**Pulmonary embolism or Pneumocystis jiroveci pneumonia?**

**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 workup 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.

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

| Investigation                        | Result | Normal range |
|--------------------------------------|--------|--------------|
| **Vital signs**                      |        |              |
| Temperature °C                       | 36.6   | 36.5–37.5    |
| Respiratory rate cycles·min⁻¹        | 22     | 12–20        |
| Heart rate beats·min⁻¹               | 88     | 60–100       |
| Blood pressure mmHg                  | 126/64 | 90–120       |
| O₂ saturation %                      | 91     | 90–100       |
| **Haematological counts and coagulation** |        |              |
| White cells ×10⁹·L⁻¹                  | 6.8    | 4.0–10.0     |
| Platelets ×10⁹·L⁻¹                    | 123    | 150–350      |
| Haemoglobin g·dL⁻¹                   | 9.3    | 12.0–16.0    |
| Prothrombin time s                   | 12.8   | <13.0        |
| Partial prothrombin 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   | 7.40–7.52    |
| PΟ₂ mmHg                             | 26     | 35–45        |
| PO₂ mmHg                             | 57     | 75–100       |
| O₂ saturation %                      | 94     | 92–99        |
| Pa₆Ο₂ gradient mmHg                  | 62     | <10          |
| HIV ELISA                            | Non-reactive | Non-reactive |

LDH: lactate dehydrogenase; PE₆Ο₂: partial pressure of carbon dioxide; PO₂: partial pressure of oxygen; PA₆Ο₂: alveolar–arterial oxygen tension.

**Figure 1**

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

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

### 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).

### 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.

### Task 2
Interpret the CT scan pulmonary angiography.

### Task 3
Interpret the photomicrographs.

---

**Figure 2**
Spiral CT scan pulmonary angiography.

**Figure 3**
Photomicrographs of BAL using a) Gomori methenamine silver and b) Giemsa stain.
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 postoperative anticoagulation and inferior vena cava filter placement remain undefined [20].

In the current study, where there had been a diagnosis of oligodendroglioma, 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 pretest 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 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-acknowledged 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

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).
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 (PaO₂) 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 (PaO₂ <9.3 kPa or PaO₂< aO₂ >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, interleukin2 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
References
1. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O’Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998; 158: 585–593.
2. Moser KM, Fedullo PF, Littlejohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. JAMA 1994; 271: 233–235.
3. Thompson OM, Rodgers LR. Analysis of the autopsy records of 157 cases of carcinoma of the pancreas with particular reference to the incidence of thromboembolism. Am J Med Sci 1952; 223: 469–478.
4. Attems J, Arbes S, Spolar G, Bohmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. Wien Med Wchnschr 2004; 154: 159–162.
5. Futterman LG, Lemberg L. A silent killer: often preventable. Am J Crit Care 2004; 13: 431–436.
6. Goldhaber SZ. Pulmonary embolism. N Engl J Med 1998; 339: 93–104.
7. Horlander KT, Mannino DM, Leeper JK. Pulmonary embolism mortality in the United States, 1979–1998: an analysis using multiple-cause mortality data. Arch Intern Med 2003; 163: 1711–1717.
8. Rickles FR, Levine M, Dorak HB. Abnormalities of hemostasis in malignancy. In: Colman RW, Hirsh J, Marder VJ, Clowes A, George JN, eds. Hemostasis and Thrombosis. Philadelphia, Lippincott, Williams & Wilkins 2000; pp. 1132–1152.
9. Goodnough LT, Saito H, Moini A, Jones PK, Pearson GH. Increased incidence of thromboembolism in stage IV breast cancer patients treated with a five-drug chemotherapy regimen. A study of 159 patients. Cancer 1984; 54: 1264–1268.
10. Rasmussen KS. Preventing thrombotic complications in cancer patients after surgery: a role for prolonged thromboprophylaxis. Cancer Treat Rev 2002; 28: 141–144.
11. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 2003; 21: 3665–3675.
12. Barbui T, Finazzi G, grassi A, Marchioli R. Thrombosis in cancer patients treated with hematopoietic growth factors-a meta-analysis. On behalf of the Subcommittee on Haemostasis and Malignancy of the Scientific and Standardization Committee of the ISTH. Thromb Haemost 1996; 75: 368–371.
13. Harris LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer 2000; 89: 640–646.
14. Sawaya R, Zuccarello E, Ellahmily M, Nishiyama H. Postoperative venous thromboembolism and brain tumors: Part I. Clinical profile. J Neurooncol 1992; 14: 119–125.
15. Dhami MS, Bona RD, Calogero JA, Hallman RM. Venous thromboembolism and high grade gliomas. Thromb Haemost 1993; 70: 393–396.
16. Brandes AA, Scelzi E, Salimastro G, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. Eur J Cancer 1997; 33: 1592–1596.
17. Hamada K, Kuratsu J, Saitoh Y, Takeshima H, Nishi Y, Usui Y. Expression of tissue factor correlates with grade of malignancy in human glioma. Cancer 1996; 77: 1877–1883.
18. Sawaya R, Ramo OJ, Glas-Greenwald P, Wu SE. Plasma fibrinolytic profile in patients with brain tumors. Thromb Haemost 1991; 65: 15–19.
19. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. Arch Intern Med 2000; 160: 2327–2332.
20. Levin JM, Schiff O, Loeffer JS, Fine HA, Black RM, Wen PY. Complications of therapy for venous thromboembolic disease in patients with brain tumors. Neurology 1993; 43: 1111–1114.
21. Brown MD, Lau J, Nelson RD, Kline JA. Turbidimetric D-dimer test in the diagnosis of pulmonary embolism: a metaanalysis. Clin Chem 2003; 49: 1846–1853.
22. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003; 348: 1227–1235.
23. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med 2004; 140: 589–602.
24. Seitz R, Rippe N, Kraus M, et al. Activation of coagulation and fibrinolysis in patients with lung cancer: relation to tumour stage and prognosis. Blood Coagul Fibrinolysis 1993; 4: 249–254.
25. Blackwell K, Hurwitz H, Lieberman G, et al. Circulating D-dimer levels are better predictors of overall survival and disease progression than carcinoembryonic antigen levels in patients with metastatic colorectal carcinoma. Cancer 2004; 101: 77–82.
26. Kahl M, Fink LM, Spencer NJ, Zent CS. Advanced prostate cancer activates coagulation: a controlled study of activation markers of coagulation in ambulatory patients with localized and advanced prostate cancer. Blood Coagul Fibrinolysis 2002; 13: 1–5.
27. Gaine GJ, Lip CV, Stonekow PS, Ryan P, Blann AD. Platelet activation, coagulation and angiogenesis in breast and prostate carcinoma. Thromb Haemost 2004; 92: 185–190.
28. Nakashima J, Tachibana M, Ueno M, Boku S, Tazaki H. Tumor necrosis factor and coagulopathy in patients with prostate cancer. Cancer Res 1995; 55: 4881–4885.
29. Sagrignani A, Carpi A, Baichi U. The measurement of plasma D-dimer in the follow-up after tyrothricin for cancer: preliminary data. Thyroidology 1991; 3: 31–35.
30. Saducki S, Baichi U, Marra R, et al. Pretreatment plasma levels of fibrinoprotein-A (FPA), D-dimer (DD), and von Willebrand factor (vWF) in patients with operable cervical cancer: influence of surgical-pathological stage, tumor size, histologic type, and lymph node status. Gynecol Oncol 1993; 49: 354–358.
31. Vithalani V, Acan M, Deneau D, Meunier F. Pneumocystis carinii pneumonia in patients with cancer. An increasing incidence. Cancer 1993; 71: 481–485.
32. Kovacs JA, Hiennazon JW, Macher AM, et al. Pneumocystis carinii pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984; 100: 663–671.
CASE PRESENTATION

