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Primary pulmonary epithelioid trophoblastic tumor co-existing with choriocarcinoma

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Abstract:

A 28-year old, G5P4 (4014), noted neck lymph nodes associated with cough. A chest X-ray was done showing a left nodular opacity. Antibiotics were prescribed with a resolution of symptoms. Five months after, a routine chest X-ray revealed interval progression in size of the lung nodule. A chest computed tomography (CT) scan and positron-emission tomography scan were done subsequently showing the precise location and size of the nodule and with no other focus of tumor seen. Transvaginal ultrasound was normal. With an initial diagnosis of lung carcinoma, a percutaneous needle aspiration biopsy under CT scan guidance was done. Immunohistochemical staining panel showed that beta-human chorionic gonadotropin (hCG) was positive. Subsequently, a serum beta-hCG done showed low levels from 33.48 to 59.7 mIU/ml. The final diagnosis given was a poorly differentiated malignancy highly suggestive of malignant trophoblastic tumor. A video-assisted left upper lobectomy was performed with histopathology and immunohistochemistry consistent with epithelioid trophoblastic tumor with co-existing choriocarcinoma elements. Postoperative beta-hCG level dropped to normal and remained so for 2½ years.

Keywords:

Choriocarcinoma, epithelioid trophoblastic tumor, human chorionic gonadotropin

Introduction

Epithelioid trophoblastic tumor (ETT) is a rare type of gestational trophoblastic neoplasia (GTN) arising from intermediate trophoblasts of the chorion laeve. The most common symptom is vaginal bleeding (57%–67%) associated with an endomyometrial mass mostly seen in the lower uterine segment and the cervix (71%). A review of literature showed that rarely, it can present in extrauterine sites most commonly in the lungs and in other sites such as the small bowel, vagina, Fallopian tube, broad ligament, and gallbladder.[1-3] Primary extrauterine ETT co-existing with choriocarcinoma is even a more uncommon occurrence.

Case Report

A 28-year-old G5P4 (4014) presented with a nodular opacity located on the left superior lobe seen on chest X-ray done because of cough and palpable neck lymph nodes. She was treated with antibiotics and advised workup to rule out Koch's infection. With the resolution of cough, no consult and follow-up were done. After 5 months, on a routine physical checkup, chest X-ray was done which showed an increase in the size of the previous nodule seen [Figure 1]. There were no other associated signs and symptoms. Transvaginal ultrasound was normal. A chest computed tomography (CT) scan revealed a 2.7 cm × 3.3 cm × 2 cm noncalcified, pedunculated soft tissue mass in the lingula of the left lung [Figure 2]. Positron-emission tomography/CT showed the same lung mass to be multilobulated, nonenhancing (on CT), noncalcified, in the

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superior lingula, fluorodeoxyglucose (FDB)-avid, with a maximum standardized uptake value of 4.7.

Menstrual and reproductive history

Menarche was at age 16. Subsequent menses occurred at regular monthly intervals with no associated dysmenorrhea. At the time of diagnosis and even after the video laparoscopic lobectomy, menses were regular with no episode of amenorrhea. The patient had a hydatidiform mole (2nd pregnancy) 6 years ago for which a suction curettage was performed. There was no follow-up done after. Four other pregnancies were normal full-term deliveries, the last three occurring after the hydatidiform mole. After the last normal delivery, 2 years from the time of diagnosis, an intrauterine device was inserted as a form of contraception.

A percutaneous needle biopsy under CT scan guidance of the mass was done. The result was read as poorly differentiated malignancy associated with extensive necrosis. Immunohistochemical staining panel was requested with the following results: beta-human chorionic gonadotropin (ßhCG), positive; sal-like protein 4 (SALL4), positive in rare cells; cytokeratin (CK), positive, diffuse; p40, positive, diffuse; thyroid transcription factor 1, negative; and leukocyte common antigen, negative. A serum ßhCG assay was subsequently requested showing low levels, 33.48 mIU/ml increasing to 37.18 mIU/ml after 4 days. The serum ßhCG a day before the contemplated surgery slightly increased to 59.7 mIU/ml [Figure 3]. With these findings, the final diagnosis given was a poorly differentiated malignancy highly suggestive of malignant trophoblastic tumor.

