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Case Report

A 54-year-old Man with Primary Mediastinum Choriocarcinoma

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Abstract

Primary mediastinum choriocarcinoma, an extragonadal germ cell tumor, is a rare malignant tumor that is more common in men. We present a case of primary mediastinum choriocarcinoma in a male patient who initially presented with gynecomastia and progressed to superior vena cava syndrome. Both surgical biopsy and pathologic diagnosis were challenging. After standard induction chemotherapy, the resected tumor underwent squamous cell transformation, which has rarely been reported in cases of choriocarcinoma. His critical condition was resolved using induction chemotherapy with a combination of bleomycin, etoposide, and cisplatin, followed by resection of the residual tumor. However, tumor recurrence occurred 9 months later, and he was treated with salvage radiotherapy and chemotherapy. This was a rare and challenging case from the aspects of initial approaches, pathologic differential diagnosis, and different treatment modalities.

Keywords: Outcome, primary mediastinal choriocarcinoma, treatment

Introduction

Primary mediastinal choriocarcinoma, an extragonadal germ cell tumor (GCT), is a rare malignant tumor that is more common in men. Testicular GCTs comprise over 95% of all testicular malignancies, and fewer than 5% of GCTs have an extragonadal origin. GTCs diagnosed during early metastasis have a poor prognosis. The management of primary mediastinal choriocarcinoma includes induction chemotherapy and surgery. Herein, we present the case of a male diagnosed with primary mediastinal choriocarcinoma who initially presented with gynecomastia, followed by progression to dyspnea and a puffy face.

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Case Report

A 54-year-old male bus driver presented with pain and fullness in the left breast, without discharge, for 3 months, following onset in March 2015. A general surgeon identified a left induration mass on physical examination. Ultrasonography of his breast did not reveal any tumors; however, the symptoms persisted. He had a smoking history of 35 years, as well as a history of hypertension, which was controlled with medication.

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Two months later, he suffered an acute onset of severe chest pain radiating from the left side to the back and cold sweats. He also reported facial swelling and dyspnea upon exertion occurring for several days prior to the onset of chest pain. A chest examination revealed mild respiratory distress, right decreased breath sounds, and right jugular vein engorgement. A chest X-ray showed mediastinum widening and haziness of the right lower chest field [Figure 1]. Computed tomography (CT) of his chest identified an anterior mediastinum mass measuring 5 cm × 11.7 cm, with invasion of the anterior wall of the superior vena cava (SVC), right upper lobe (RUL) and right middle lobe (RML), and right pleural effusion. It also showed a hypodense segment 4 liver mass measuring 4.2 cm, and a nodule over the left lingular lobe measuring 0.8 cm, which was thought to be metastases [Figure 2]. A biopsy of the mediastinum mass via video-assisted thoracoscopic surgery (VATS) with mediastinotomy was inconclusive. Carcinoma was eventually identified after testing frozen biopsy sections multiple times. Levels of alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-HCG), both of which are GCT markers, were 4.80 ng/mL and 18086.6 mIU/mL, respectively.

Immunohistochemical (IHC) analysis of the mediastinum mass revealed it was negative for CD5, Thyroid transcription factor-1, CK5/6, CD56, AFP, CD30, GPC-3, OCT3/4, SOC2, and a-inhibin, but positive for HCG [Figure 3a] and AE1/AE3 [Figure 3b], indicating that it was unlikely to be lung cancer, thyroid cancer, yolk sac tumor, embryonal carcinoma, or seminoma. Ultrasonography of the testis was normal. The final pathologic report diagnosed the tumor as a primary mediastinum choriocarcinoma.

