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Case Report

Three cases of presumed pneumocystis pneumonia in patients receiving bortezomib therapy for multiple myeloma

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ABSTRACT

Introduction: This paper presents three probable cases of pneumocystis pneumonia in patients receiving bortezomib therapy for multiple myeloma.
Presentation of cases: Three patients receiving bortezomib therapy for multiple myeloma presented with dyspnoea, non-productive cough, and fevers. These patients deteriorated despite receiving broad-spectrum antibiotic therapy with piperacillin + tazobactam and azithromycin and an assortment of other antimicrobials but promptly responded to sulfamethoxazole + trimethoprim therapy. Only one of the patients exhibited a positive *Pneumocystis jirovecii* PCR test but testing was sub-optimal.
Discussion: Although only one of the patients exhibited a positive sputum *P. jirovecii* PCR test, the diagnosis of PCP in these three patients is supported by their; clinical and radiological features consistent with PCP, deterioration despite receiving broad-spectrum antibiotic therapy, and prompt responses to sulfamethoxazole + trimethoprim therapy. In the patients with negative *P. jirovecii* PCR bronchoalveolar lavage specimens were not obtained as these patients were deemed too high risk to undergo the procedure. Although the three patients were also receiving dexamethasone therapy, the doses and durations were at the threshold of those expected to cause PCP.
Conclusion: 26S proteosome inhibitor therapy for multiple myeloma may be a risk factor for PCP and clinicians should adopt a high level of suspicion for PCP in patients receiving these medications until conclusive evidence is obtained.

Introduction

Pneumocystis jirovecii is an airborne fungus which exclusively colonises the respiratory tract of humans. In immunocompromised individuals it may cause pneumocystis pneumonia (PCP), which typically exhibits an insidious course in HIV-infected individuals and a more fulminant course in non-HIV-infected individuals [1–8]. *P. jirovecii* polymerase chain reaction of bronchoalveolar lavage (BAL) specimens is the current gold standard diagnostic test for PCP in these patients [9]. Bortezomib is a reversible mammalian 26S proteosome inhibitor used for remission induction and maintenance in multiple myeloma. It has been implicated in several cases of pulmonary disease and one case of PCP has been reported [10–12]. This paper presents three probable cases of PCP in patients receiving bortezomib therapy.

Presentation of cases

Written informed consent was obtained from the patient or, in cases where the patient did not have the capacity to give informed consent, from their next of kin for publication of this case series. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Case 1

A 76-year-old male with multiple myeloma presented with malaise, confusion, pleuritic chest pain, dyspnoea, non-productive cough, and fevers for ten days. His past medical history included; type 2 diabetes mellitus, iatrogenic primary adrenal insufficiency, Parkinson disease, ischaemic heart disease, and non-melanoma skin cancers. Fourteen days previously, he had commenced his first cycle of cyclophosphamide 500 mg

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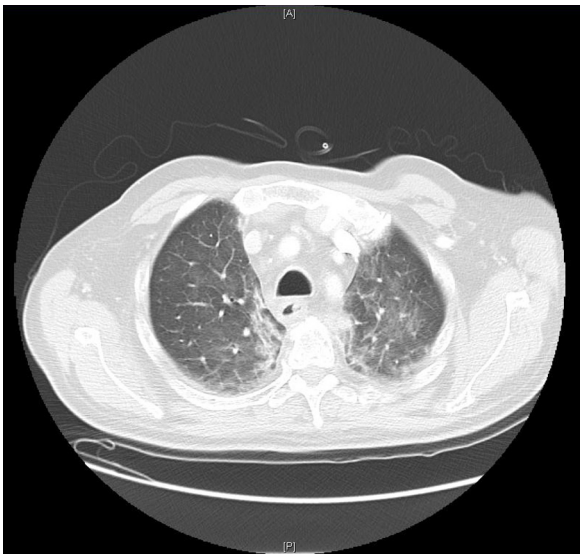

Fig. 1. CT chest demonstrating left and right upper lung lobe ground-glass infiltration.

