Pulmonary embolism or *Pneumocystis jiroveci* pneumonia?

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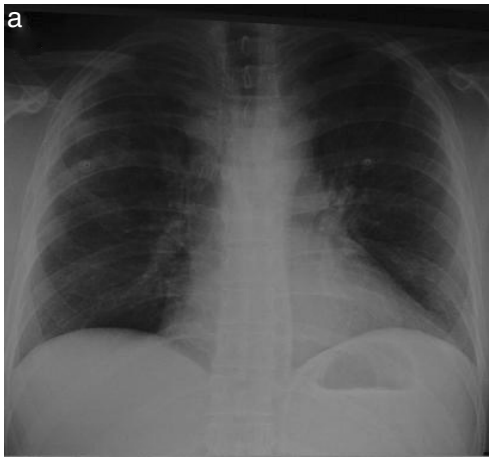
Case report

A 33-year-old male presented to the emergency department with a 5-day history of exertional dyspnoea, dry cough, lethargy and an ongoing fever of 38.9°C. He had been previously diagnosed with left-frontal oligodendroglioma during a work-up following a new-onset seizure 4 months earlier. After successful tumour resection and adjuvant radiotherapy, the patient totally recovered without any residual paresis. He was maintained on valproic acid and dexamethasone at a dose that was tapered down to 2 mg·day^{-1}.

The physical examination was unremarkable. The patient was haemodynamically stable but hypoxaemic and anaemic (table 1). Chest radiography and computed tomography (CT) were performed and the results are shown in figure 1.



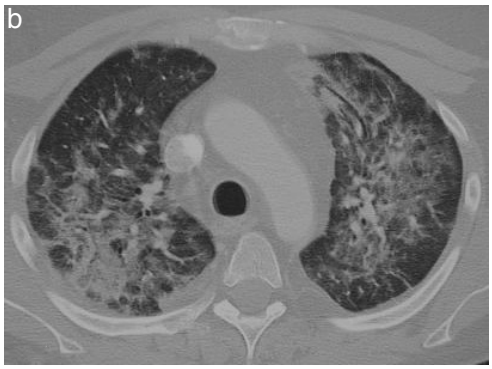


Figure 1
Chest radiography (a) and CT scan (b).

Table 1 ***Vital signs and laboratory test results at presentation***

Investigation	Result	Normal range
Vital signs		
Temperature °C	36.6	
Respiratory rate cycles·min^{-1}	22	
Heart rate beats·min^{-1}	88	
Blood pressure mmHg	126/64	
O_2 saturation %	91	
Haematological counts and coagulation		
White cells ×10^9·L^{-1}	6.8	4.0–10.0
Platelets ×10^9·L^{-1}	123	150–350
Haemoglobin g·dL^{-1}	9.3	12.0–16.0
Prothrombine time s	12.8	<13.0
Partial prothrombine time s	22.2	22.0–35.0
Serum chemistry		
Sodium mmol·L^{-1}	137	135–145
Potassium mmol·L^{-1}	4.0	3.5–5.0
Chloride mmol·L^{-1}	107	96–106
Carbon dioxide mmol·L^{-1}	21	22–30
Anion gap mmol·L^{-1}	9	4–10
Urea nitrogen mg·dL^{-1}	26	8–18
Creatinine mg·dL^{-1}	0.9	0.5–1.2
LDH IU·L^{-1}	950	313–618
D-dimer µg·mL^{-1}	>0.9	<0.9
Arterial blood gas analysis		
pH	7.52	7.48–7.52
P_{CO_2} mmHg	26	35–45
P_{O_2} mmHg	57	75–100
O_2 saturation %	94	92–99
$P_{A\text{-}a,O_2}$ gradient mmHg	62	<10
HIV ELISA	Non-reactive	Non-reactive

LDH: lactate dehydrogenase; P_{CO_2}: partial pressure of carbon dioxide; P_{O_2}: partial pressure of oxygen; $P_{A\text{-}a,O_2}$: alveolar–arterial oxygen tension.

Task 1
Interpret the chest radiograph and CT scan, and suggest a diagnosis.

