A young lady with prolonged menstruation and a large lung mass

Julian Wei Ee Tong, Sze Shyang Kho, Swee Kim Chan and Siew Teck Tie

Division of Respiratory Medicine, Dept of Medicine, Sarawak General Hospital, Ministry of Health, Kuching, Sarawak, Malaysia.

Corresponding author: Julian Wei Ee Tong (juliantongweiee@gmail.com)

A 33-year-old woman was admitted to our hospital for prolonged menstruation, fever and productive cough of 2 weeks’ duration. Her past medical history was notable for a molar pregnancy that had been treated with suction and curettage 5 years previously, with sustained decrease in serum beta-human chorionic gonadotropin (β-hCG) hormone levels during post-operative follow-up. This had been followed by a successful spontaneous vaginal delivery 3 years prior to this current presentation.

On examination, the patient appeared pale and emaciated. She weighed 40 kg at 160 cm, with a body mass index of only 15.6 kg·m^{-2}. Her blood pressure was 108/68 mmHg, with regular heart rate of 62 beats per min and body temperature of 37.2°C. Her respiratory rate was 20 breaths per min, with oxygen saturation of 100% in ambient air. Chest examination revealed dull percussion notes over the left hemithorax with reduced breath sounds. The remainder of the examination was unremarkable: there were no palpable abdominal or pelvic masses, nor lymph nodes; normal first and second heart sounds; and no rash or oral thrush. Her neurological examination was normal. A plain chest radiograph was performed in the emergency unit.

The abnormal chest radiograph raised the suspicion of an intrathoracic mass; hence, contrast-enhanced computed tomography (CT) was arranged. Blood investigations revealed hypochromic microcytic anaemia with a haemoglobin level of 9.2 g·dL^{-1}. Renal and liver function tests were normal. Serum β-hCG was significantly elevated at 27 645 mIU·mL^{-1} and remained persistently so for 1 month.

Further imaging with contrast-enhanced CT of the brain, abdomen and pelvis did not demonstrate any focal enhancing brain lesion or abnormal leptomeningeal enhancement. The uterus was homogeneously enhancing with no focal lesions and normal ovaries bilaterally. The rest of the intra-abdominal organs were normal. Flexible bronchoscopy was performed next, in view of the suspicious CT finding. This revealed a yellowish intraluminal mass obstructing the distal left main bronchus, with normal adjacent bronchial mucosa (figure 3).
Pending histopathological examination of the endobronchial mass biopsies, a provisional high-confidence diagnosis of recurrent gestational trophoblastic disease (GTD) with lung metastasis was made on the basis of an elevated serum β-hCG post molar pregnancy and radiological evidence of thoracic metastasis [1]. The patient was thus started on systemic chemotherapy with a 2-weekly etoposide–methotrexate–actinomycin (EMA) regimen.

The histopathological examination of the endobronchial biopsies revealed florid septated fungal hyphae with dichotomous branching, highly suggestive of *Aspergillus* with no evidence of malignancy. Bronchoalveolar lavage was negative for fungal culture. Our clinical impression was *Aspergillus* colonisation of endobronchial GTD mass. In view of her immunocompromised state during ongoing chemotherapy (post third cycle by this time), oral voriconazole was initiated. Meanwhile, her serum β-hCG level had responded dramatically, falling to 22.1 mIU·mL$^{-1}$ after three cycles of EMA.

Unfortunately, 3 days before commencement of her fourth cycle of chemotherapy, the patient presented to hospital with progressively worsening effort tolerance and an incessant cough. On examination, she was

![Chest radiograph on presentation.](https://doi.org/10.1183/20734735.0009-2022)

![CT of the thorax on admission.](https://doi.org/10.1183/20734735.0009-2022)
breathless and distressed. Her oxygen saturation under ambient air was 88%. She remained anaemic with haemoglobin of 9.2 g·dL$^{-1}$, with a total white cell count of 10.7×10$^3$ per μL and platelets of 603×10$^3$ per μL. A chest radiograph showed the left lung mass had shrunk, but also showed multiple new nodules in the right lung field. Empirical antibiotic therapy was commenced with intravenous piperacillin–tazobactam. CT pulmonary angiogram for severe type 1 respiratory failure was also performed and was negative for pulmonary embolism.

