Clinical Case Report

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Extrauterine epithelioid trophoblastic tumors presenting as lung mass

A case report and literature review

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Abstract

Rationale: Extrauterine epithelioid trophoblastic tumors (ETT) is a rare variant of gestational trophoblastic neoplasms. Here we aim to learn more clinical and pathological characteristics of ETT patient with an isolated pulmonary mass without uterine lesions, through a rare case of extra-uterine ETT and 7 cases published in English periodicals literature.

Patient concerns: A 31-year-old Chinese woman, presented with low-level elevation of serum human chorionic gonadotropin (HCG) for more than 2 years without abnormal symptoms. Dilation and curettage (D&C) was performed and histopathology revealed a secretory phase of endometrium. Chest computed tomography (CT) scan showed a 0.8 cm nodular lesion in the upper left lobe. Then a thoracotomy with left upper lobe segmentectomy was performed.

Diagnosis: After pathological and immunohistochemistry diagnosis, the case was confirmed as ETT(III).

Interventions: According to FIGO guideline, the patient took 3 cycles of multivalent chemotherapy consisting of cisplatin and etoposide, alternating with etoposid, methotrexate dactinomycin (EP-EMA).

Outcomes: The patient had no obvious signs of recurrence after 13 months of follow-up.

Lessons: When a fertile age woman persistently shows abnormal low-level escalation of HCG, ETT should be taken into consideration, especially lung X-ray or CT showing lesions without apparent abnormality of the uterus.

Abbreviations: CT = computed tomography, D&C = dilation and curettage, ETT = epithelioid trophoblastic tumors, HCG = human chorionic gonadotropin, PLAP = placental alkaline phosphatase, PSTT = placental site trophoblastic tumors.

Keywords: epithelioid trophoblastic tumors, pathology, pulmonary lesion

1. Introduction

Gestational trophoblastic neoplasms (GTN) contain a heterogeneous group of trophoblastic tumors including choriocarcinomas, epithelioid trophoblastic tumors (ETTs), and placental site trophoblastic tumors (PSTTs).[1] ETT is extremely rare occurrence, which is originated from intermediate trophoblastic cells of the chorion laeve and usually located in the uterine about 71%. Very few ETTs show aggressive clinical performance, and the sites of metastases include lung, small bowel, fallopian tube, broad ligament, and endocervix.[1,2] Abnormal vaginal bleeding is a common symptom in 57% to 67% of patients, with atypical symptoms and signs including abdominal pain, bloating, amenorrhea. Dyspnea, gasp or hemoptysis may happen to the patients with extra-uterine ETT, sometimes even asymptomatic.[3] It is very meaningful to diagnose correctly before therapy, making differential diagnosis including serious kinds of GTD, squamous cell carcinoma of the cervix, and especially primary or metastatic squamous carcinoma of the lung.[4] Here we report a rare case of extra-uterine ETT with isolated pulmonary mass and review related literature, aiming to learn more clinical and pathological characteristics of ETT.

2. Case presentation

A 31-year-old Chinese woman, presented with low-level elevation of serum human chorionic gonadotropin (HCG) for more than 2 years, without abnormal vaginal bleeding, abdominal pain, cough, hemoptysis, chest tightness, or other symptoms. The last pregnancy of the patient was an early pregnancy with menolipsis for 35 days with serum HCG examination positive but no intrauterine pregnancy certified by ultrasound 2 years ago.

The patient took oral mifepristone treatment with little vaginal bleeding. Two months later, serum HCG remained at 31.07mIU/mL (normal level is 5.3mIU/mL), without abnormal image under ultrasound examination. Serum HCG was detected regularly maintained at a low level and slowly increased, fluctuating from 20 to 40mIU/mL. Dilation and curettage (D&C) was performed and histopathology revealed a secretory phase of endometrium. One month later, chest computed tomography (CT) scan (Fig. 1) showed a 0.8 cm nodular lesion in the upper left lobe at local

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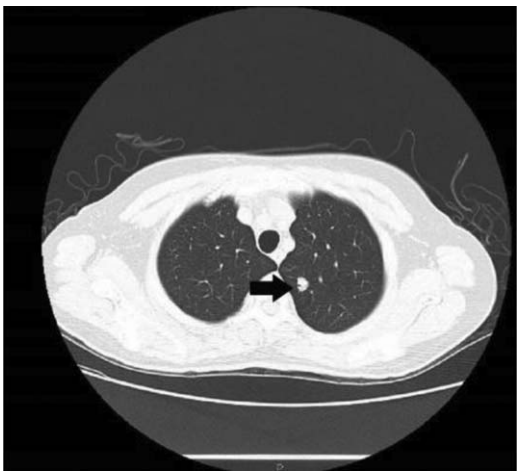