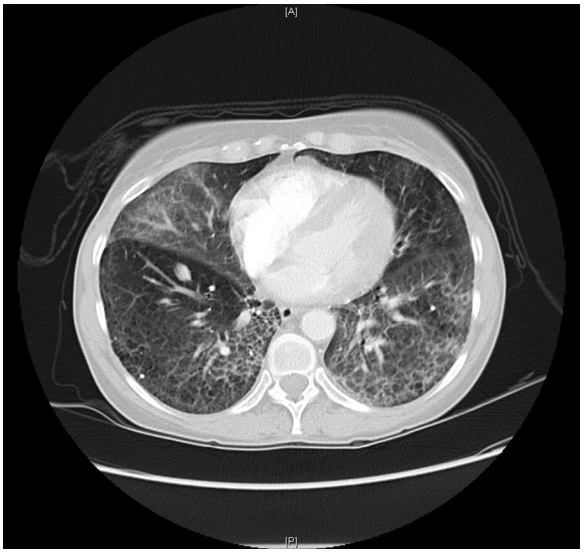

Fig. 2. CT chest demonstrating left and right lower lung lobe extensive interstitial fibrotic changes with honey-combing.

intravenously, bortezomib 2.8 mg subcutaneously, and dexamethasone 20 mg orally on days one, eight, and 15. He had previously been receiving prednisone 10 mg orally daily for his adrenal insufficiency. The patient's vital signs were within normal ranges. He was emaciated. Coarse inspiratory crepitations were auscultated over the left and right lower lung zones. A full blood count (FBC) demonstrated a white cell count (WCC) of 3.44×10^9/L and a neutrophil count of 2.0×10^9/L and a lymphocyte count of 1.0×10^9/L, a blood haemoglobin concentration (HbC) of 104 g/L, and a platelet count (PtC) of 74×10^9/L. The serum C-reactive protein (CRP) concentration was 123 mg/L. Serum protein electrophoresis and immunofixation demonstrated hypergammaglobulinaemia with an IgG kappa paraprotein. The serum electrolytes, urea, creatinine (EUC), calcium, magnesium, and phosphate (CMP) concentrations, liver function tests (LFT), and coagulation studies were within normal ranges. A chest radiograph demonstrated reticular middle and lower lung zone opacities bilaterally. A chest computed tomography scan (CT) demonstrated left and right lower lung lobe patchy consolidation and left and right upper lung lobe ground-glass infiltration (Fig. 1). Two blood culture sets demonstrated nil growth. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* serology and urine Legionella and Pneumococcal antigen tests were negative. After receiving benzylpenicillin 1.2 g intravenously every 6 h and doxycycline 100 mg orally every 12 h for two days, the patient did not improve clinically. The antimicrobial regimen was changed to piperacillin + tazobactam 4 g + 0.5 g intravenously every 8 h and azithromycin 500 mg intravenously every 24 h. He was also transfused with two units of packed red blood cells. Five days later he continued to exhibit hypoxaemia with a SpO_2 of 88% on room air and fevers of 37.8 °C. The antibiotic regimen was again changed to sulfamethoxazole + trimethoprim 1600 + 320 mg orally every 8 h. An expectorated sputum specimen obtained one day later exhibited a negative *P. jirovecii* β-tubulin real-time polymerase chain reaction (qPCR) test. BAL specimens could not be obtained as the patient's respiratory failure and frailty precluded bronchoscopy. *P. jirovecii* microscopy was not ordered. Over the following five days the patient improved clinically and his serum CRP concentration normalised. He continued oral sulfamethoxazole + trimethoprim to complete a total of 21 days of therapy.

Case 2

A 55-year-old female with multiple myeloma presented with malaise, dyspnoea, non-productive cough, and fevers for two days. Her past medical history included; chronic obstructive pulmonary disease, hypertension, gastro-oesophageal reflux disease, recurrent herpes zoster, non-melanoma skin cancers, major depressive disorder, and appendicectomy. Eighteen days previously, she had commenced her third cycle of doxorubicin 28 mg orally on days one and four and bortezomib 1.8 mg subcutaneously and dexamethasone 20 mg orally on days one, four, eight, and 11. She was tachycardic at 137 beats per minute and febrile at 37.7 °C but neither hypotensive nor hypoxaemic. Coarse inspiratory crepitations were auscultated over the left and right lower lung zones. A FBC demonstrated a WCC of 3.13×10^9/L and a neutrophil count of 1.9×10^9/L and a lymphocyte count of 0.7×10^9/L, a HbC of 100 g/L, and a PtC of 519×10^9/L. Serum protein electrophoresis and immunofixation demonstrated hypogammaglobulinaemia with an IgA lambda paraprotein. The serum IgG, IgA, and IgM concentrations were 3.02 g/L, 0.59 g/L, and 0.51 g/L respectively. EUC, CMP, LFT, and coagulation studies were within normal ranges. The serum CRP concentration was 140 mg/L. A chest radiograph demonstrated reticular opacities within the right middle and lower and left lower lung zones. A chest CT demonstrated left and right lower lung lobe extensive interstitial fibrotic changes with honey-combing (Fig. 2). Three blood culture sets demonstrated nil growth. *C. pneumoniae* and *M. pneumoniae* serology and urine Legionella and Pneumococcal antigen tests were negative. After receiving piperacillin + tazobactam 4 + 0.5 g intravenously every 8 h and azithromycin 500 mg intravenously every 24 h for three days the patient did not improve and exhibited a SpO_2 of 80% and a PaO_2 of 59.7 mmHg whilst receiving oxygen at a rate of 15 L/min via non-rebreather mask and a fever of 39.1 °C. An expectorated sputum specimen exhibited a negative *P. jirovecii* immunofluorescence test but a positive β-tubulin qPCR test. The antibiotic regimen was changed to sulfamethoxazole + trimethoprim 1200 + 240 mg intravenously every 8 h. After five days the patient improved clinically and her serum CRP concentration normalised. She continued sulfamethoxazole + trimethoprim 800 + 160 mg orally every 6 h to complete a total of 21 days of therapy.