Answer 1

The chest radiograph reveals diffuse bilateral perihilar interstitial infiltrates, predominantly in the upper right lobe. The CT scan shows bilateral infiltrate in upper lobes, superimposed on a mild ground-glass appearance. The clinical presentation is suggestive of ***Pneumocystis jiroveci*** **pneumonia (PcP)**.

Trimethoprim-sulphamethoxazole was initiated, but due to the development of an immediate skin rash, treatment was changed to pentamidine. As a result of significant hypoxia (table 1), the dose of dexamethasone was increased to 8 mg daily. The combined presentation of hypoxaemia and hypocapnia, along with the features of new right ventricular strain on ECG (right bundle branch block and right atrial enlargement) suggested pulmonary embolism (PE). A positive D-dimer latex assay (Diagnostica Stago, Parsippany, NJ, USA) was followed by spiral CT scan pulmonary angiography (figure 2).

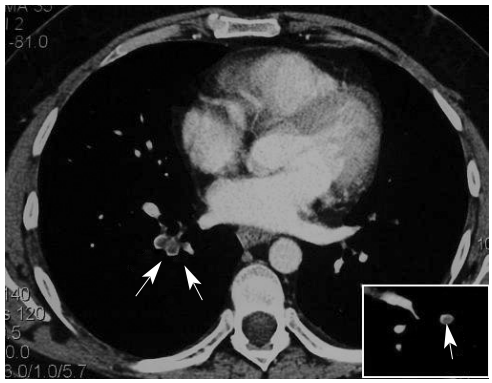


Figure 2
Spiral CT scan pulmonary angiography.

Task 2

Interpret the CT scan pulmonary angiography.

Answer 2

The CT scan shows bilateral thrombi in the pulmonary arteries of the lower lobes (arrow) and in the right upper pulmonary arterial branches (window panel), confirming PE.

Intravenous heparin therapy was initiated. The next day, a bronchoalveolar lavage (BAL) was performed and the results are shown in figure 3.

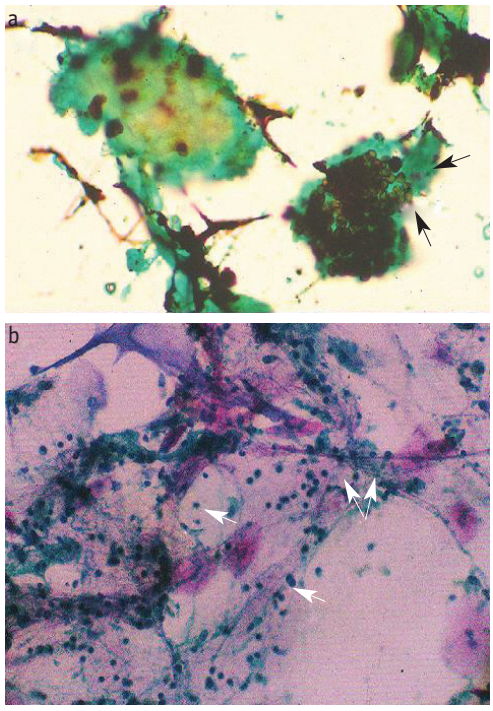


Figure 3
Photomicrographs of BAL using a) Gomori methenamine silver and b) Giemsa stain.

Task 3

Interpret the photomicrographs.

Answer 3

Figure 3a shows clusters of brown-to-black cysts (4–7 μm) containing intracystic bodies (arrows) with the characteristic appearance of "crushed ping pong balls".

Figure 3b reveals small **Pneumocystis jiroveci (carinii)** trophozoites (1–5 μm), where only the nuclei (stained purple) are visible (arrows).

Lower extremity duplex ultrasound identified a deep venous thrombosis (DVT) extending from the middle of the calf up to the left distal femoral vein. Although it was hard to establish a separate relationship between the presenting symptoms of this patient and those of PcP and PE, it is believed that both entities were symptomatic. The patient's condition improved over the following days, and he was discharged home on low-molecular-weight heparin.

