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Case Report

Primary choriocarcinoma of the lung: a case report and literature review

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Abstract: Choriocarcinoma is a highly aggressive malignant germ cell tumor containing syncytiotrophoblasts and secreting β-hCG with a poor prognosis. Most of the choriocarcinomas are associated with gestational events and occur in the female genital tract. Primary choriocarcinoma of the lung is extremely rare and fewer than 30 cases have been reported to date. Here we report a surgically treated case of primary pulmonary choriocarcinoma in a 37-year-old woman. Surgery was followed by chemotherapy with bleomycin, etoposide, and cisplatinum. The patient was alive at 3-year follow-up and was in good condition.

Keywords: Choriocarcinoma, lung, human β-hCG

Introduction

Choriocarcinoma is a highly aggressive germ cell neoplasm composed of syncytiotrophoblasts, cytotrophoblasts, and variable intermediate trophoblasts and secreting human chorionic gonadotropin β-subunit (β-hCG). Most cases of choriocarcinoma occur in the female genital tract after a gestational event such as molar pregnancy, term pregnancy, or ectopic pregnancy. Outside the uterus, it can rarely occur as a midline lesion in the mediastinum, retroperitoneum, or pineal gland in both sexes. Primary pulmonary choriocarcinoma is extremely rare with only less than 30 cases in the literature to date [1-4]. Herein we report a case of primary pulmonary choriocarcinoma in a 37-year-old woman initially mimicking squamous cell carcinoma histopathologically.

Case report

A 37-year-old woman without pregnancy history (G_0P_0) presented to our hospital with cough, dyspnea, chest pain, and hemoptysis with weight loss of 4 kilograms. She also had a smoking history for ten years with one pack per day. Chest computed tomography (CT) scan image revealed a huge 16 × 14 cm heterogeneous enhancing mass with necrosis in the right lower lobe of lung (**Figure 1**). Initial laboratory data showed alpha-fetoprotein (AFP) level was 1.24 ng/mL, and squamous cell carcinoma-associated antigen (SCC-Ag) was 0.27 ng/mL. With the impression of malignant lung cancer, she was referred to thoracic surgery unit and underwent video-assisted thoracoscopic wedge resection of the right lower lobe of lung for tissue proof of the lesion.

Histopathologic examination of the tumor mass showed extensive hemorrhage and necrosis. Foci of cohesive sheets of viable tumor cells showed prominent cellular atypia, and nuclear pleomorphism with hyperchromatic nuclei (**Figure 2A**). Multinucleated tumor giant cells were also seen (**Figure 2B**). Poorly differentiated squamous cell carcinoma (SCC) was initially considered. However, diagnostic features of SCC such as intercellular bridge or keratin formation were not present in the tumor. In addition, immunohistochemical stains for SCC marker P40 and adenocarcinoma marker TTF-1 (thyroid transcription factor-1) were negative (**Figure 2C**, **2D**). Further immunostains revealed that tumor cells were reactive for cytokeratin AE1/AE3, strong and diffusely positive for β-hCG and HSD3B1 (hydroxy-delta-5-steroid

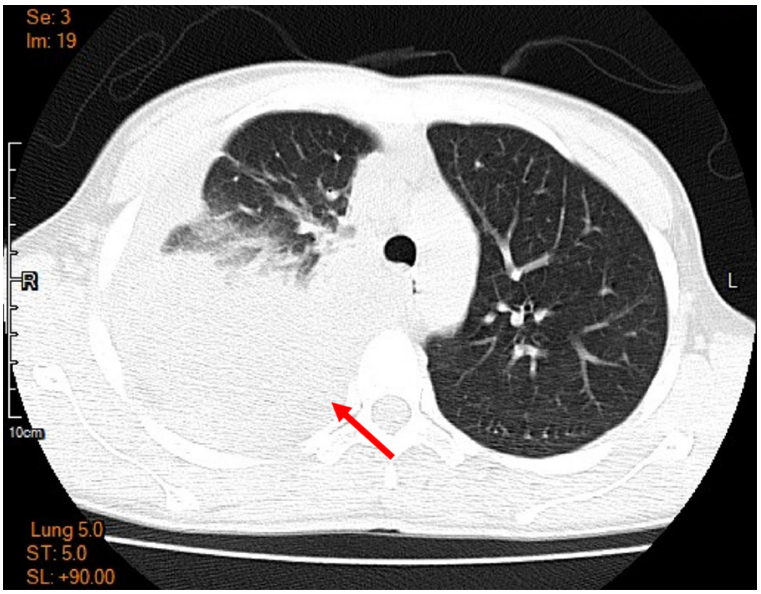

Figure 1. Chest CT (lung window setting) showed a huge 16 × 14 cm tumor mass in the right lung (arrow).

