CLINICAL

Placental site trophoblastic tumour – a rare cause of recurrent spontaneous pneumothoraces and conjunctival metastasis

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ABSTRACT Spontaneously occurring primary pneumothorax in the young is uncommon but well documented as a complication of primary or secondary lung malignancy. We report the case of a 24-year-old female patient with placental site trophoblastic tumour presenting as recurrent pneumothorax, despite initial surgery and chemotherapy. Later, despite further chemotherapy, she developed conjunctival metastasis. To the best of our knowledge, this is the first case of a placental site trophoblastic tumour metastasising to the conjunctiva to be reported in the literature. Clinicians should keep in mind the possibility of pneumothorax due to lung metastasis when no obvious primary lung disorder is apparent.

KEYWORDS Conjunctival metastasis, gestational trophoblastic tumours, placental site trophoblastic tumour, pneumo-mediastinum, pneumothorax, trophoblastic neoplasia

DECLARATION OF INTERESTS No conflict of interests declared.

CASE REPORT

A 24-year-old woman was admitted with a six-hour history of left-sided pleuritic chest pain and shortness of breath, two weeks after a hysterectomy. She did not smoke. On examination, she had a heart rate of 90/min, respiration of 23/minute, blood pressure of 110/60 mmHg and oxygen saturation of 94% on room air. Systemic examination was unremarkable. An initial diagnostic possibility of pulmonary embolism was made in casualty, and the patient was initiated on treatment with low molecular weight heparin.

Further investigations gave the following data: arterial blood gases pH 7.48, $PaCO_2$ 4.2 kPa, PaO_2 10.9 kPa, D-dimer 1318 U (normal <250), normal chest X-ray, right bundle branch block on the electrocardiogram and normal echo-cardiogram. An initial thoracic computerised tomography (CT) scan confirmed a small pneumothorax, and a CT pulmonary angiogram excluded pulmonary embolism. The patient remained breathless with saturations of 90% on room air. Heparin was discontinued.

The patient was first diagnosed to have a right-sided pneumothorax eight months earlier when she had presented with similar symptoms (Figure 1). A chest drain was employed, but there was a recurrence of the pneumothorax. A further drain was unsuccessful, and the


FIGURE 1 Chest X-ray showing a large right-sided pneumothorax when the patient had presented with similar symptoms of pleuritic chest pain and shortness of breath.

patient was referred to the thoracic surgeons. At surgery, a large pneumothorax was confirmed without any pleural abnormality. Extensive sessile bullae were seen at the right lobe apex; these were oversewn, and an apical pleurectomy was performed. Follow-up four weeks later was normal.

Three months prior to her current admission, the patient had re-presented with similar right pleuritic pain,
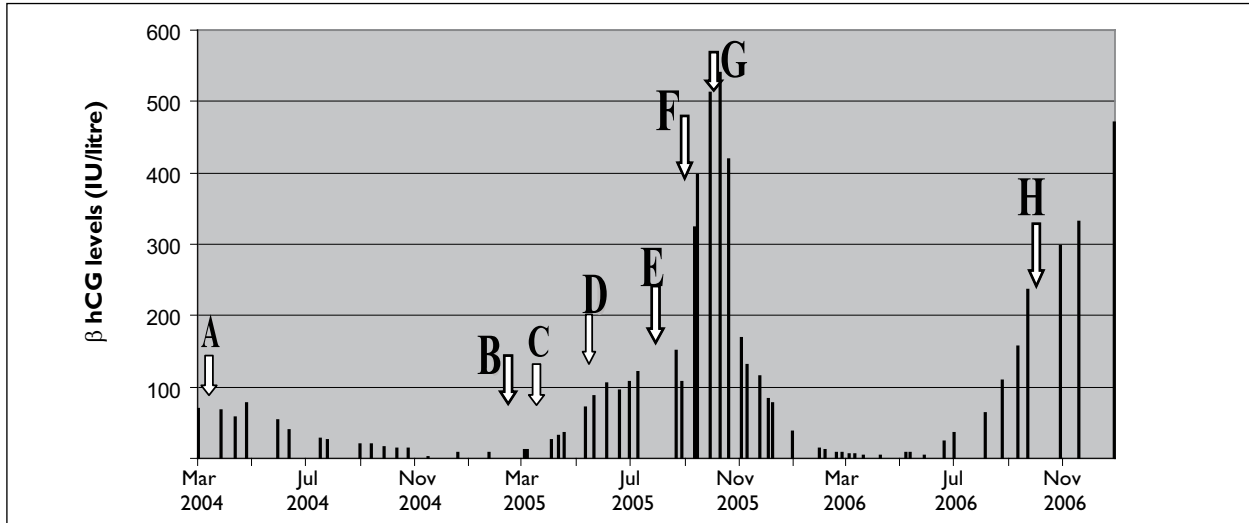
FIGURE 2 Graph showing β hCG levels at different times of illness. A: First referral to trophoblastic unit for raised β hCG; B: First presentation to our hospital with pneumothorax; C: Thoracic surgery for non-resolving pneumothorax; D: Second presentation to our hospital with pneumothorax; E: Hysterectomy; F: Admission to our hospital with dyspnoea and again diagnosed to have a pneumothorax; G: Open lung biopsy at referral centre; H: Conjunctival biopsy.