Discussion

Approximately 250,000 patients are hospitalised in the USA each year because of venous thromboembolism [1]. PE is frequently an occult disease. In patients with DVT, the incidence of silent PE (40–50%) is five-fold that of symptomatic disease [2]. In cancer patients particularly, although half have been found to have some degree of PE on autopsy [3], only one in four cases has been clinically diagnosed before death [4]. PE mortality is elevated (17% at 3 months) [5], and despite advances in diagnosis, prophylaxis and supportive care, the overall mortality has not improved much in the last few decades [6], or barely decreased [7]. The association of DVT with malignancy is strong, with a lifetime risk of 20%. Cancer patients with the most elevated risk of DVT and PE are those who have been diagnosed with pancreatic adenocarcinoma, advanced gastrointestinal adenocarcinoma, brain tumour or locally recurrent rectal cancer receiving radiation [8]. Compared with early-stage breast cancer patients, those with metastatic disease have a three-fold increase in the lifetime risk for thromboembolism (17.3 *versus* 5%) [9]. Neoplasm-independent risk factors for DVT in cancer patients include all types of surgery [10], indwelling central vein catheters [11], the use of adjuvant haematopoietic growth factors [12] and any increased immobility.

Patients with brain tumours are at particular risk of developing DVT (3–60%) [13]. Indeed, the incidence of PE in high-grade gliomas is elevated (24–60%) [14], particularly in patients with lower-extremity paresis [15]. Other contributing factors in this population are related to chemotherapy and corticosteroids, which have prothrombotic effects [16], and the diverse procoagulants [17] and fibrinolytic inhibitors released by brain tumour cells and surrounding tissue [18]. Although heparin's efficacy and safety for DVT prophylaxis in elective neurosurgery is proven [19], guidelines for post-operative anticoagulation and inferior vena cava filter placement remain undefined [20].

In the current study, where there had been a diagnosis of oligodendrioglioma, treatment with corticosteroids and later presentation with hypoxia, the patient was at an increased risk for PE despite the absence of extremity paresis. The suspicion of PE was lowered by the initial consideration of a highly probable diagnosis of PcP. In an outpatient setting of a low-to-moderate pre-test probability of PE, quantitative D-dimer assay (ELISA or immunoturbidimetric assays) is a sensitive (overall sensitivity 93%) but not specific test (overall specificity 51%) for establishing an accurate diagnosis, although it yields reliable information to rule out an acute PE [21]. Due to its high negative predictive probability (between 94 and 100%), a negative D-dimer ELISA assay (<400–500 $ng \cdot mL^{-1}$) safely excludes the diagnosis of either DVT [21] or PE in low-probability outpatient settings [22, 23]. The D-dimer assay has been proven in all disease outpatient settings, but in cancer patients, because of their chronic D-dimer elevation, its specificity is lowered further, yielding to a lower positive predictive value, although it does not affect its negative predictive value. Increased D-dimer levels have been documented in the plasma of patients with various solid tumours, such as in the lung [24], colon [25], breast [26], prostate [27, 28], thyroid [29] and cervix [30].

A positive test does not confirm the diagnosis, so an angiogram or nuclear scan is necessary for confirmation. In the current patient, the positive D-dimer test was followed by a CT scan angiogram that revealed bilateral PE. Since the incidence of PcP in patients with cancer is increasing [31], the simultaneous occurrence of two common complications (PcP and PE) in patients with highly prevalent disease (*i.e.* cancer) is probably under-accounted for. Therefore, in the event of a diagnosis of PcP, clinicians should not exclude the likelihood of a coexisting life-threatening diagnosis of PE, if the latter is otherwise suspected. This is even more significant in patients with brain tumours who are also at a higher risk of PcP. In fact, PcP occurs at a

higher incidence in immunosuppressed patients with AIDS, cancers, prolonged corticosteroid therapy or post-organ transplantation. Cancer patients with haematological malignancies, primary or metastatic brain tumours and the recipients of bone marrow transplants are at the highest risk. Unlike AIDS-related PcP, PcP in non-AIDS patients is usually distinguished by a rather fulminant accelerated presentation (5 *versus* 28 days) [32], severe hypoxaemia (arterial oxygen tension (P_{a,O_2}) of 6.9 *versus* 9.2 kPa) [33] and a lower parasite load [34]. The outcome in non-AIDS patients is worse with a higher rate of hospital admissions (97 *versus* 69%), transfers to intensive care units (52 *versus* 7%), more endotracheal intubations (66 *versus* 5%) and higher overall mortality (39–50 *versus* 17–20%) [35]. Therefore, PcP in non-AIDS patients remains a challenging clinical diagnosis because of its aggressive course, the usual lack of CD4 monitoring and the broader spectrum of differential diagnoses. Typically, patients present clinically with fever, elevated serum lactate dehydrogenase and normal chest radiograph findings. Increased awareness of PcP and greater efforts to consider it in the differential diagnosis of patients at increased risk, *e.g.* cancer patients, would allow more successful and timely accurate diagnoses.