dehydrogenase, 3 beta- and steroid delta-isomerase 1, a highly specific trophoblast-associated marker) [5], and had nuclear staining for SALL-4 (Sal-like protein 4) (**Figure 2E-H**). There were no tumor emboli found in the specimen. Based on the morphology and immunohistochemical study results, the tumor was diagnosed as choriocarcinoma. Immediate measurement of serum β-hCG level of the patient after diagnosis was 233,318 mIU/mL (normal <5 mIU/mL). Subsequent gynecologic examination by ultrasonography, whole body CT scan including pelvis and brain showed no abnormal findings. The patient received bleomycin/etoposide/cisplatinum (BEP) chemotherapy regimen and the serum β-hCG level decreased to 164.9 mIU/mL two months after initial treatment, and further decreased to 24.5 mIU/mL four months after chemotherapy. The patient underwent a second operation for right lower lobe lobectomy and right middle lobe wedge resection for complete tumor removal five months after initial chemotherapy. Pathologic examination of the residual tumor mass showed complete necrosis with surrounding granulation tissue and fibrotic stroma, consistent with status post chemotherapy (not shown). The patient regularly attends the outpatient department for follow-up care and no recurrence or distant metastasis was noted up to 3 years after operation.

Discussion

Choriocarcinoma is a rare malignant germ cell tumor of trophoblastic origin composed of trimorphic trophoblasts, including multinucleated syncytiotrophoblasts, mononuclear cytotrophoblasts, and intermediate trophoblasts. The syncytiotrophoblasts are responsible for the production of β-hCG. The pathogenesis of primary choriocarcinoma of lung remains elusive. Three hypotheses have been proposed for the development of primary pulmonary choriocarcinoma [6-11].

First, the most common form of choriocarcinoma is gestational choriocarcinoma, which is developed intra- or extrauterinely following a gestational event such as complete hydatidiform mole, or less often from partial hydatidiform mole. Choriocarcinoma may also develop after a normal or an ectopic pregnancy [10, 12]. Typical gestational choriocarcinoma usually presents with abnormal vaginal bleeding and extremely high β-hCG level in serum or urine. Up to 3/4 of patients have lung metastasis at the time of diagnosis [13]. Choriocarcinoma of the lung may represent metastases from undetected trophoblastic disease, which might undergo a spontaneous regression and only leaving scarring of uterine, the so called “burn-out” phenomenon that is a unique and specific feature of choriocarcinoma which is likely to be metastatic before detection of the primary lesion [6, 7]. It is also possible that the lung choriocarcinoma develops from trophoblastic emboli in lung related to molar pregnancy after a long period of latency.

Second, choriocarcinoma outside of a gestational event, that is, non-gestational choriocarcinoma, occurs in children and young adults in some midline structures such as gonads, mediastinum, retroperitoneum, intracranium (pineal gland, pituitary gland), liver, bladder, stomach, colon, and lung. It has been hypothesized that the retained primordial germ cells may migrate abnormally during embryonic development into