cough and dyspnoea and was found to have a small right basal pneumothorax. This was her second admission to hospital with a pneumothorax. Serial chest X-rays during this admission did not demonstrate any increase in size of the pneumothorax or worsening of her symptoms, and she was managed conservatively. Two weeks later in clinic it was noticed that the pneumothorax was still persisting, although her symptoms were stable. Further options of thoracic surgery or another trial of chest drain insertion were discussed. The patient was not keen on either, and a further clinic appointment was made which she failed to attend, being then lost to thoracic/medical follow-up.

The patient's medical history was complicated (see Figure 2). She had her first child by a Caesarean section in 1998 and her second in 2002 by normal delivery. Eighteen months prior to her current medical admission, she was referred to hospital for abdominal pain and per vaginal bleeding to exclude a suspected ectopic pregnancy. At that time she was found to have raised beta human chorionic gonadotrophin (β hCG) at 69 international units (IU)/litre (normal <2 IU/litre). Histological examination of the evacuate from the uterus showed only blood. However, the patient was noted to have a persistently raised β hCG level subsequently, prompting diagnostic laparoscopy and curettage which did not show any evidence of conception or neoplasia.

As her β hCG levels remained elevated, the patient was registered with the regional trophoblastic tumour screening unit where her β hCG levels were monitored. Serial abdominal ultrasound and CT scans were all normal. She was initiated on chemotherapy with methotrexate, dactinomycin and etoposide, but her β hCG levels continued to rise. A positron emission tomography (PET) scan was normal. Review opinion raised the possibility of placental site trophoblastic tumour (PSTT). The patient then underwent a hysterectomy two weeks prior to her third admission in an attempt to make a definite diagnosis of trophoblastic tumour, but no neoplasia was found in the myometrial, endometrial or cervical tissues.

The cause of the patient's dyspnoea and pleuritic chest pain remained elusive until the opportunity arose for the admitting team to consult with the regional trophoblastic screening centre. The possibility of an association of these recurrent pneumothoraces secondary to occult metastasis of the PSTT was considered. This concern was also shared by the specialists at the referral centre.

A high-resolution chest CT (Figure 3) showed the development of multiple small nodules of variable size, the largest measuring 8 mm. New focal cystic change, probably secondary to focally dilated bronchi, had developed. One such cyst contained a nodule within its wall. In addition, there were enlarged mediastinal nodes within the aorto-pulmonary window and pre-tracheal space. There was also a localised pneumo-mediastinum anterior to the heart and a small right pleural effusion. The patient was referred to the thoracic surgical centre for open lung biopsy.

The histology (Figure 4) showed lung parenchyma with grey-cream nodular areas measuring up to 4 mm in diameter, and revealed nodular and fibrotic lung tissue with unremarkable pleura. The nodular areas showed a population of moderately pleomorphic polygonal cells, some showing polynucleate forms. Immunohisto-chemistry showed positive placental alkaline phosphatase (PLAP), cytokeratin, β hCG and human placental lactogen

(hPL) reactivity. A proliferation fraction of 50% was noted. Some of the features suggested a lymphangitic pattern of spread and the close association to endothelial surfaces was noted. The intervening lung parenchyma showed slight fibrosis, scattered iron laden macrophages and some oedema. The overall features were regarded as consistent with metastatic PSTT.

The patient underwent further chemotherapy (cyclophosphamide, etoposide, cisplatin) with stem cell rescue, but represented with a one-month history of a rapidly enlarging lump on the inner aspect of her lower eyelid. Lid eversion revealed a 7-mm diameter, fixed, pink, hemispherical, fleshy, vascular lesion present on the tarsal aspect of her lower lid, encroaching onto the lower lid margin (Figure 5). Prominent conjunctival feeder vessels were seen. No leukoplakia was present. The rest of the ophthalmological examination was unremarkable, with no pre-auricular lymphadenopathy being identified. An incision biopsy (Figure 5) revealed conjunctival tissue, the substantia propria of which contained a malignant neoplasm. This was composed of groups of polygonal, pleomorphic, eosinophilic to clear epithelioid cells alternating with zones of eosinophilic fibrinoid necrosis. Immunohistochemistry showed diffuse staining for cytokeratin, alpha inhibin and focal positivity for β hCG and hPL. The tumour was negative for melanoma and soft tissue tumour markers.

