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Case report

Amenorrhea and elevated βhuman chorionic gonadotropin of unknown origin: An unexpected location of choriocarcinoma

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ABSTRACT

Choriocarcinoma is a rare malignancy originating from trophoblastic cells that is known to arise from the placenta. In this report, we describe the case of a 28-year-old female who consulted for amenorrhea and elevated βhCG mimicking a pregnancy of an unknown location, which ultimately turned out to be primary choriocarcinoma of the lung.

1. Introduction

Choriocarcinoma is a rare malignancy originating from trophoblastic cells. It is composed of cytotrophoblasts and syncytiotrophoblasts producing βhuman chorionic gonadotropin (βhCG) (Yen et al., 2019). Mostly, these tumors arise from the placenta. They are known to metastasize to the lungs, the liver, and to the brain (Yen et al., 2019). In rare cases, choriocarcinomas can originate in extragenital areas, mainly in midline structures such as the retroperitoneum, mediastinum, and pineal gland (Yen et al., 2019). In very few cases, choriocarcinomas were reported to arise in the stomach, the bladder and in the lung. (Nguyen et al., 2020).

Herein we report a case of a young premenopausal female diagnosed with primary choriocarcinoma of the lung (PCL) presented as a pregnancy of an unknown location.

2. Case description

A 28-year-old female presented to the gynecology department in 2014 for three-month amenorrhea, vomiting, and right-sided chest pain. The patient was in a good health condition and had a history of two pregnancies: one early spontaneous miscarriage in 2009 and one pregnancy carried to term in 2011. No histopathological verifications were performed after these two pregnancies. Transvaginal and pelvic ultrasonography did reveal neither intra nor extrauterine pregnancy. Blood tests were performed revealing a βhCG level of 1965 mIU/mL (normal < 1.2 mIU/ml), which remained stable after 48 h. The patient was admitted to the gynecology department and underwent exploratory laparoscopy ruling out extrauterine pregnancy. Ovaries had normal presentation without any abnormal mass or cyst. Suction dilation and curettage under ultrasound control were performed and the pathology exam confirmed the absence of an intrauterine pregnancy. Since the patient reported lower right-sided chest pain, a chest x-ray was performed revealing a heterogeneous opacity with ill-defined borders (Fig. 1). One day later, an MRI of the chest, abdomen, and pelvis was performed revealing a 5 × 5 × 4.6 cm complex cystic and solid tumor of the superior segment of the lower lobe, with a heterogeneous T2 enhancement and a central T1 and T2 enhancement. No fatty components were identified within the mass and no other abnormalities were described in the abdomen and pelvis.

The patient was referred to the department of thoracic surgery and underwent a right inferior lobectomy with a nodal assessment. The tumor presented as a 5 × 4.5 intrapulmonary brownish-yellow mass with extensive necrosis and hemorrhage and well-defined borders within the superior segment of the lower lobe. Microscopic examination showed a poorly-differentiated tumor made of large cells with variable morphology (round, spherical and fusiform cells) displaying abundant eosinophilic cytoplasm and large multinucleated cells with multi-

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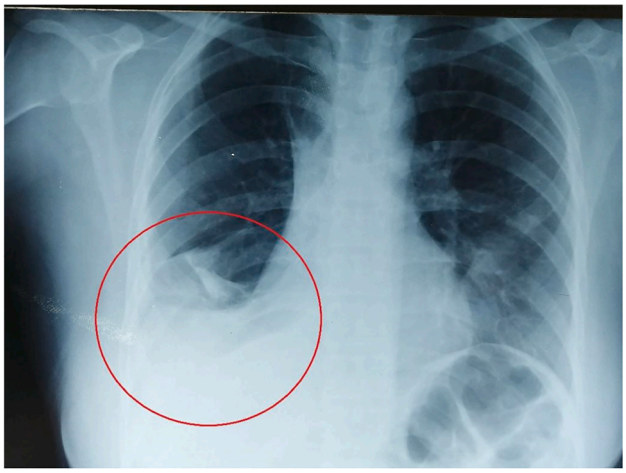

Fig. 1. Chest x-ray was performed revealing heterogeneous opacity with ill-defined borders.