The patient underwent four cycles of induction chemotherapy with monthly bleomycin/etoposide/cisplatin (BEP), after which the level of beta-HCG decreased to 2.9 mIU/mL, dyspnea and facial swelling symptoms subsided, and the metastases totally regressed. However, invasion of the SVC, RUL, and RML by the residual anterior mediastinum mass, which measured 7 cm, was still noted on CT. He underwent *en bloc* resection of the anterior mediastinum mass, wedge resection of the tumor-attached RUL and RML, and tumor separation from the SVC by VATS. IHC analysis of the resected tumor revealed that it had poorly differentiated features [Figure 4a] and that it was positive for both P40 [Figure 4b] and P63 [Figure 4c]. After histological and IHC analyses, two rare differential diagnoses of HCG-secreting large cell lung cancer and primary mediastinum choriocarcinoma with squamous cell transformation were considered. The former may have resulted from *in situ* lung cancer cells invading the mediastinum, with the subsequent appearance of a residual lung cancer lesion following induction chemotherapy. This case was passed to our tumor board for discussion. Although both tumor types are sensitive to a BEP chemotherapy regimen, large cell lung cancer is generally more aggressive with a poor prognosis. The response rate of GCTs when using a standard BEP regimen is 70%. Therefore, from the pathologic report and clinical course,

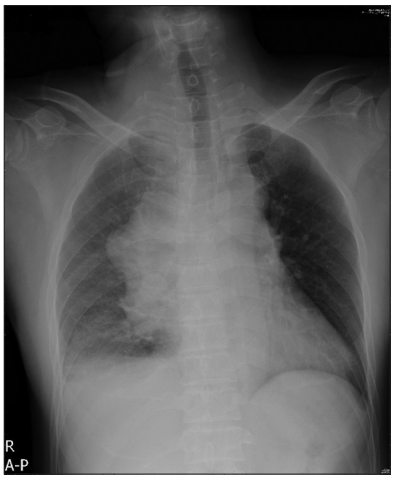

Figure 1: A chest radiograph showed mediastinum widening and haziness of the right lower chest field

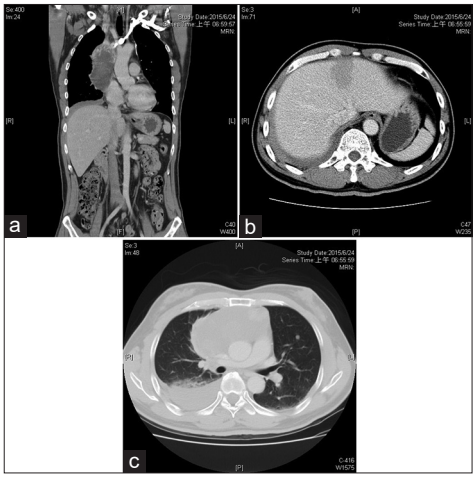

Figure 2: Computed tomography revealed an anterior mediastinum mass with invasion of the superior vena cava, right upper lobe, and right middle lobe (a), a hypodense segment 4 liver mass, (b), and a nodule over the left lingular lobe (c)

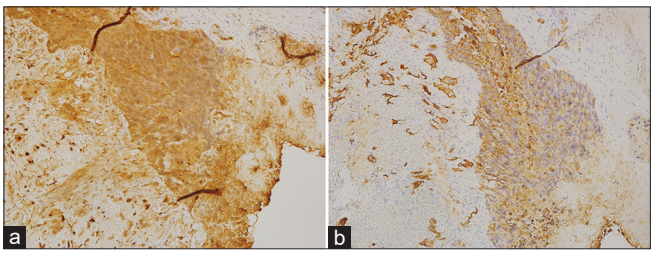

Figure 3: Immunohistochemical analysis of the mediastinum mass revealed human chorionic gonadotropin+ (a) and AE1/AE3+ (b) Negative markers were not observed

the tumor board made a final diagnosis of primary mediastinum choriocarcinoma with squamous cell transformation.

Nine months postoperatively, the beta-HCG level had increased to 243.6 mIU/mL. Positron emission tomography/CT identified recurrence of the anterior mediastinal mass with contralateral hilar nodal metastasis. The patient received local irradiation