Unfortunately, despite all further therapy, the patient's condition progressed and she died nine months after presenting with the eyelid nodule.

DISCUSSION

Spontaneously occurring primary pneumothorax in the young is uncommon[1] but well documented as a complication of primary or secondary lung malignancy.

Gestational trophoblastic disease[2] (GTD) includes hydatidiform mole, invasive mole and choriocarcinoma. However, one of the less common subtypes is PSTT; this is thought to be derived from intermediate trophoblast tissues. Placental site trophoblastic tumour accounts for 1% of all GTDs.[3] It usually affects premenopausal women in the third and fourth decade of life and generally presents a few months following pregnancy. In PSTT the intermediate trophoblast cells usually produce and secrete mainly human placental lactogen and scant amounts of β hCG.[3] Hence β hCG does not correlate well with the burden or malignant behaviour of PSTT. Although β hCG does not reflect the burden or malignant behaviour of PSTT, most relapses of PSTT are associated with a rise in serum β hCG level.[3] Human placental lactogen is very difficult to measure and most laboratories do not have these facilities. Thus, β hCG is still the best commonly available marker to follow disease and treatment course.[4]
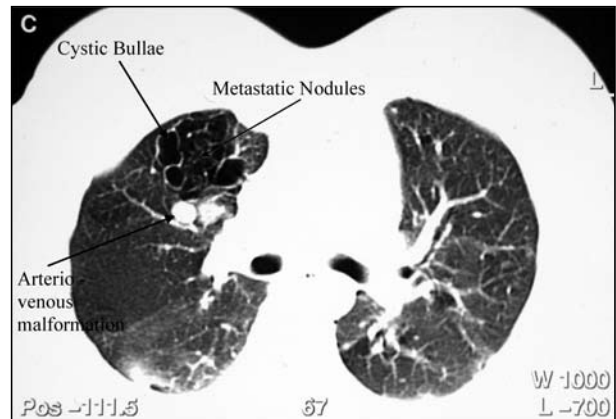
FIGURE 3 CT Scan of the thorax showing multiple small nodules of varying size with new focal cystic change and some that have coalesced to form cystic bullae along with multiple arterio-venous malformations.
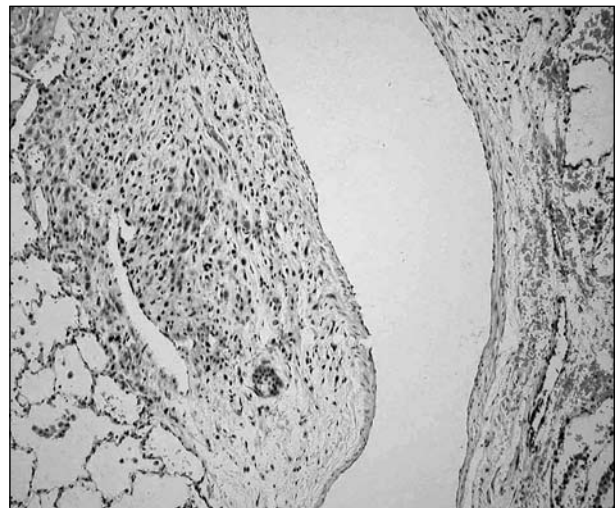
FIGURE 4 Histology of the lung revealed pulmonary tissue with infiltrating PSTT adjacent to a vascular channel (original magnification x 200).
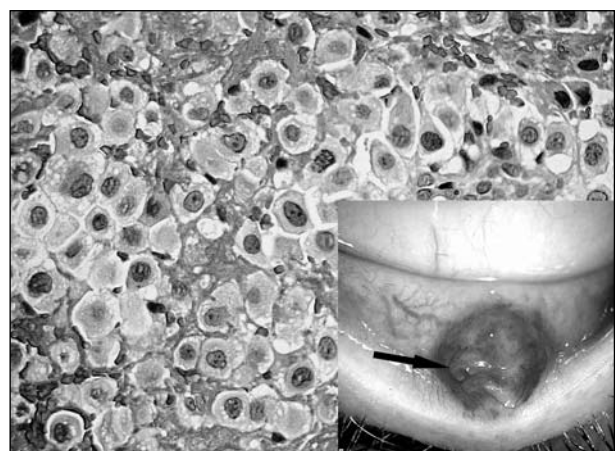
FIGURE 5 Conjunctival biopsy revealed a pleomorphic tumour consistent with recurrent PSTT (original magnification x 400). Inset shows a macroscopic view of the biopsy site with feeder vasculature arrowed.