The patient underwent a video laparoscopic left upper lobectomy. The resected tumor was 3.8 cm in its widest dimension with no pleural invasion [Figure 4]. Histopathologic report was as follows: trophoblastic malignancy, favors ETT with no definite lymphovascular invasion [Figures 5 and 6]. There was a note of co-existing choriocarcinoma elements, 15% [Figure 7]. Immunohistochemistry studies showed the following: P63 – positive in approximately 60% of the tumor cells [Figure 8]; beta-human chorionic gonadotropin – negative in mononuclear cells; positive in multinucleated cells [Figure 9]; Ki-67 – positive, high (approximately 80%); and human placental lactogen – negative.

The patient had an unremarkable postoperative course. The serum ßhCG after the procedure dropped to normal and has remained so, 2½ years after lobectomy. Transvaginal ultrasound is done every 6 months with normal results.

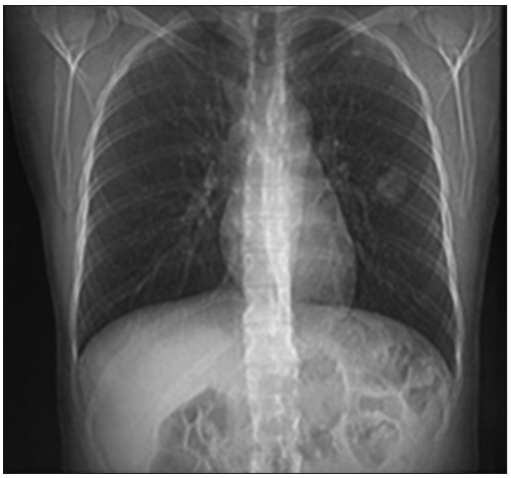

Figure 1: Chest X-ray showing a multilobulated, nonenhancing, noncalcified mass at the superior lingula, left

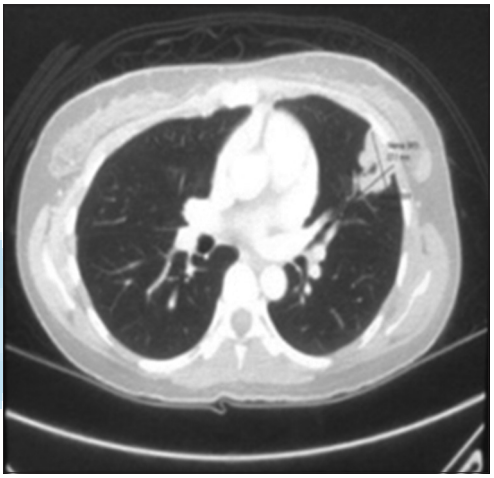

Figure 2: Chest computed tomography scan showing a 2.7 cm × 3.3 cm × 2 cm mass at the lingula

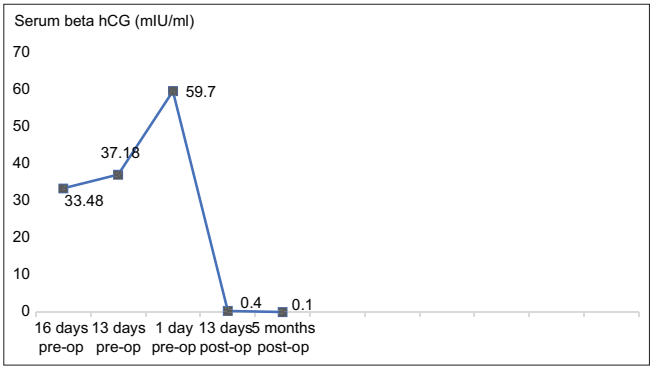

Figure 3: Pre/postoperative serum beta-human chorionic gonadotropin levels

Discussion

ETT was first described as a separate entity in 1998 by Shih and Kurman when they presented 14 cases of ETT without a previous history of chemotherapy. Before this, it was believed to be an "atypical

