hCG had decreased to 16 mIU/mL; by 4 weeks postoperatively the β -hCG had normalized to <3 mIU/mL. Due to case reports of the aggressive nature of PPC, the patient received 3 cycles of adjuvant chemotherapy with bleomycin, etoposide and cisplatin (BEP) with a stable and normal β -hCG throughout treatment. Treatment side-effects included alopecia, fatigue, thrush,

bleomycin rash, Raynaud's Syndrome, and pancytopenia, all of which were manageable. After extensive discussions with the patient, the patient underwent a total laparoscopic hysterectomy with bilateral oophorectomy post-chemotherapy. Surgical pathology confirmed no evidence of malignancy in the gynecologic organs.

The patient was monitored with physical exams and β -hCG levels for 5 years with no evidence of recurrent disease. At the time of this report, 9 years after diagnosis, the patient remains alive and without disease.

2. Discussion

There are three primary theories for the mechanism by which a choriocarcinoma may originate outside the gonads (Onishi, 2022). The first of these is the primary lung lesion represents a metastatic lesion from a primary gonadal tumor which has spontaneously regressed by the time of diagnosis. PPC has also been postulated to arise from embryonic germ cells that inappropriately migrated from genitourinary structures to the lung. This is also what is thought to occur in primary choriocarcinomas discovered in the retroperitoneum, mediastinum, or cranium. Alternatively, some have postulated that PPC is a primary lung adenocarcinoma that has mutated to develop trophoblastic features, based on reports of lung lesions in which histologic adenocarcinomatous and choriocarcinomatous features were closely integrated in the same tumor (Yamamoto et al., 2006). Genomic analysis of PPC favors a non-gestational origin of disease, with no mutations in gestational genes, typically chromatin remodeling genes (*SMARCD1*, *EP300*, *ARID1A*). This is further supported by reports of PPC diagnosed in males, and postmenopausal and nulligravid females. Genomic analysis also shows frequent mutations in *EGF-R*, but no mutations in *TP53* or *K-RAS*.

Presenting symptoms of PPC are typically chest pain, dyspnea, vaginal bleeding, and seizures (due to brain metastases), and these symptoms generally represent advanced disease (Serno, 2012). Additionally, patients with PPC are noted to have high β -hCG or positive pregnancy test. It is notable the patient described here had a relatively mild elevation in β -hCG compared to those reported in the literature. A form of hCG with function independent of β -hCG, hcg-H, has also been noted to be elevated in cases of trophoblastic disease and is thought to drive progression (Cole, 2007). A hcg-H to β -hCG ratio of $> 40\%$ is indicative of an aggressive neoplasm. It should be noted that choriocarcinoma can be challenging to identify using PET imaging, with mixed reports of avidity studied in non-seminomatous tumors (Thomas et al., 2020). Most reports studying germ cell tumor imaging has been performed in the setting of testicular germ cell tumors. In one study, PET had slightly lower false negative rates than CT, and the authors suggested PET had utility primarily in the setting of indeterminate findings on CT (de Wit, 2008).

A review by Kim et al. in 2020 characterized all then-known cases of PPC (Kim et al., 2020). Median survival for patients with PPC was 8 months (Serno, 2012). Poor prognostic factors include tumor size > 5 cm, age > 40 years, smoking status, and advanced stage disease. Age at time of diagnosis had a wide range, from 4 months to 77 years. Only 51 of the reported 65 patients received treatment and 17 of those died of their disease. The remaining 14 patients died prior to being able to receive treatment. Male patients were more likely to die of this disease. Additionally, the average age of female patients at diagnosis was 18 years younger than men at diagnosis. Women with history of prior pregnancy, abortion, or molar pregnancy had better prognosis (Snoj et al., 2017). The review showed similar outcomes regardless of whether the patient received surgery only, chemotherapy only, or surgery and chemotherapy +/- radiation (Kim et al., 2020). However, a review by Snoj et al in 2017 indicated better survival outcomes for patients treated with both surgery and chemotherapy (Snoj et al., 2017).

PPC is invariably fatal without treatment. Like choriocarcinoma originating in the gonads, PPC has most commonly been treated with chemotherapy regimens of BEP or etoposide-methotrexate-actinomycin-D-cyclophosphamide-vincristine (EMACO). Due to reports of PPC diagnoses in males and genomic analysis suggesting gonadal rather than gestational origin, BEP chemotherapy was chosen for adjuvant treatment for our patient. It is notable that VIP has less risk of pulmonary toxicity compared to BEP, and should be considered in patients with PPC who undergo lung resection (Hinton, 2003). In a review of 14 male patients with PPC, only two survived longer than 5 years (Ji and Park, 2021). All patients were treated with multiagent chemotherapy, including BEP, etoposide-ifosfamide-cisplatin (VIP), EMACO, and cisplatin-vincristine-methotrexate-bleomycin (POMB). Regardless, most

disease develops resistance to cytotoxic therapy despite initial response, partially contributing to the high mortality for PPC.

PD-L1 has been shown to be highly expressed in choriocarcinoma syncytiotrophoblasts (Veras et al., 2017), and there are studies demonstrating efficacy of checkpoint inhibitors for treatment of gestational trophoblastic neoplasia. One case report showed efficacy of a checkpoint inhibitor for treating metastatic and chemoresistant gestational trophoblastic neoplasia, with normalization of β -hCG and decreased size of lung nodules. She had stable disease for 22 months and was re-started on pembrolizumab when new lymphadenopathy was identified on surveillance PET-CT at time of publication (Goldfarb et al., 2020). In a clinical trial using avelumab to treat methotrexate-resistant gestational trophoblastic disease, 53% of participants had normalization of β -hCG. Of the patients who had been successfully treated, none had recurrence after median follow up time of 29 months (You, 2020). The response of non-gestational choriocarcinoma to checkpoint inhibitors is less clear. Genetic analysis comparing gestational vs. non-gestational choriocarcinoma has shown gestational choriocarcinoma has significantly more somatic mutations than non-gestational choriocarcinoma (Lazare, 2019). Additionally, non-gestational choriocarcinoma had many enhancements in genes that are also enriched in graft-vs-host disease indicating that efficacy of immunotherapy may be more limited in non-gestational choriocarcinoma. It is unclear at this time what these genomic observations indicate for future treatment options and much genomic analysis remains in the basic or translational level of study.

In conclusion, PPC remains a difficult disease to treat in the metastatic setting due to relative chemoresistance compared to its gestational counterpart. Early identification of disease which is amenable to surgical resection has the potential for cure. An index of suspicion and evaluation of sites of disease outside of the reproductive tract in the setting of an unexplained persistently elevated β -hCG may result in earlier diagnosis and better outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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