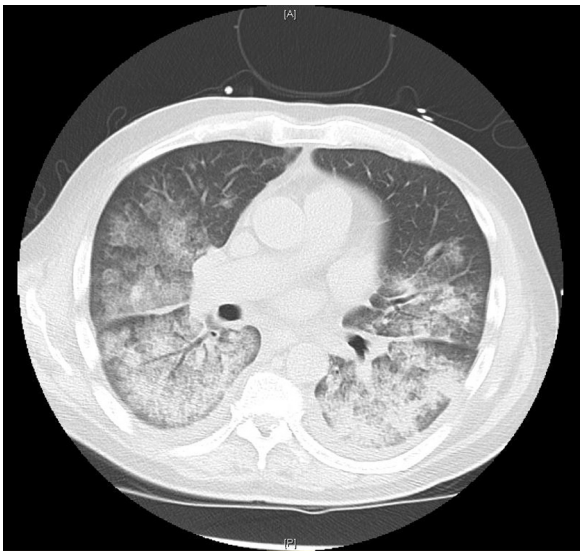

Fig. 3. CT chest demonstrating diffuse airspace consolidation and small pleural effusions bilaterally.

Case 3

A 74-year-old male with multiple myeloma presented with dyspnoea, non-productive cough, right-sided pleuritic chest pain, and fevers for one day. His medical history also included; gastro-oesophageal reflux disease, peptic ulcer disease, recurrent herpes zoster, gout, glaucoma, and inguinal hernia repair. Nine days previously, he had commenced his fourth cycle of cyclophosphamide 500 mg intravenously on day one and bortezomib 2.2 mg subcutaneously and dexamethasone 20 mg orally on days one, four, eight, and 11. He was tachycardic at 110 beats per minute, hypotensive at 86/53 mmHg, tachypnoeic at 26 breaths per minute, hypoxaemic with a SpO_2 of 93% and a PaO_2 of 63.5 mmHg whilst receiving oxygen at a rate of 15 L/min via non-rebreather mask, and febrile at 38.5 °C. Bronchial breath sounds and coarse inspiratory crepitations were auscultated throughout the lung zones bilaterally. A FBC demonstrated a WCC of 15.83×10^9/L and a neutrophil count of 11.3×10^9/L and a lymphocyte count of 0.7×10^9/L, a HbC of 138 g/L, and a PtC of 190×10^9/L. The serum CRP concentration was 114 mg/L. Serum protein electrophoresis and immunofixation demonstrated an IgA lambda paraprotein. The serum IgG, IgA, and IgM concentrations were 2.36 g/L, 0.50 g/L, and 0.24 g/L respectively. EUC, CMP, LFT, and coagulation studies were within normal ranges. A chest radiograph and a CT chest demonstrated diffuse airspace consolidation and small pleural effusions bilaterally (Fig. 3). He was admitted to the high dependency unit and commenced continuous positive airway pressure ventilation via high flow nasal prongs and piperacillin + tazobactam 4 + 0.5 g intravenously every 8 h, azithromycin 500 mg intravenously every 12 h, vancomycin 1.5 g intravenously every 12 h, and oseltamivir 75 mg orally every 12 h. Three sets of blood cultures also demonstrated nil growth. *C. pneumoniae*, *Bordetella pertussis*, *M. pneumoniae*, and Influenza virus serology and urine Legionella and Pneumococcal antigen tests were negative. Influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza virus nasopharyngeal aspirate immunofluorescence tests were negative. After three days there was no improvement clinically and the serum CRP concentration increased to 281 mg/L. He commenced sulfamethoxazole + trimethoprim 1200 + 400 mg intravenously every 8 h and prednisone 40 mg orally every 12 h and received 60 g of intravenous immunoglobulin. An induced sputum specimen obtained one day later demonstrated light growth of upper respiratory tract flora and mixed *Candida* species on culture and negative *P. jirovecii* immunofluorescence and β-tubulin qPCR test tests. BAL specimens could not be obtained as the patient's respiratory failure and septic shock precluded bronchoscopy. After four days, the patient improved clinically and the blood WCC and serum CRP concentration normalised. He was discharged to home five days later and continued sulfamethoxazole + trimethoprim 1600 + 320 mg orally every 8 h to complete a total of 21 days of therapy.