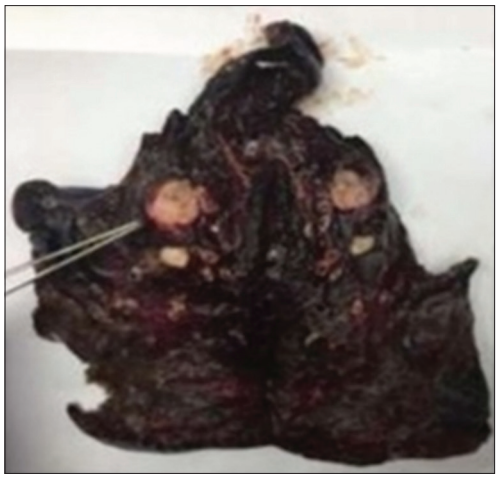

Figure 4: Gross specimen, left upper lobectomy done with 3.8 cm tumor with no pleural invasion

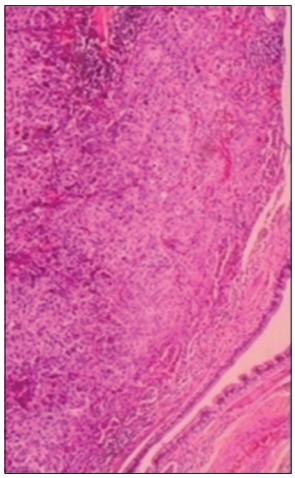

Figure 5: ETT area, ×100. Epithelioid cells in nesting pattern; adjacent bronchial epithelium is seen

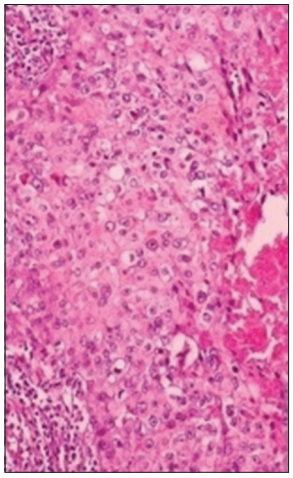

Figure 6: ETT area, ×400. Epithelioid cells with prominent nucleoli and distinct nuclear membrane

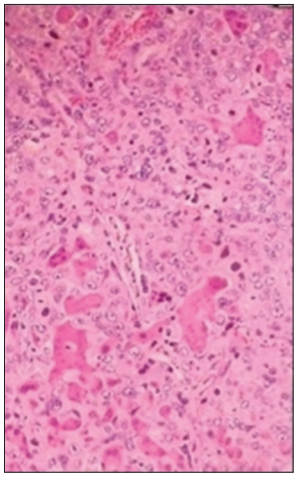

Figure 7: Choriocarcinoma area, ×400. Biphasic pattern with cytotrophoblasts and syncythiotrophoblasts

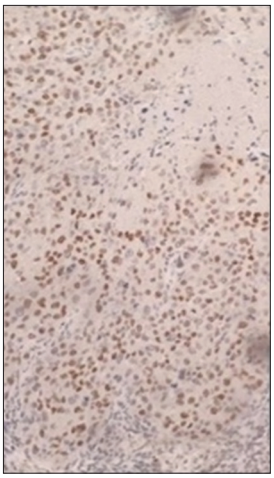

Figure 8: ETT area, ×400, p63 immunostaining shows most nuclei of the ETT staining positive. Note: p63 – positive in approximately 60% of the tumor cells

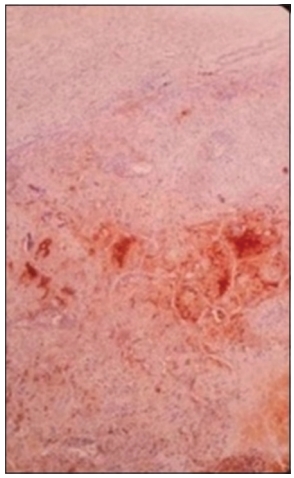

Figure 9: Human chorionic gonadotropin immunohistochemistry, ×100. Choriocarcinoma area showing dark brown staining of syncytiotrophoblasts. Note: Human chorionic gonadotropin negative in mononuclear cells; positive in multinucleated cells

choriocarcinoma" that developed because of an inadequate response to chemotherapy.[4,5] Since then, there have been only 130 cases of ETT reported in literature. The most common presenting symptom of ETT is abnormal vaginal bleeding (67%) associated with an endomyometrial mass (40%)/cervical

mass (31%). It can present in extrauterine sites most commonly in the lungs and in other sites such as the small bowel, vagina, Fallopian tube, broad ligament, and gallbladder.[1-5]