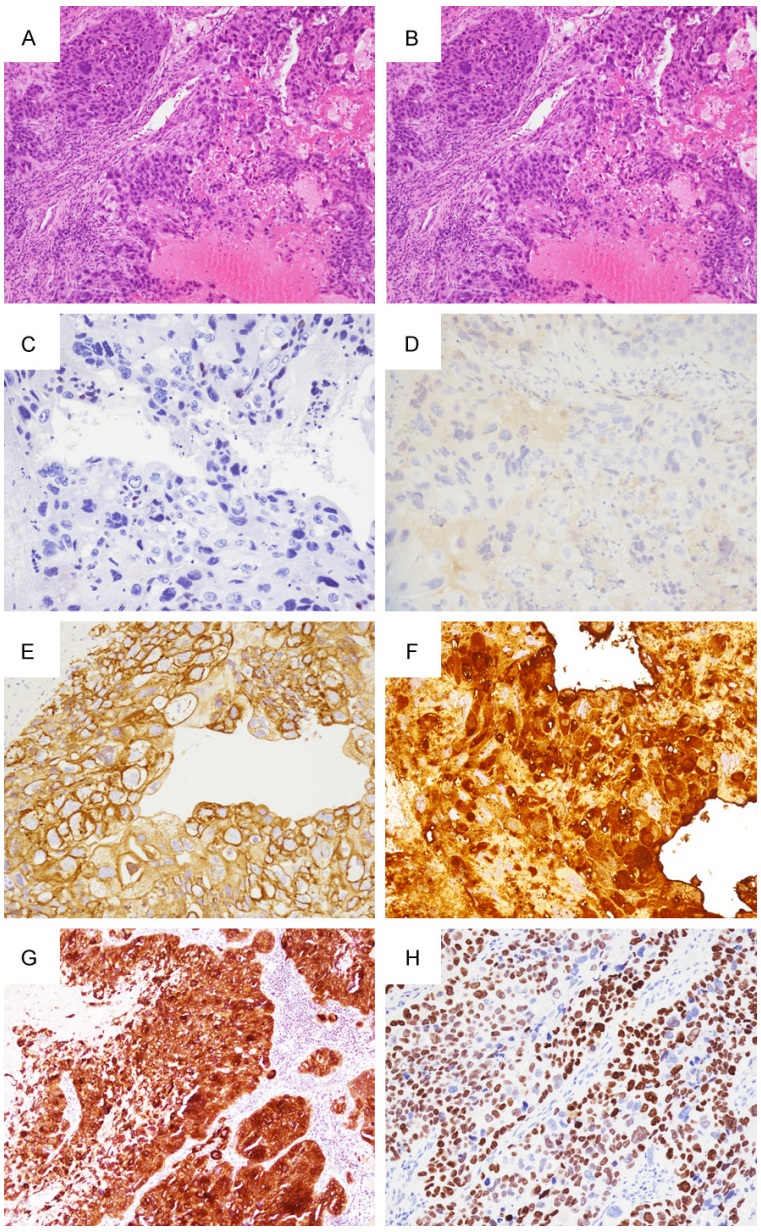

Figure 2. (A) Hemotoxylin and eosin (H&E) stain of the right lung tumor showed sheets of highly pleomorphic tumor cells with hyperchromatic nuclei and large areas of hemorrhage and tumor necrosis (bottom) (100 ×). (B) Higher magnification of tumor showed a large, hyperchromatic multinucleated syncytiotrophoblast (arrow) and surrounding mononuclear cytotrophoblasts and intermediate trophoblasts (200 ×, H&E stain). Immunohistochemical stains for squamous cell carcinoma marker P40 (C), and adenocarcinoma marker TTF-1 (D) were negative in tumor cells. Tumor cells were immunoreactive for cytokeratin AE1/AE3 (E), diffuse strongly positive for β-hCG (F), trophoblastic marker HSD3B1 (G), and germ cell marker SALL4 (H) (200 ×).

the above-mentioned locations and develop into choriocarcinoma [7-9, 11]. Although there is no morphologic difference between gestational choriocarcinoma and non-gestational choriocarcinoma, the behavior of non-gestational choriocarcinoma is much more aggressive with poorer prognosis, and resistant to various treatments including surgery, radiotherapy, and chemotherapy [14].

The third hypothesis of the origin of primary pulmonary choriocarcinoma postulates that it may arise from dedifferentiation or trans-differentiation from nongonadal tissue such as primary lung cancer to trophoblast. It has been reported that trophoblastic differentiation may occur in primary lung carcinoma such as adenocarcinoma [11]. Immunohistochemical findings including TTF-1, β-hCG, placental alkaline phosphatase, epithelial membrane antigen, and surfactant apoprotein A support a combination of choriocarcinoma and adenocarcinoma of lung [11].

In the present case, both the possibilities of non-gestational choriocarcinoma of lung and a trophoblastic differentiation from lung parenchymal tissue could not be completely ruled out. The pathologic findings showed syncytiotrophoblasts and cytotrophoblasts without a component of primary lung squamous carcinoma, adenocarcinoma or tumor emboli. This may also rule out a metastatic choriocarcinoma and trans-differentiation from primary lung cancer. Albeit rare, the diagnosis of choriocarcinoma arising in the lung should be made carefully with combination of morphology and immunohistochemical tools in the light of the differential diagnosis.

Disclosure of conflict of interest

None.

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