Discussion

Although a positive *P. jirovecii* sputum PCR test result was only obtained in case 2, the clinical and radiological features observed in all three cases were consistent with PCP. All three cases deteriorated despite receiving broad-spectrum antibiotic therapy with piperacillin + tazobactam and azithromycin and an assortment of other antimicrobials, suggesting the presence of a pathogen resistant to these agents. Although pneumonia due to *Toxoplasmosis gondii* and viruses may be clinically and radiologically indistinguishable from PCP, it was thought that PCP was the most likely diagnosis. All three cases responded promptly to sulfamethoxazole + trimethoprim therapy.

The paucity of investigation results supporting the diagnosis of PCP in these cases may be attributed to the lack of appropriate investigations. No investigations for the identification of *P. jirovecii* were performed prior to the commencement of sulfamethoxazole + trimethoprim therapy in cases 1 and 3. Furthermore, expectorated and induced sputum specimens were tested in all three cases because the high risk of respiratory deterioration precluded bronchoscopy to obtain BAL specimens. *P. jirovecii* PCR testing of induced sputum specimens exhibits a sensitivity of 78.9% and a specificity of 89.0% compared with BAL specimens in HIV-infected individuals [13]. The lower fungal burden of non-HIV-infected individuals with PCP compared with HIV-infected individuals may also have contributed to the lack of evidence to confirm the diagnosis of PCP in cases 1 and 3 [14,15].

All three cases received oral dexamethasone therapy at doses which may precipitate PCP, so these cases cannot be directly attributed to treatment with bortezomib. However, the doses of dexamethasone therapy in all three cases were at the threshold of those expected to cause PCP, equivalent to 20 mg of prednisone daily for greater than four weeks [16,17].

A review of the literature identified one reported case of PCP caused by bortezomib [13] and no reported cases of PCP caused by carfilzomib, a second generation 26S proteosome inhibitor. Both agents inhibit the chymotrypsin-like activity of the mammalian 26S proteosome, thereby preventing proteolysis of ubiquitinated proteins and causing activation of signalling cascades, cell-cycle arrest, and apoptosis [18]. As *P. jirovecii* is an obligate intracellular fungus, it is possible that failure of host cell apoptosis may facilitate its reproduction and transition from respiratory tract coloniser to pathogen. Furthermore, all three cases exhibited lymphopaenia, which may have predisposed them to developing PCP. Patients receiving bortezomib or carfilzomib therapy for multiple myeloma also exhibit a higher incidence of herpes zoster compared with those receiving dexamethasone therapy, but there does not appear to be any correlation with the lymphocyte count [19–21], suggesting that 26S proteosome inhibitors may also predispose to opportunistic infections by impeding lymphocyte function.

In non-HIV-infected individuals, PCP exhibits a mortality rate of 90–100% in the absence of appropriate treatment [22] whilst PCP associated with acute respiratory failure, as observed in the three cases described in this series, exhibits a mortality rate of up to 67% despite appropriate treatment [23]. Guidelines have been

developed for the use of PCP prophylaxis with sulfamethoxazole + trimethoprim in patients with cancer [24] and a meta-analysis of 12 randomised controlled trials with 1245 non-HIV-infected patients with immunocompromise observed a 91% relative risk reduction and a number needed to treat of 15 for sulfamethoxazole + trimethoprim PCP prophylaxis with an incidence of adverse effects warranting prophylaxis cessation of 3.1% [25]. There is currently insufficient evidence to support the use of PCP prophylaxis in patients receiving 26S proteosome inhibitor therapy for multiple myeloma. However, in the event that further surveillance confirms the existence of an association between PCP and 26S proteosome inhibitor therapy, PCP prophylaxis may be indicated in these patients.