Figure 1. Pulmonary CT showed a 1.0 x 0.8 cm high-density nodule (arrowed) in the upper left lobe with clear border, without exudative or space-occupying lesions and enlarged lymph nodes in hilus pulmonis and mediastinal. The Pleura is smooth and complete with normal shape and size of heart shadow. CT = computed tomography.

hospital, with serum HCG 97.86mIU/mL. The patient then came to Women's Hospital, Zhejiang University for further diagnosis and treatment. After a series assessment, quiescent gestational trophoblastic tumor was first considered. HCG level was slowly increased from 64.97 (May 2017) to 168.1 IU/L (late August 2017). Chest CT confirmed a 1.0x0.8 cm high density knot section in the upper left lobe. Then a thoracotomy with left upper lobe segmentectomy was performed in another general hospital to clarify histological type and pathological diagnosis. Postoperative serum HCG was 29.4mIU/mL and decreased to normal level 1 month later.

After operation, gross examination showed the tumor nodule was 1.0 cm * 0.8 cm. Pathological diagnosis showed the lesions contained epithelial cell nodules with degeneration of eosinophils, with focal hemorrhage and extensive necrosis, consistent with the features of ETT. No tumor cells were found in the 3 groups lymph nodes. (Fig. 2A and B) Immunohistochemistry showed strong positive of cytokeratin (CK) 7, HCG, moderate staining for placental alkaline phosphatase (PLAP), mild positive for human placental lactogen (HPL). The Ki-67 proliferative index was about 50%. (Fig. 2C and D) The morphological and immunohistochemical features of these epithelial cells were consistent with the characteristics of ETT (III). According to FIGO guideline, the patient took 3 cycles of multivalent chemotherapy consisting of cisplatin and etoposide, alternating with etoposid, methotrexate dactinomycin (EP-EMA) without recurrence evidence of the disease for 13 months.

3. Literature review

3.1. Data sources and search strategy

A comprehensive of the PubMed (1999–December2017), Embase (1999–December2017) was performed. The search terms included "Epithelioid Trophoblastic Tumors," "Pulmonary Lesion," "Pulmonary Carcinoma," "Gestational trophoblastic disease," "Lung mass," and "Pathology." The references of the identified studies were manually searched.