ETT presenting as a primary pulmonary lesion is quite rare with seven cases reported by Wen Li *et al*.[6] A synchronous tumor composed of ETT with choriocarcinoma elements presenting as a primary pulmonary mass, as in the index patient, is an even rare occurrence. One of the seven patients in the series had a pathologic diagnosis of ETT with minor choriocarcinoma elements after lobectomy.[7] In a recent extensive literature review of mixed GTN, co-existing choriocarcinoma, and/or placental site trophoblastic tumor (PSTT) and/or ETT, only 2 out of 34 patients (16 patients from the retrospective study and 18 patients from previous reports) were diagnosed to have ETT with choriocarcinoma component presenting primarily as pulmonary lesions.[8]

What could have brought about this phenomenon of extrauterine ETT in the lungs with normal findings in the uterus? The proposed pathogenesis could be that the pulmonary lesion may develop after the spontaneous resolution of a uterine ETT. A second theory could be that trophoblastic cells that were lodged in the lungs from an antecedent pregnancy transformed to ETT.[6] The second theory could be true of the index patient having no complaint of irregular bleeding in between pregnancies.

The proposed pathogenesis of mixed GTN is still poorly understood. Choriocarcinoma is more primitive composed of a mixture of cytotrophoblast, syncythiotrophoblast, and intermediate trophoblast compared to the more differentiated PSTT and ETT, with cytotrophoblast differentiating into chorionic type intermediate trophoblasts in ETT. For those patients who underwent chemoresistance, the initial theory of intermediate trophoblastic tumor (ITT) developing from an initial choriocarcinoma can come into play, as the remaining tumor cells unresponsive to chemotherapy differentiated into intermediate trophoblasts.[9-11] The index patient has no previous history of chemotherapy for GTN.

Presentation

Mixed GTN has been reported in women of reproductive age with an age range of 15–60 years old. The index patient is 28 years old during the time of diagnosis. The most common presenting symptom is still abnormal vaginal bleeding with only 3 out of 34 patients presenting with cough and a lung mass/nodules in the report by Kong *et al*.[8] The index patient did not present with any form of irregular vaginal bleeding except for a pulmonary nodule noted on routine chest X-ray increasing in size after 5 months.

Causative pregnancy

The most common antecedent pregnancy in mixed GTN is a previous normal pregnancy in 70% of cases, hydatidiform mole in 20%, and abortion in 10%.[9] In the patients reported by Kong *et al*., antecedent pregnancies were identified to be a normal pregnancy in 7 out of 16 patients (43.8%) and abortion in 9 out of 16 patients (56.2%) with none of the patients with a history of a previous mole. For the 2 patients who initially presented with lung nodules, the antecedent pregnancies were a normal pregnancy and an abortion.[8]

The interval between the causative pregnancy and the diagnosis of the mixed GTN was noted to range from 7 months to 38 years.[9] The index patient had a history of a hydatidiform mole 6 years ago and there were three more intervening normal pregnancies, the last of which was 2 years from diagnosis. The causative pregnancy cannot be positively identified without genetic studies to show the chromosomal makeup of the tumor. If performed and the tumor is biparental, the causative pregnancy is a normal pregnancy, and if with a purely paternal component, then it will mean that the tumor arose from the hydatidiform mole. In addition, if genetic testing of the tumor in the index patient turned out to be biparental, identification of which of the four normal pregnancies gave rise to the tumor may be in order, to more or less assess the prognosis in the index patient.