The majority of the patients have an indolent local disease course, but disseminated disease can occur with aggressive potential (particularly to brain and lung).[5,6] Since PSTT is less sensitive to chemotherapy than other forms of GTD and since most patients present with disease limited to the uterus, hysterectomy is the primary mode of therapy.[7] The role of adjuvant chemotherapy for disease localised to the uterus has not yet been established and remains controversial.[8] In patients with disease extension beyond the uterus, adjuvant treatment with multi-drug chemotherapy is required.[7] Further discussion regarding the various chemotherapeutic regimens is beyond the scope of this report. Patients with disease confined to the uterus usually have an excellent prognosis with survival rates of about 95%, whereas approximately 70% of patients presenting with disease extension beyond the uterus have progression of disease and die despite surgery and aggressive chemotherapy.[4,7,8]

Spontaneously occurring pneumothorax is a well-documented complication of primary or secondary lung malignancy.[9] Out of the malignancies associated with pneumothorax, uterine sarcomas are well recognised.[10] In a review of 1,143 patients with spontaneous pneumothorax, only ten cases were attributed to lung metastasis[11] and five of these were secondary to metastatic sarcoma.[11] At the time of diagnosis, 31% of the patients had disease spread beyond the uterus, with the lung being the most common site of metastasis.[12] Lung metastases may manifest as spontaneous pneumothorax, as in this case, even after chemotherapy.[13] Surgery may have a role for lung-limited disease,[14] although chemotherapy is the mainstay of treatment.[15,16] Late recurrence (more than one year) after primary treatment can occur rarely.[17] PET scanning (not useful in this case) soon after hysterectomy may be beneficial in the quantitation of lung metastases.[18] There is some evidence of excess tumour cell transcription of *INSL4*, *BRM S1*, *KiSS-1* and *KiSS-1R* with regard to tumour invasion and metastases.[19] Pneumothorax is an unusual complication of these tumours[20] and, to the best of our knowledge, only a few such cases have been reported in the literature.[13,21]

There are several mechanisms that are involved in the pathogenesis of malignancy-related pneumothorax. The rupture of a subpleural malignant focus and consequent formation of a bronchopleural fistula have been implicated as one mechanism.[9] Rapid lysis of tumour cells has been proposed as a mechanism in patients receiving chemotherapy.[22] Partial bronchial obstruction by tumour causing obstructive emphysema and cystic bullae formation

and subsequent rupture is another postulated theory.[10] Multiple cystic bullae were seen on the CT scan (Figure 3). It is possible that the latter two were the mechanisms of pneumothorax in our patient.

In general, metastases to the eye usually have an affinity for the uvea[23] (choroid, ciliary body and iris) and orbit.[24] Metastatic deposits to the conjunctiva are very rare. In a previous study involving the review of 2,455 conjunctival lesions, only one was a conjunctival metastasis.[25] In a second study examining ten patients with conjunctival metastases, the primary tumours were from the breast, lung, larynx and skin (melanoma), with one of indeterminate origin.[26] In all ten cases, the primary tumour had been diagnosed before the conjunctival presentation.[26] Conjunctival metastasis can present several months after primary malignancy and can provide a clue to diffuse systemic disease.[27,28] Only rarely have conjunctival metastases been reported to be the initial presenting feature of a systemic malignancy.[29] Conjunctival metastases often present with a rapidly growing fixed fleshy nodule, with episcleral and conjunctival feeder vessels.[26]

While there is an established literature on carcinoma[26] and haematological malignancy[30] metastasising to the conjunctiva, this is the first demonstration of a malignant PSTT manifesting in the conjunctiva. Previous case reports have noted choriocarcinoma metastasising to the choroid and anterior chamber of the eye[31–33] but not to the conjunctival compartment. In the series noted, the presence of a conjunctival metastasis was associated with a poor outcome.[26] In this case, the conjunctival metastasis occurred despite chemotherapy, suggesting the evolution/selection of a therapy-resistant and aggressive tumour subclone with a poor prognosis.

CONCLUSION

This report illustrates the rare presentation of a metastatic PSTT with recurrent pneumothoraces and later with conjunctival metastases. Clinicians should keep in mind the rare causes of secondary pneumothoraces, particularly when the problem is recurrent. In such cases, a full understanding of all medical history is advisable when the cause of pneumothorax is unclear. The value of β hCG serology in PSTT has been discussed in some detail in this report. It has also been observed that resistance to chemotherapy and conjunctival metastasis is a guide to poor prognosis.

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