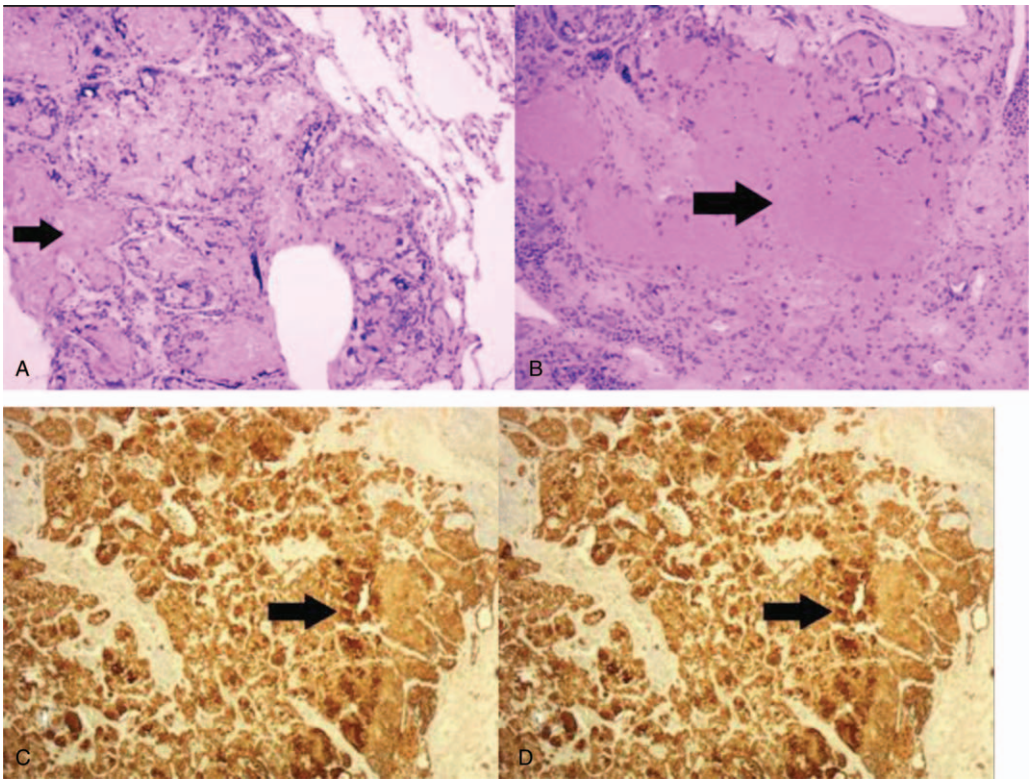

Figure 2. Microscopic examination of hematoxylin–eosin and immunohistochemistry. Typical focal eosinophilic necrosis (arrow) were illustrated in pulmonary epithelioid cell nodules under a light microscope for original magnification (A) × 100, (B) × 200. (C) Tumor cells show diffuse cytoplasmic positive for CK7 (+) (arrow), × 200.(D) Tumor cells of nuclear positivity show the proliferative rates of Ki-67 is 50%(arrow), × 200.

Table 1

Clinical features of ETT only presenting as lung mass.

Case	Ages	Clinica presentation	HCG, mIU/mL	Antecedent pregnancy history	time interval, mo	Pathological diagnosis	Immunohistochemical features	Treatment	Follow-up, mo	Ref. No
1	38	No Symptoms	400	unknown	unknown	ETT (with a minor choriocarcinomatous component)	HPL (+)PLAP(-)TTF-1(-) mib-1(50%+)	Wedge resection, lobectomy	90	[4]
2	49	vaginal bleeding	400	Miscarriage	12	ETT	pancytokeratin (+) hCG (focally +), HPL (-), S100 (-), TTF-1 (-)	EMA/EP, lobectomy, LAVH, BSO	45	[4]
3	34	irregular menses	426	Full-term delivery	24	ETT	p63 (+) CK18 (+), mib-1 (+10% to 60%) HPL (-) hCG (-), TTF-1 (-)	Segmentectomy, EMA/EP, hysterectomy	22	[4]
4	40	abnormal uterine bleeding	1100	Unknown	Unknown	ETT	cytokeratin AE1/AE3(+), cytokeratin 18 (+), inhibin-a(+), b-HCG(+), p63. (focally +)HPL(-)	lobe lobectomy with mediastinal lymph node dissection cisplatin/etoposide chemotherapy	12	[5]
5	35	abdominal pain, nausea, and vomiting	Unknown	multiparous(Specific unknown)	Unknown	ETT	p63 (+) cytokeratin(+), β-hCG(+), cytokeratin(+), inhibin (+), placental alkaline phosphatase (+) HPL(-), α-AFP (-), CD30 (-).	lobectomy with mediastinal lymph node dissection.	Unknown	[6]
6	26	delayed and relatively heavy menstruation	11.37 (after lobectomy)	subclinical miscarriage	Unknown	ETT	β-hCG (focally+) p63 (diffusely+) cytokeratin (CK5/6)(-), vimentin (-), thyroid transcription factor 1 (-)	lobectomy with mediastinal lymph node dissection, etoposide, adjuvant chemotherapy (methotrexate, dactinomycin, cyclophosphamide, and vincristine)	9	[7]
7	32	No Symptoms	normal	Unknown	unknown	ETT	cytokeratin AE1/AE3 (+) cytokeratin 18 (+)pIA1P (-)	right upper lobectomy	36	[8]

BSO = bilateral salpingo-oophorectomy, EMA/EP = Combined chemotherapy consisting of etoposide, methotrexate, dactinomycinalternating with cisplatin, etoposide, ETT = Epithelioid Trophoblastic Tumors, HCG = human chorionic gonadotrophin, HPL = human placental lactogen, PLAP = placental alkaline phosphatase, TTF-1 = thyroid transcription factor 1.

3.2. Inclusion criteria

With pathological diagnosis and immunohistochemistry confirmed, the cases were diagnosed as epithelial trophoblastic tumor, and the presence of lung metastasis was confirmed. The case provided a complete treatment plan.

3.3. Exclusion criteria

Ultrasound, CT, MRI, diagnostic curettage, and hysteroscopy suggested that there might be tumor lesions in the reproductive system, which were confirmed by pathological or immunohistochemistry diagnosis. Cases that did not provide immunohistochemical results were also excluded.

3.4. Data analysis

There were 7 cases that met the requirements mentioned below (Table 1).[4–8] All cases were women of reproductive age and the average age was about 36.28 years old. Abnormal vaginal bleeding or abnormal menstruation (irregular or unperiodic disturbances) was the most common symptoms, accounting for 4/7. All the ultrasonography showed no abnormalities in the uterus as well as D&C. Serum HCG levels were below 2500 mIU/mL, ranged from 400 to 1100 mIU/mL. The interval between the last pregnancy and ETT was unclear. According to literatures, the interval was varied from 1 year to 18 years.[9] HPL was positive in 1 case of ETT with a minor choriocarcinomatous component, while the rest were negative. HCG, p63, and CK18 were positive in most cases. All patients selected lung lesion resection. Some patients (3/7) received hysterectomy or chemotherapy on the basis of lung lesion resection, and chemotherapy regimens were discrepant. Follow-up time was varied from 9 to 90 months. Medical ethics committee of Obstetrics and Gynecology Hospital of Zhejiang University School has approved the study, which was coded 20180171.