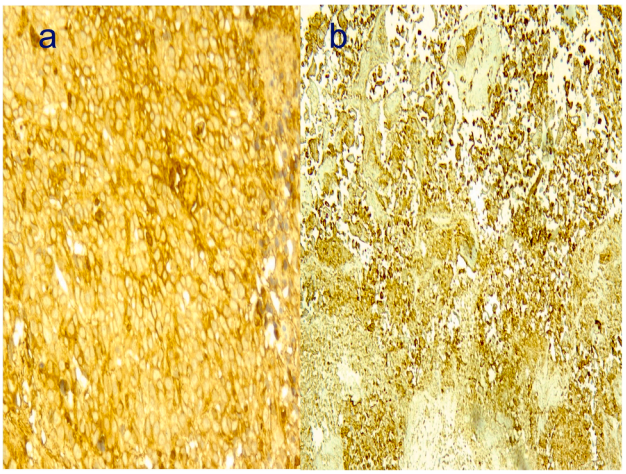

Fig. 3. Malignant cells expressing cytokeratin (a) and βhCG (b) in immunohistochemistry (x250).

lobulated nuclei suggesting syncytiotrophoblastic origin (Fig. 2). The tumor infiltrated the visceral pleura and vascular invasions were observed. Immunohistochemistry analysis showed the expression of the cytokeratin (Fig. 3), the cytokeratin 7, EMA, and βhCG antigens (Fig. 3). The tumor cells did not express the CD117 antibody. Facing these morphological and immunohistochemical features, the diagnosis of choriocarcinoma was made. On day 7 postoperatively, the βhCG level was 5.8 mIU/mL. Brain MRI was performed ruling out brain metastases. The multidisciplinary team decided to conduct adjuvant methotrexate-based chemotherapy every two weeks (1 mg/kg on days 1,3,5,7 with 0.1 mg/kg leucovorin on days 2, 4, 6, and 8). The patient received a total of 4 courses of methotrexate. Decline of βhCG levels was noted after the first cycle. Currently, the patient is disease-free and completely asymptomatic after a six-year follow-up period. She had one normal term delivery at a three-year follow-up and now, she is 18 weeks pregnant.

3. Discussion

Our report illustrates a tricky case where the diagnosis of PCL was unexpected at the gynecology department facing amenorrhea with elevated βhCG levels.

In fact, PCL is an extremely rare disease that was first described in 1956 by Schulz et al (Rali et al., 2017), and up to 2017, only 55 cases have been reported. To understand the genesis of this disease, some theories have been postulated previously: PCL could have originated from (1) a metastasis of an unnoticed gestational choriocarcinoma that regressed spontaneously, (2) a trophoblastic embolus during the gestational event with prolonged latency, (3) germ cells that have migrated abnormally during embryogenesis, (4) a primary lung cancer with trophoblastic differentiation, and finally (5) there is a possibility that giant cell carcinoma of the lung and primary lung choriocarcinoma would be the same entity eventually (Rali et al., 2017; Snoj et al., 2016; Yen et al., 2019). Diagnosis is established based on four main diagnostic criteria (Rali et al., 2017; Di Crescenzo et al., 2013; Snoj et al., 2016) including: (1) the absence of gestational trophoblastic disease history, (2) the clinical presentation of the tumor as a solitary or predominant lung lesion after ruling out a gestational origin, (3) elevated βhCG levels and their normalization after surgical excision and/or appropriate chemotherapy and finally (4) a microscopic diagnosis of the disease.

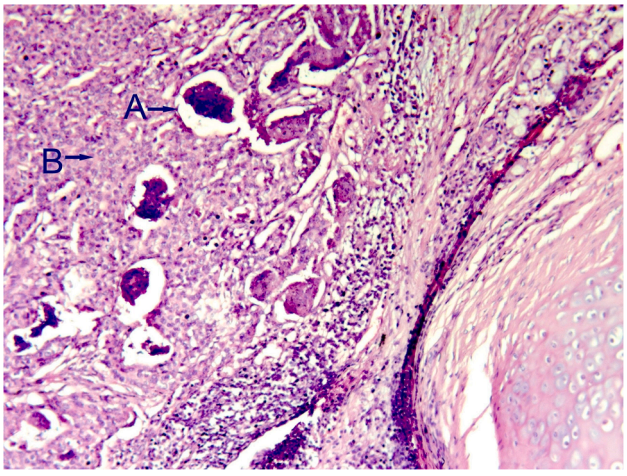

Fig. 2. Microscopic view of an undifferentiated malignant proliferation made of syncytiotrophoblast (A) and cytotrophoblast (B) cells (HEx250).