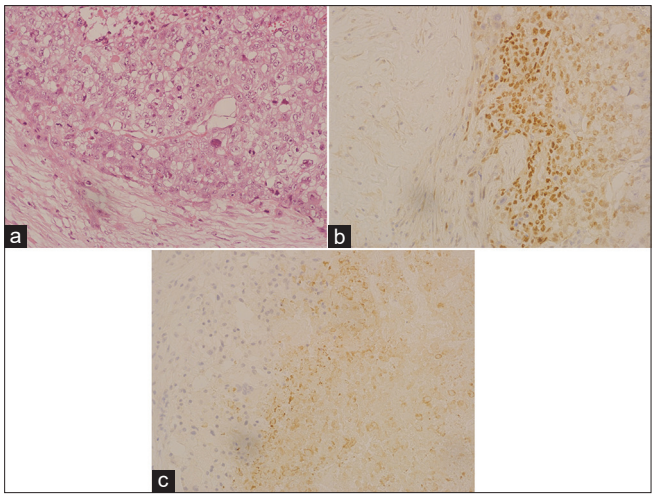

Figure 4: Immunohistochemical analysis of the resected tumor showed that it had poorly differentiated features (a) and that it was positive for both P40 (b) and P63 (c)

with 6600 cGy/33 fractions and 5600 cGy/28 fractions to the left hilar and anterior mediastinum mass, respectively. One month after irradiation (December 2016), he developed an unsteady gait and left-sided weakness and numbness lasting for 4 days. A neurologic examination showed mildly decreased left upper and lower proximal muscle power without obvious sensory loss and left arm dysmetria. Brain magnetic resonance imaging revealed a right pontomesencephalic tumor measuring 29 mm in diameter. A systemic workup including chest CT revealed regression of the left hilar lesion without local recurrence of the mediastinum tumor. However, nodular metastases in the inferior lingular segment of the left upper lobe, RML, right lower lobe, and spleen were noted. Beta-HCG and AFP levels were 1514.7 mIU/mL and 7.90 ng/mL, respectively. The AFP level remained within the normal range. He then received whole-brain irradiation with 3000 cGy/10 fractions, and palliative chemotherapy of gemcitabine/cisplatin followed by gemcitabine alone, from January to May 2017 and August to November 2017, respectively. After completing doublet chemotherapy, the beta-HCG level decreased to 22.3 mIU/mL but increased to 176 mIU/mL during monotherapy. Repeat CT revealed disease progression with enlarged left pulmonary hilum and bilateral lung metastases. He developed a serologic response to another course of palliative chemotherapy using vinblastine, ifosfamide, and cisplatin (VIP). However, the symptoms of unsteady gait and ataxia recurred. Follow-up brain CT showed multiple brain metastases in bilateral cerebral hemispheres, which were treated with whole brain irradiation with 3000 cGy/10 fractions. Due to disease progression and despite receiving multiple lines of chemotherapy, the patient died on July 14, 2019.

Discussion

The most common causes of gynecomastia in men are persistent pubertal gynecomastia (25% of cases), drugs (10%–25%), idiopathic (25%), cirrhosis or malnutrition (8%), and hypogonadism (8% primary, 2% secondary). Less frequent etiologies include testicular tumors (3%), hyperthyroidism (1.5%), and chronic renal insufficiency (1%).[1] A careful history should be taken from patients, including symptoms of liver and kidney disease, hyperthyroidism, and hypogonadism, and the use of medications, dietary supplements, and herbal products. Physical examinations should include nutritional status, abdomen palpation, and testicular size/consistency. Measuring serum levels of testosterone, follicle-stimulating hormone, luteinizing hormone, HCG and its beta form, testosterone, and estradiol may be helpful in making a diagnosis. The classic triad of symptoms for primary mediastinum choriocarcinoma in men includes cough, gynecomastia, and chest pain. Gynecomastia is linked to the production of chorionic gonadotropin and has been reported in two-thirds of men with mediastinum choriocarcinoma.[2] Other reported symptoms include dyspnea, chest pain, cough, and SVC syndrome.[3]

The reported prevalence of anterior mediastinal masses is low, accounting for 0.4% of diagnoses after lung cancer CT screening of asymptomatic people in the United States.[4] The most commonly found anterior mediastinal masses are thymoma, GCT, lymphoma, and thyroid tissue. A biopsy of adequate tissue is needed to confirm the diagnosis of mediastinal masses. Extragonadal GCTs are typically diagnosed by a core-needle or open biopsy. In rare cases, treatment may begin before histological confirmation because of severe symptoms; otherwise, a biopsy and tumor marker levels should be obtained prior to treatment. Minimally invasive approaches including mediastinoscopy and VATS can be tried prior to open surgical approaches. Assessment of the adequacy of biopsy samples should be carried out with frozen sections. If necessary, additional biopsies should be performed while the patient is still sedated or anesthetized.