4. Discussion

Epithelioid trophoblastic tumor was first defined by Shih and Kurman in 1998.[10] The common group of ETT with a mean age about 38, which is close to our study findings (36.3 years old). According to relevant 7 English kinds of literature, abnormal vaginal bleeding is a common symptom, even some patients are asymptomatic. ETT is usually characteristic with slightly elevated b-HCG level, less than 2500 mIU/mL, and lower than typical choriocarcinoma.[5] There is not determined relevant relationship between metastatic or disseminated of ETT and serum hCG level.

ETT is considered to be an organ-confined disease and the uterus and cervix are the most common primary sites. Involvement of lung always suggests metastasis in published cases.[1] The possible pathogenesis of this rare clinical phenomenon include original transformation of trophoblastic cells passed to the lung during antecedent pregnancy. The other potential hypothesis indicates that pulmonary lesions may be the consequence of spontaneous resolution of an antecedent uterine ETT.[10]

Pulmonary squamous cell carcinoma and other kinds of GTD should be taken into consideration when making differential diagnoses. Pulmonary squamous cell carcinomas are usually found in old patients, especially smokers, expression of CK5/6, without expression of CK18, CD10, and 3beta-hydroxysteroid dehydrogenase/delta(5)-delta(4) isomerase type I or hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase (1HSD3B1), however, p63 expression would be expected in both tumors.[4] The presence of paternal DNA would be favor to a diagnosis of ETT in the right morphologic context.[4]

Choriocarcinoma possesses dimorphic trophoblastic population of tumor cells, with HCG showing diffusely positive.[10] Tumor cells of monomorphic population of ETT tend to be aggregated into nests and cords. Hemorrhage is less common and serum HCG is focally positive in ETT lesions. Generally, ETTs contain abundant chorionic-type intermediate trophoblast with proliferative rates of Ki-67 which is usually less than 25%. While choriocarcinoma always exceeds 70%.[10]

PSTT is derived from implantation of site and usually diploid and monomorphic. Microscopically, these tumors show no chorionic villi and are characterized with proliferation of mononuclear intermediate trophoblast cells with oval nuclei and abundant eosinophilic cytoplasm. While necrosis and eosinophilic hyaline-like material are distinctive features of ETT.[11] They have similar clinical behavior, such as low serum hCG titer, resistant to conventional chemotherapy. Whole-exome sequencing and immunochemistry outcomes show they have different morphologic and immunohistochemical features.[12] In terms of immunohistochemical characteristics, PLAP, E-cadherin, and epidermal growth factor receptors are positively expressed in patchy and focal. The intermediate trophoblastic cells at the site of implantation are always diffusely strongly expressed in the latter 2 molecules.[4] The level of p63 in ETT is in the range of 45% to 65%, which is absent in PSTT.[9]

As for treatment and prognosis, ETT is not sensitive to chemotherapy, compared to choriocarcinoma. Hysterectomy and local lesion resection of isolated metastases are recommended as first-line treatment.[13] The rates of preoperative and postoperative chemotherapy of ETT patients are 29%, 48% respectively, with unideal results because of the chemoresistance. Recently whole-exome sequencing was performed to study the underlying mechanisms of chemoresistance.[14] The underlying mechanisms of chemoresistance may relate to genetic alterations in DNA repair, drug-metabolizing enzymes, drug uptake proteins, and cell-death pathway.[15] More studies are required to explore mechanistic about chemoresistance of ETT.

Another attractive thing is high metastatic rates. According to the published literature, the overall metastatic rates were 25% and the death rates was10% to 13%.[4] These factors may suggest a poor prognosis, such as time interval of Extra-uterine ETT from antecedent pregnancy more than 4 years, the patient age over 40 and a mitotic count more than 5 per 10 HPFs.[3] More sufficient data and further study were need to insights into the prognosis of isolated pulmonary lesion in ETT.

5. Conclusion

Therefore, when a fertile age woman persistently shows abnormal low-level escalation of HCG, especially lung X-ray or CT showing lesions without apparent abnormality of the uterus, ETT should be taken into consideration, despite nomanifested vaginal bleeding, cough, hemoptysis, and other symptoms and signs.

Author contributions

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