Simultaneously, a transthoracic echocardiogram, performed for frequent ventricular bigeminies with premature atrial contractions, revealed a free-floating 1.75×1.44 cm left atrial mass originating from the pulmonary vein (figure 5). There was also a small non-tamponading pericardial effusion.

Flexible bronchoscopy was repeated, and debulking of the now necrotic tissue at the left main bronchus revealed a hyperaemic and unhealthy left lower lobe bronchus. The mucosa at the posterior wall was eroded and covered by a pseudomembrane, and the apical segment of the left lower lobe (B6) ostium was no longer visible. Endobronchial cryobiopsy from the left main bronchus yielded only fibro-necrotic tissue with no granulomas or malignant cells. Bronchial washing grew *Pseudomonas aeruginosa*, while cultures for fungus and mycobacterium were again negative. Serum galactomannan was also negative.

**FIGURE 3** Flexible bronchoscopy showed a yellowish intraluminal mass obstructing the distal left main bronchus.

**FIGURE 4** CT of the thorax prior to the fourth cycle of chemotherapy.
The constellation of CT and echocardiographic findings prompted us towards the diagnosis of invasive pulmonary aspergillosis. The endobronchial biopsy that yielded florid septated hyphae prior to initiation of chemotherapy further supported our clinical suspicion. The possibility of worsening lung metastasis was deemed unlikely, as the patient demonstrated therapeutic response to chemotherapy in terms of serum β-hCG normalisation and also showed shrinking of the left hemithorax mass on the repeated CT scan.

The patient was commenced on intravenous amphotericin B and completed the 2-week course uneventfully. She was also anticoagulated with low-molecular-weight heparin. Her breathlessness improved and oxygen supplementation was gradually discontinued.

The patient was eventually discharged with maintenance oral itraconazole for a total duration of 6 months. The remainder of her chemotherapy regimen was uneventful and routine post-treatment gynaecological follow-up showed complete and persistent suppression of serum β-hCG level. After 6 months of antifungal therapy, she improved remarkably, with resolution of cough and improvement in her functional status, with weight gain of 20 kg. Serial chest radiographs and a repeat CT of the thorax demonstrated marked improvement, with only cicatrisation bronchiectasis over the apical segment of the left lower lobe (figure 6), consistent with a scarred left B6 on surveillance bronchoscopy. Cardiac magnetic resonance imaging showed complete resolution of the left atrial mass with no structural heart lesion, further supporting the diagnosis of direct cardiac Aspergillus invasion. The patient remained well, 1 year after initial presentation. She continues to attend follow-up visits in gynaecological and respiratory clinics.

Discussion

GTDs are characterised by the abnormal proliferation of trophoblasts of the placenta. Incidence is higher in Asians compared to the rest of the world [3]. These diseases include a spectrum of tumours, from complete and partial hydatidiform moles to placental site trophoblastic tumours to choriocarcinomas, which vary in their propensity for local invasion and metastasis. As the presence of metastases in GTD will influence treatment strategy, clinicians should search for any potential metastases, which commonly occur in lung, vagina, liver or brain [4]. The International Federation of Gynecology and Obstetrics (FIGO) recommends that CT or magnetic resonance imaging of the brain may be performed to diagnose brain metastases [1]. Hence, our patient underwent contrast-enhanced CT of the brain, which was fortunately negative. Magnetic resonance imaging of the brain is a more sensitive imaging modality and is helpful in the evaluation of high-risk patients [4].
Lungs remain the most common site of distant metastasis, with an incidence of up to 76% [5]. The majority of these lung metastases are symptomatic, with dyspnoea, chest pain, cough or haemoptysis, and with abnormal radiological findings [5]. However, metastatic choriocarcinoma presenting as a large lung mass is relatively rare, with only a few cases reported in the literature [6]. Although there is a lack of histological evidence in our case, the temporal relationship, between significant size reduction of the lung mass as well as normalisation of serum β-hCG level with treatment, highly supports the diagnosis of recurrent GTD with lung metastasis. Moreover, our patient demonstrated a persistent elevated serum β-hCG level for 1 month prior to treatment initiation. This hormonal elevation without other plausible