Diagnosis

Based on reports of the most frequent manifestation of vaginal bleeding, the initial diagnosis of mixed GTN was based on pathologic findings after a dilatation and curettage was done to address the bleeding. There were seven patients in the series of Dr. Kong that were diagnosed primarily after a curettage. These patients eventually had a hysterectomy verifying the diagnosis of mixed GTN. Another seven patients were diagnosed after undergoing chemoresistance with an initial diagnosis of choriocarcinoma based on elevated hCG levels. One patient was diagnosed with a biopsy of the cervical mass. Only one patient was similar to the index patient with an initial diagnosis of lung carcinoma. The diagnosis of mixed GTN was based on the histopathologic findings after the patient underwent lobectomy.[8] In the index patient, the initial diagnosis of possible ETT was entertained based on the positive beta hCG immunohistochemical staining in a percutaneous needle aspiration biopsy of the lung mass. A serum ßhCG was subsequently requested showing a low level of 33.48 mIU/ml. The choriocarcinoma element admixed with ETT was assessed to be only 15% and was evident on the lobectomy specimen with the diagnosis verified by immunostaining.

ETT arises from intermediate trophoblasts of the chorion laeve. That is why hCG levels in ETT are reported to be

low compared to the visible tumor with 69% of patients presenting with hCG levels <2500 mIU/ml.[4,6] Patients with mixed GTN presenting with higher levels of GTN (>10,000 mIU/ml) were explained by the predominance of choriocarcinoma elements in the tumor. These patients were initially diagnosed to have choriocarcinoma and treated with chemotherapy with a good response but eventually became chemoresistant due to the coexistence of ITT.[8] The serum ßhCG levels in mixed GTN therefore will be dictated by the predominant component. It is low when the ITT component of the tumor is greater compared to the choriocarcinoma element. The index patient had only 15% of the choriocarcinoma element present in the tumor, thus the low level of serum ßhCG.

The use of immunostaining to verify the diagnosis of concomitant ETT cannot be overemphasized. p63 is a nuclear stain expressed in chorionic type intermediate trophoblasts and therefore expressed in ETT in a strong and diffuse pattern. It is absent in PSTT and only focally present in choriocarcinoma.[4-6] The histologic slide of the index patient was predominantly positive for p63 [Figure 8] and focally positive for hCG in the areas exhibiting choriocarcinoma elements [Figure 9]. Both these stains are available in most laboratories in the country. Other immunostains that are diffusely positive for ETT include inhibin alpha, CK AE1/AE3, epithelial membrane antigen, E cadherin, propyl 4-hydroxylase, and epidermal growth factor receptor.[4-6]

Management

ITTs, PSTT and ETT, behave differently from the common choriocarcinoma, as they are relatively chemoresistant tumors compared to choriocarcinoma. Due to this, surgery remains to be the primary treatment of choice. This is particularly true for mixed GTN. The patients with higher hCG levels >10,000 mIU/ml were initially diagnosed as probable choriocarcinoma and treated with chemotherapy up to the time that chemoresistance was encountered necessitating adjuvant surgery showing co-existent ITT. It was recommended in mixed GTN that adjuvant surgery be performed at a time when hCG levels are low to attain good outcomes. In the 16 patients reported by Dr. Kong, 2 patients who were still desirous of pregnancy were managed with chemotherapy alone and 14 patients underwent surgery with chemotherapy. The most common chemotherapy regimens given included etoposide, methotrexate, actinomycin D/cyclophosphomide, vincristine (EMA-CO), floxuridine, actinomycin D, etoposide and vincristine (FAEV), and EMA/etopiside and cisplatin (EMA-EP). Surgeries done were hysterectomy (10), laparoscopic radical hysterectomy (1), tumor resection (1), and lobectomy (3). Fifteen patients achieved complete remission (93.8%) and one patient died. Five out of the 15 who achieved complete remission had a tumor relapse after 3–9 months (33.3%) and were subsequently managed with chemotherapy and lobectomy. Three out of the five had complete remission and two were lost to follow-up.[8]