Conclusion

26S proteosome inhibitor therapy for multiple myeloma may be a risk factor for *Pneumocystis jirovecii* pneumonia. Clinicians should adopt a high level of suspicion for PCP and may consider lowering the threshold for PCP prophylaxis in patients receiving these medications until conclusive evidence is obtained.

Conflicts of interest statement

There are no conflicts of interest to declare.

References

[1] Arend SM, Kroon FP, van't Wout JW. *Pneumocystis carinii* pneumonia in patients without AIDS, 1980 through 1993. An analysis of 78 cases. Arch Intern Med 1995;155:2436–41.

[2] Ewig S, Bauer T, Schneider C, Pickenhain A, Pizzulli L, Loos U, et al. Clinical characteristics and outcome of *Pneumocystis carinii* pneumonia in HIV-infected and otherwise immunosuppressed patients. Eur Respir J 1995;8(September (9)):1548–53.

[3] Kovacs JA, Hiemenz JW, Macher AM, Stover D, Murray HW, Shelhamer J, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984;100(5):663–71.

[4] 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(3):704–11.

[5] Reid AB, Chen SC-A, Worth LJ. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools. Curr Opin Infect Dis 2011;24:534–44.

[6] Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis 2002;34(8):1098–107.

[7] Ward MM, Donald F. *Pneumocystis carinii* pneumonia in patients with connective tissue diseases: the role of hospital experience in diagnosis and mortality. Arthritis Rheum 1999;42(4):780–9.

[8] Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc 1996;71(1):5–13.

[9] Azoulay A, Bergeron A, Chevret S, Bele N, Schlemmer B, Menotti J. Polymerase chain reaction for diagnosing pneumocystis pneumonia in non-HIV immunocompromised patients with pulmonary infiltrates. Chest 2009; 135(3):655–61.

[10] Miyakoshi S, Kami M, Yuji K, Matsumura T, Takatoku M, Sasaki M, et al. Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. Blood 2006;107(May (9)):3492–4.

[11] Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 2004;127(October (2)):165–72.

[12] Wondergem MJ, Grünberg K, Wittgen BP, Wittgen BP, Sonneveld P, Zweegman S. Interstitial pneumonitis caused by *Pneumocystis jirovecii* pneumonia (PCP) during bortezomib treatment. Histopathology 2009;54:631–3.

[13] Aderaye G, Woldeamanuel Y, Asrat D, Lebbad M, Beser J, Worku A, et al. Evaluation of toluidine blue O staining for the diagnosis of *Pneumocystis jirovecii* in expectorated sputum sample and bronchoalveolar lavage from HIV-infected patients in a tertiary care referral center in Ethiopia. Infection 2008;36(3):237–43.

[14] Jacobs JA, Dieleman MM, Cornelissen EI, Groen EA, Wagenaar SS, Drent M. Bronchoalveolar lavage fluid cytology in patients with *Pneumocystis carinii* pneumonia. Acta Cytol 2001;45(3):317–26.

[15] Limper AH, Offord KP, Smith TF, Martin 2nd WJ. *Pneumocystis carinii* pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis 1989;140:1204–9.

[16] Sepkowitz KA. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome: who should receive prophylaxis. Mayo Clin Proc 1996;71:102–3.

[17] Sepkowitz KA, Brown AE, Armstrong D. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome: more patients, same risk. Arch Intern Med 1995;155:1125–8.

[18] MIMS Online. https://www.mimsonline.com.au [Accessed 29.03.14].

[19] Chanan-Khan A, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008;26(29):4784–90.

[20] Kim SJ, Kim K, Kim BS, Lee HJ, Kim H, Lee NR, et al. Bortezomib and the increased incidence of herpes zoster in patients with multiple myeloma. Clin Lymph Myeloma 2008;8(4):237–40.

[21] Kortuem KM, Stewart AK. Carfilzomib. Blood 2013;121(6):893–7.

[22] Hughes WT, Feldman S, Sanyal SK. Treatment of *Pneumocystis carinii* pneumonitis with trimethoprim-sulfamethoxazole. Can Med Assoc J 1975;112(13):47–50.

[23] Festic E, Gajic O, Limper AH, Aksamit TR. Acute respiratory failure due to pneumocystis pneumonia in patients without human immunodeficiency virus infection: outcome and associated features. Chest 2005;128(2):573–9.

[24] National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Prevention and treatment of cancer-related infections. Version 1.2013; 2014, http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf [Accessed 29.03.14].

[25] Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 2007;82(9): 1052–1059.