BAL remains the confirmatory test of choice. It is more sensitive (79–98%) and less invasive than transbronchial biopsy, especially with the use of specific immunostaining [36]. The antibiotic treatment duration for non-AIDS-related PcP is 2 weeks instead of 3 weeks, often with early clinical improvement (on day 4 or 5), rather than the delayed and slow response that is observed in patients with AIDS-related PcP.

In AIDS-related PcP, adjunctive corticosteroid therapy is recommended in moderate-to-severe cases of hypoxaemia (P_{a,O_2} <9.3 kPa or $P_{A\text{–}a,O_2}$ >4.7 kPa). It decreases the rate of early respiratory deterioration (6 *versus* 42%) and early mortality (10 *versus* 31%), and improves survival (75 *versus* 18%) [37], but with only mild increased risk of localised herpetic lesions (26 *versus* 15%) [38]. The role of corticosteroid therapy in non-AIDS patients with PcP remains to be established [39].

Prolonged corticosteroid therapy predisposes non-AIDS patients to develop PcP [35], and the depletion of CD4 lymphocytes in the lungs and blood, and suppression of alveolar macrophages may be responsible for this [40]. The dose and duration of corticosteroid therapy that lead to the increased risk are unclear. Just a brief 1-month course of prednisone at 20 mg·day^{-1} may be enough to put the patient at an increased risk of PcP [40]. Other predisposing factors to PcP in patients with brain tumours are steroid-independent immunological alterations, such as severe T-cell lymphopenia, impaired T-cell signalling pathways, interleukin-2 receptor defects in T-cell lymphocytes and depressed immunoglobulin production [41]. There is no strong evidence to recommend systemic PcP prophylaxis in patients with brain tumours. One single-institution retrospective review identified the risk of PcP in patients with brain tumour as ~1.7% [42]. A higher index of suspicion should be considered though if patients have been treated with corticosteroids (a mean of 2.75 months) or chemotherapy [42].

To the current authors' knowledge, the simultaneous clinical diagnosis of both PcP and PE has not been previously reported in the medical literature. In one anecdotal case, the diagnosis of PE was delayed because initially only the HIV-specific complication, PcP, was considered in the differential diagnosis [43]. In another case, a patient with breast cancer on tamoxifen developed PcP, and was later diagnosed during the course of her hospital stay with PE by CT scan angiography [44]. It is suspected that this comorbid presentation in cancer patients is underdiagnosed. The role of PcP prophylaxis in high-risk cancer patients has not been established [45]. Prospective studies of the benefits and risks of PcP chemoprophylaxis in patients with brain tumours, whether treated with corticosteroids or not, are warranted. Meanwhile, CD4 lymphocyte counts have been suggested as a helpful clinical marker to monitor these patients and provide an early identification of high-risk individuals [46]. Trimethoprim-sulphamethoxazole (160/800 mg) is an effective, well-tolerated first-line prophylaxis [47]. Although therapeutic anticoagulation has proven to be safe in patients with brain tumour, the benefits of systematic prophylactic anticoagulation remain to be established.

This case presentation serves to remind clinicians of the higher incidence of PcP in susceptible high-risk non-AIDS patients, such as patients with cancer. Physicians caring for patients with cancer who present with either a clinical picture of PcP or PE should maintain a high index of suspicion for the possibility of concomitant presentation of both diseases, *i.e.* one diagnosis cannot exclude the other. This is particularly so for patients with brain tumour. The early initiation of therapy in both diseases is critical for outcome improvement and mortality decrease. Applying

evidence-based guidelines for the diagnosis of PcP and PE allows accurate diagnosis and prompts management of an unusual, although probably not infrequent, concomitant presentation of both complications. This is another exception to the Occam's principle of parsimony that "one should not make more assumptions than the minimum needed".

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