The two patients in the review who presented with pulmonary nodules and underwent a lobectomy both received postoperative chemotherapy in the form of methotrexate, etoposide, and actinomycin D (MEA) and FAEV, as hCG levels persisted after the lobectomy. There was no available information regarding the eventual outcome of the patient managed with MEA (1 of 18 Mixed GTN patients from previous reports). The patient (one of 16 patients in the retrospective study) who received FAEV had initial remission but had tumor relapse and was eventually managed with an immune checkpoint inhibitor, pembrolizumab.[8] Pembrolizumab is monoclonal antibodies targeting programmed death protein 1 inhibitory signaling which is one of the multiple suppressive mechanisms to regulate anticancer T-cell activity. The efficacy of pembrolizumab in chemoresistant GTN including mixed GTN has been reported. Clinical trials are ongoing to validate its use.[12,13]

At present, there are no existing guidelines in mixed GTN when postoperative chemotherapy should be initiated. It appeared in the study by Dr. Kong that persistently elevated serum ßhCG even after surgery was used as an indication to give further chemotherapy. For the index patient, no chemotherapy was given. The predominant component of the tumor was ETT with very low levels of hCG prior to surgery. Unlike the two patients with pulmonary nodules included in the review of Dr. Kong who still had abnormal levels of hCG postlobectomy, the serum ßhCG level of the index patient readily dropped down to normal after surgery and remained so up to the present time (2.5 years postsurgery). The follow-up done in the index patient was based on published local guidelines on ETT: monthly hCG determination for 6 months, every 2 months for the next 6 months, every 3 months for the 2nd year and every 6 months thereafter; transvaginal ultrasound every 6 months; and chest X-ray yearly.[14] The need for additional imaging may be dictated based on a notable increase in the hCG levels and development of associated signs and symptoms referrable to tumor recurrence.

The current profile of the patient (low levels of serum beta-human chorionic gonadotropin preoperatively dropping to normal levels after surgery; low percentage of choriocarcinoma elements) may be used as a basis for identifying a group of patients with mixed GTN that can effectively be managed with surgery alone without chemotherapy. However, further studies will be needed to come up with management guidelines given the rarity of the condition.

Prognosis

Based on the study by Kong *et al*., 33.3% of patients with mixed GTN had relapses. However, no conclusion can be drawn due to the small sample size brought about by the rarity of the disease.[8]

The factors reported to have a poor prognosis include time interval from the antecedent pregnancy of more than 4 years, age over 40, and a mitotic count more than 5 per 10 HPFs. Further studies are needed to validate these prognostic factors in mixed GTN.[6] For the index patient, she is young at 28 years of age and she delivered normally 2 years prior to the diagnosis of mixed GTN. Determining the exact causative pregnancy by genetic studies may be quite prohibitive with four previous pregnancies and a hydatidiform mole and these studies are not readily available in local laboratories. If it was done, the result may be a basis to decide on the need for additional postoperative chemotherapy if the causative pregnancy was 4 years or more from the diagnosis of the tumor. Meanwhile, with normal hCG levels and disease-free imaging results maintained more than 2 years from the definitive procedure, the index patient adheres to regular follow-up as advised.

Learning points/take-home messages

- GTN may present with signs and symptoms referrable to the site of metastasis and should be considered in a reproductive-aged woman with a metastatic focus from an unknown primary. A thorough reproductive history is needed in these cases
- A diagnosis of ETT may be considered in a reproductive-aged woman presenting primarily with a lung mass with no referable symptoms and pathology in the reproductive tract. This rare type of GTN presents with low levels of human chorionic gonadotropin
- A detailed histologic review should be done, including immunohistochemistry, to be able to diagnose rare cases of mixed GTN
- Due to the rarity of mixed GTN, the ideal mode of management cannot be ascertained. However, with the presence of ITT, surgery remains to be the mainstay of treatment. Additional multiple agent chemotherapy may be given depending on the presentation of the patient, postoperative status, and presence of poor prognostic factors
- The use of immunotherapy in the form of pembrolizumab has recently been shown to be effective in these cases. Further studies are ongoing to validate its efficacy.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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