| TABLE 1 Definitions for invasive fungal disease |
|-----------------------------------------------|
| **Proven disease**                           |
| Hyphae seen and accompanied by evidence of associated tissue damage from examination of a specimen obtained by needle aspiration or sterile biopsy or Culture obtained from a sterile site |
| **Probable disease**                          |
| All three of the following criteria must be met: |
| 1) Host factors (one of the following)        |
| Recent history of neutropenia (<500 neutrophils·mm$^{-3}$) for 110 days |
| Recipient of an allogenic stem cell transplant |
| Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg·kg$^{-1}$·day$^{-1}$ of prednisone equivalent for 13 weeks |
| Treatment with other recognised T-cell immunosuppressants |
| Inherited severe immunodeficiency |
| 2) Clinical features (one of the following three signs on CT) |
| Dense, well-circumscribed lesion(s) with or without a halo sign |
| Air-crescent sign |
| Cavity |
| 3) Mycological criteria (one of the following) |
| Direct test (cytology, direct microscopy or culture) on sputum, BAL fluid or bronchial brush indicating presence of fungal elements or culture recovery Aspergillus species |
| Indirect tests: galactomannan antigen detected in plasma, serum or BAL fluid |
| **Possible disease**                          |
| Presence of host factors and clinical features but absent or lacking mycological findings |

From the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG). Reproduced and modified from [11] with permission.
clinical explanation in a patient with previous molar pregnancy is supportive of a diagnosis of recurrent GTD, even without a histological diagnosis [1].

Aspergilli are ubiquitous fungi that spread via airborne spores and may cause severe disease in immunocompromised hosts. Disease manifestations range from invasive pulmonary aspergillosis in immunocompromised hosts to chronic necrotising aspergillosis in patients with chronic lung disease, aspergillomas in patients with cavitary lung diseases as well as hypersensitivity reaction such as allergic bronchopulmonary aspergillosis [7]. *Aspergillus* colonisation of large central obstructive endobronchial airway tumours has been infrequently reported, and can obscure diagnosis of the underlying malignancy [8]. Hence, clinical acumen is required to correctly diagnose the underlying malignancy in the context of a non-diagnostic endobronchial biopsy. Clinicians should also be wary that patients with *Aspergillus* colonisation may develop invasive disease if they become immunocompromised, as demonstrated in our case. Recognition of host factors and imaging clues should prompt early search for histological and mycological evidence. Empirical antifungal therapy should be commenced without delay if clinical diagnostic criteria are met, as survival rates for invasive aspergillosis are as low as 52.2%, especially in immunocompromised hosts [9].

Locally invasive aspergillosis is a rapidly progressing disease with high mortality that occurs most commonly in immunocompromised individuals [10]. The disease principally involves the sino-pulmonary tract, which may lead to local invasion into surrounding mediastinal organs as seen in our case. This case demonstrates the post-chemotherapy invasive progression of *Aspergillus*: as an initial coloniser, to invasion through the endobronchial tree, with eventual intracardiac extension. However, diagnosis of invasive aspergillosis can be challenging, due to non-specific symptoms and relatively low sensitivity of cultures. Hence, well-validated clinical diagnostic criteria for invasive fungal disease, such as defined by the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG), have been formulated to aid clinicians in making this difficult diagnosis (table 1) [11]. Our patient fulfilled criteria for proven disease, with endobronchial biopsy specimens showing florid septated fungal hyphae highly suggestive of Aspergillus. Furthermore, she also had the host factor of being immunocompromised due to chemotherapy, with CT scan demonstrating a halo sign. Fortunately, this prompted early antifungal treatment, with an exceptional outcome for her.

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**Answer 1**

This chest radiograph in anterior–posterior projection shows a total opacification of the left hemithorax.

[Go to Task 1]

**Answer 2**

The CT shows a large left lung mass with hydropneumothorax and mediastinal lymphadenopathy. The lung mass measured 7.2×9.7×11.1 cm.

[Go to Task 2]

**Answer 3**

The CT shows significant reduction in size of the previous lung mass and extensive bilateral consolidations with diffuse ground-glass nodules associated with a halo sign. The halo sign is a feature seen on CT of the thorax, which is described as a ground-glass opacity surrounding a pulmonary nodule or mass, typically found in angio-invasive aspergillosis.

[Go to Task 3]

**Answer 4**

Locally invasive pulmonary aspergillosis with direct mediastinal invasion to heart and lung in recurrent GTD with lung metastasis.

[Go to Task 4]

**Answer 5**

Treatment duration is recommended for a minimum of 6–12 weeks. Other factors that influence treatment duration are duration and degree of immunosuppression, site of disease and response to antifungal therapy [2].

[Go to Task 5]
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