In our patient, the disease presented as amenorrhea which was the result of elevated βhCG levels, with an exclusive lung tumor mimicking primary lung cancer. To rule out a gynecologic origin, we performed transvaginal and pelvic ultrasonography, an MRI with a focus on the pelvic area, and an exploratory laparoscopy to eliminate extrauterine pregnancy. Hysterectomy was not performed since the patient was still of reproductive age. Positron emission tomography (Pet-FDG) could have been of further assistance to reveal other sites of the disease (Seckl et al., 2013), notably in the genital tract. Unfortunately, due to lack of availability at that time, it was not performed in our patient.

The pathology report showed an extensively hemorrhagic mass which is characteristic of choriocarcinomas and suggested that complete surgical excision, in this case, was the appropriate strategy to avoid biopsy-induced hemorrhage. In the microscope, the predominance of large multinucleated cells with multi-lobulated nuclei with the positivity of βhCG was highly suggestive of the diagnosis. However, to the best of our knowledge, there is no characteristic immunohistochemical profile to conclude whether choriocarcinoma has originated primarily in the lungs or it is a metastasis from a gestational origin. Interestingly, previous data highlighted the utility of genetic testing in differentiating gestational from non-gestational choriocarcinomas using short tandem repeats (STRs). For STR analyses, DNA is extracted from normal lung tissue and tumor tissue using polymerase chain reaction (PCR). The genotype of the tumor is then compared to the genotype of the normal tissue at each locus to investigate the presence of unique paternal alleles in the tumor (that are not present in normal lung tissue) indicating the gestational origin of the tumor. Precision genotyping is now endorsed by the United States and Canadian Academy of Pathology (USCAP) for the diagnosis of lung tumors with trophoblastic differentiation in all young

women (Buza et al., 2019).

What was unusual in our case is the long follow-up period (six years) without any recurrence which is very uncommon in PCL (Seckl et al., 2013) and that was the trigger to review the pathology slides. In fact, primary choriocarcinoma of the lung is notorious for its poor prognosis with a five-year overall survival rate of less than 5% and a median survival of 8 months (Rali et al., 2017; Snoj et al., 2016). However, combined modality treatment seems to offer better survival results than surgery or chemotherapy alone. In fact, a recent systematic review of 55 PCL cases found that the 5-year overall survival has shifted from 5% to 49% as a consequence of a combined modality treatment (surgery and chemotherapy). In fact, patients treated with combination of surgery and chemotherapy survived longer than patients without combination of surgery and chemotherapy ($p = 0.010$). Chemotherapeutic regimens mainly included methotrexate-based regimens and BEP regimen (Bleomycin-Etoposide-Cisplatin). Several prognostic factors were identified in the statistical analysis. Good prognostic factors were younger patients (<40 years), tumor size (<5 cm), the absence of metastases at presentation, no smoking history, women with history of a gestational event within a period time of less than 7 years, and the combination of surgery and chemotherapy rather than chemotherapy or surgery alone (Snoj et al., 2016). Among all these factors, two had an independent prognostic value in the multivariate analysis, which are the combination of chemotherapy and surgery and the tumor size. Of note, our patient had all the good prognostic factors, which provides a rationale for our patient's long survival period which is the longest reported so far.

Nonetheless, the scenario of a dormant gestational trophoblastic tumor with late metastatic recurrence remains also plausible. Our patient had two previous gestational events: one early spontaneous abortion and one pregnancy carried to term with spontaneous delivery 5 years and 3 years earlier, respectively. Previous data suggested that a prior complete hydatidiform mole and a partial mole can be associated with late recurrence of choriocarcinoma in 2–3% and less than 0.1% of women, respectively (Seckl et al., 2000; Smith et al., 2003). This denotes the importance of the microscopic examination of the uterine products after a failed pregnancy. Incidental intraplacental choriocarcinomas in term pregnancies have also been reported in very few case reports and thus this possibility still stands in our patient (Chung et al., 2008).

To sum up, the distinction between PCL and postmolar choriocarcinoma in the lung is sometimes problematic and is still a matter of debate. In the absence of precision genotyping, a thorough examination of the genital tract and imaging of the midline structures are mandatory.

4. Conclusions

It is important that gynecologists and obstetricians, oncologists, and pneumologists be aware of different clinical presentations of choriocarcinomas. Taking detailed physical complaints of the patient is mandatory to guide diagnosis. Genetic testing of the tissue is of tremendous help to address the diagnostic pitfalls. The prognosis of PCL seems to be improved by the combination of surgery and adjuvant chemotherapy.

Informed consent

We declare that the patient signed written consent for an anonymized publication of this case report.

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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