Pulmonary embolism or Pneumocystis jiroveci pneumonia?

33. Ewig S, Bauer T, Schneider C, et al. Clinical characteristics and outcome of Pneumocystis carinii pneumonia in HIV-infected and otherwise immunosuppressed patients. Eur Respir J 1995; 8: 1548–1553.

34. Wehle K, Schirmer M, Dunnebacke-Hinz J, Kupper T, Pflaizer P. Quantitative differences in phagocytosis and degradation of Pneumocystis carinii by alveolar macrophages in AIDS and non-HIV patients in vivo. Cytopathology 1993; 4: 231–236.

35. Mansharamani NG, Garland R, Delaney D, Koziel H. Management and outcome patterns for adult Pneumocystis carinii pneumonia, 1985 to 1995: comparison of HIV-associated cases to other immunocompromised states. Chest 2000; 118: 704–711.

36. Fraser JL, Lilly C, Israel E, Hulme P, Haniff PA. Diagnostic yield of bronchoalveolar lavage and bronchoscopic lung biopsy for detection of Pneumocystis carinii. Mayo Clin Proc 1996; 71: 1025–1029.

37. Gagnon S, Boota AM, Fischl MA, Boier H, Kirker OW, La Viole L. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med 1990; 323: 1444–1450.

38. Baxxette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med 1990; 323: 1451–1457.

39. Parejo JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV Pneumocystis carinii pneumonia. Chest 1998; 113: 1215–1224.

40. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc 1994; 71: 5–13.

41. Dix AR, Brooks WH, Rozsaun TL, Morford LA. Immune defects observed in patients with primary malignant brain tumors. J Neuroimmunol 1999; 100: 216–232.

42. Henson JW, Jalaj JK, Walker RN, Slover DE, Fels AO. Pneumocystis carinii pneumonia in patients with primary brain tumors. Arch Neurol 1991; 48: 406–409.

43. In't Veen JC, Kaufmann R. Human immunodeficiency virus, fever, dyspnoea and a dry cough. Expect the unexpected? Neth J Med 1993; 43: 5–13.

44. Clark K, Salim A, Wilks JA. Diagnosis of pulmonary embolism by spiral CT: a case study. W V Med J 1999; 95: 307–308.

45. Hughes WT, Rivera GK, Schell RJ, Thornton D, Loft L. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonia. N Engl J Med 1987; 316: 1627–1632.

46. Mansharamani NG, Balachandran D, Vohrovsky J, Garland R, Koziel H. Peripheral blood CD4+ T-lymphocyte counts during Pneumocystis carinii pneumonia in immunocompromised patients without HIV infection. Chest 2000; 118: 712–720.

47. Kovacs JA, Gill VJ, Meshnick S, Masur H. New insights into transmission, diagnosis, and drug treatment of Pneumocystis carinii pneumonia. JAMA 2001; 286: 2450–2460.