Testicular GCTs comprise over 95% of testicular malignancies, and fewer than 5% of GCTs have an extragonadal origin. The international germ cell cancer collaborative group (IGCCCG) categorized mediastinum choriocarcinoma as poor risk.[5] A 2006 IGCCCG updated meta-analysis reported 5-year survival estimates for patients with nonseminomatous GCTs classified as being good-, intermediate-, and poor-risk of 94%, 83%, and 71%, respectively.[6] The standard management of primary mediastinum choriocarcinoma includes induction chemotherapy and according to the response and tumor marker levels, surgical resection. If yolk sac, choriocarcinoma, embryonal, or seminoma elements are identified in the residual tumor, salvage chemotherapy should be administered. The role of radiotherapy is not clear after residual tumor resection or in the absence of seminoma histology. Standard first-line induction chemotherapy uses a BEP regimen.[7-9] Approximately, 6%–8% of resected tumors show evidence of non-GCT malignancy arising from malignant transformation of GCTs.[10] Limited reports exist regarding teratoma status postinduction chemotherapy and resection, in which specimens showed malignant transformation, and physicians chose

chemotherapy according to specimen histology,[11,12] while no such data are available for choriocarcinoma. Transformation of the resected mediastinum choriocarcinoma was observed in our patient. As sparse evidence of adjuvant radiotherapy to the tumor bed in mediastinum choriocarcinomas is available, we did not treat this patient with radiotherapy after resection. In addition, no study supports the addition of chemotherapy after a salvage operation for residual tumors with squamous transformation. After discussion with the patient, we did not administer chemotherapy.

Nine months postoperatively, the patient experienced tumor recurrence. For recurrence following the first-line therapy, treatment options include chemotherapy and surgery if the recurrence is a solitary lesion. There are limited data regarding the utility of radiotherapy in nonseminoma metastases outside the brain; nonetheless, we applied radiotherapy for recurrent left hilar and anterior mediastinum masses due to the difficulties with surgical intervention. However, he developed multiple metastases, including the brain. We administered gemcitabine/cisplatin and VIP chemotherapy as the second- and third-line chemotherapy regimens, respectively. Our choice of the second-line chemotherapy (gemcitabine/cisplatin) is often regarded as the next regimen beyond BEP and VIP. We chose this regimen in advance due to the pathologic report of lung cancer origin. We also referred to previous studies[11,12] on teratoma with malignant transformation and chose gemcitabine/cisplatin due to the possible lung origin with squamous histology. The patient developed a serologic response after the second- and third-line chemotherapies.

Brain metastases occur almost exclusively in patients with nonseminoma histology and are more common in patients with a high tumor burden, including lung and liver metastases and high levels of serum B-HCG (>5000 IU/L).[13] Due to the lack of evidence, the optimal management of brain metastases from nonseminoma GCTs remains controversial, and both surgical resection and radiotherapy can be considered. However, the prognosis of patients with brain metastases is poor, with >50% of patients dying within 1 year of diagnosis. Our patient survived for more than 2 years after brain metastasis.

In conclusion, we presented a case of primary mediastinum choriocarcinoma with a symptom pattern, differential diagnoses clinically and pathologically, and curative and palliative treatment regimens; this has rarely been reported previously. Although guidelines for GCTs are in place, the management of resected choriocarcinoma with pathologic squamous transformation after induction chemotherapy remains to be established. This case report provides an appropriate approach, including differential diagnosis and treatment, which may be helpful in clinical practice.

Acknowledgments

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Ethics

This study's protocol (Institutional Review Board approval number: 201900720B0) was approved by a local research ethics committee at Chang Gung Memorial Hospital, Taiwan. The Institutional Review Board agreed that no informed consent form should be submitted for this case report. The treatment for this patient was fully discussed and authorized by our tumor board.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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