Two months later, she was admitted with a five day history of worsening breathlessness, that was initially on exertion but then at rest. There was an associated dry cough and low grade fever. She was still taking prednisolone 25 mg/day and one 500mg calcium/400 international units colecalciferol tablet per day but no other regular medications.

Clinical assessment revealed normal air entry on the left side of the chest with signs of a right pneumonectomy. She was tachycardic at 101 beats per minute, respiratory rate was raised at 24 per minute, oxygen saturation was reduced at 96% on 2 L/minute of oxygen. Chest radiograph demonstrated the left lung to be clear. Blood tests showed a white cell count of 14 x 10^9 /L (normal range 4-11 x 10^9 /L) with a neutrophilia and C reactive protein of 22 mg/L (normal range <10 mg/L). Computed tomography pulmonary angiography excluded pulmonary embolus but did show new left sided patchy and widespread ground glass changes with mediastinal lymphadenopathy (Figure 1).

Treatment for community acquired pneumonia with intravenous piperacillin/tazobactam and clarithromycin was given but she failed to improve. Screens for atypical bacterial, viral and fungal pneumonia screens were negative for legionella, mycoplasma, psittacosis, Q fever.

Two months later, she was admitted with a five day history of worsening breathlessness, that was initially on exertion but then at rest. There was an associated dry cough and low grade fever. She was still taking prednisolone 25 mg/day and one 500mg calcium/400 international units colecalciferol tablet per day but no other regular medications.

Clinical assessment revealed normal air entry on the left side of the chest with signs of a right pneumonectomy. She was tachycardic at 101 beats per minute, respiratory rate was raised at 24 per minute, oxygen saturation was reduced at 96% on 2 L/minute of oxygen. Chest radiograph demonstrated the left lung to be clear. Blood tests showed a white cell count of 14 x 10^9 /L (normal range 4-11 x 10^9 /L) with a neutrophilia and C reactive protein of 22 mg/L (normal range <10 mg/L). Computed tomography pulmonary angiography excluded pulmonary embolus but did show new left sided patchy and widespread ground glass changes with mediastinal lymphadenopathy (Figure 1).

Treatment for community acquired pneumonia with intravenous piperacillin/tazobactam and clarithromycin was given but she failed to improve. Screens for atypical bacterial, viral and fungal pneumonia screens were negative for legionella, mycoplasma, psittacosis, Q fever.

Abbreviations: BAL: bronchoalveolar lavage; CD4+: cluster of differentiation 4 positive; CT: computed tomography; CTLA-4: cytotoxic T lymphocyte associated antigen-4; HIV: human immunodeficiency virus; PCP: Pneumocystis jirovecii pneumonia; PCR: polymerase chain reaction; TMP/SMX: trimethoprim/sulfamethoxazole; TNF-alpha: tumour necrosis factor-alpha

Introduction

Recently immunotherapy has been successfully used in the management of malignancies including metastatic melanoma but is associated with autoimmune complications that may require corticosteroids and other immunosuppressive therapies to manage.

We describe a case of a woman with metastatic melanoma treated with ipilimumab who developed severe Pneumocystis jirovecii pneumonia (PCP) following treatment for ipilimumab-associated colitis with corticosteroids and infliximab. We outline the approach to diagnosis and management of this opportunistic infection.

PCP is an important infection to consider in the differential diagnosis for patients who are immunosuppressed and have an acute respiratory presentation. Early diagnosis and treatment is important especially since mortality is high in patients with cancer. Bronchoalveolar lavage and polymerase chain reaction is a useful diagnostic tool. First line therapy for PCP is trimethoprim/sulfamethoxazole. Patients with melanoma treated with immunomodulating therapies are at risk of autoimmune-related adverse events that may require powerful immunosuppressive treatments with the threat of subsequent opportunistic infection. Consideration should be given to PCP prophylaxis in these patients.

Case presentation

A 52-year-old woman presented with breathlessness. She had been found to have BRAF mutant metastatic melanoma five years previously. She had been treated with vemurafenib for two years and had had a right pneumonectomy for a single site of progression at the right lung hilum. She had continued vemurafenib but had progressed six months later, and had received three cycles of ipilimumab. The third cycle had been followed by an episode of terminal ileitis and pancolitis that had been treated with high dose corticosteroids (methylprednisolone followed by a slowly reducing course of prednisolone) and two doses of infliximab 5 mg/kg.
Pneumocystis pneumonia (PCP) is caused by the unicellular fungus \textit{Pneumocystis jirovecii}. Transmission of \textit{Pneumocystis} cysts is by airborne inhalation and immunocompromised people are at risk of developing opportunistic PCP either by re-activation of latent organisms in the lung or by acute infection [2]. People with impaired T cell immunity are at highest risk, especially with CD4 positive T cell counts below 200/\muL [3].

At risk groups for PCP include human immunodeficiency virus (HIV) infected individuals while non-HIV risk factors are immunodeficiency associated with cytotoxic or immunosuppressive therapies for solid and haematological malignancy, solid organ and bone marrow transplantation and inflammatory conditions [2]. Systemic corticosteroid use appears to predispose to PCP in solid tumours, especially for patients receiving high dose dexamethasone for central nervous system disease [4]. Patients treated with the anti-TNF drug infliximab for inflammatory bowel disease and rheumatological conditions have developed PCP. TNF-alpha is important in the immune response to infection, especially within the lung, but these patients are frequently also treated with corticosteroids [5,6]. Post-marketing surveillance has shown the incidence of PCP in patients treated with Infliximab to be 0.4% [7].

Ipilimumab is a monoclonal antibody that blocks cytotoxic T lymphocyte associated antigen-4 (CTLA-4) preventing inhibition of T cell anti-tumour response. As a consequence of this it is associated with autoimmune related adverse events including a spectrum of gastrointestinal toxicities. Colitis is seen in fewer than 10% of patients but can lead to bowel obstruction and perforation [8]. Management of grade 3 (increase in stool frequency of >7 per day, fever, severe abdominal pain or peritonism) and 4 (life-threatening) colitis involves excluding gastrointestinal infection and treating with high dose steroids for example intravenous methylprednisolone converting to a tapering dose of oral prednisolone over six to eight weeks with resolution. In the absence of improvement at 48 hours infliximab can be initiated. Ipilimumab should be permanently discontinued. Surgical input may be required in the presence of bowel obstruction or perforation [9].

Clinical presentation of PCP is non-specific with dry cough and progressive breathlessness typically over one to three weeks. Fever may be present. Acute breathlessness and pleuritic chest pain may herald development of pneumothorax. Examination findings include tachypnoea, tachycardia, hypoxia including exercise desaturation and cyanosis. Auscultation of the chest is generally unremarkable [10].

The typical chest radiograph feature is bilateral perihilar interstitial shadowing that becomes more diffuse over time but it may be normal especially early in the course of the disease. More unusual features are solitary or multiple nodules and pneumothoraces. Pleural effusions and lymphadenopathy are rare [2,10]. Computed tomography (CT) of the chest usually demonstrates extensive ground glass opacification but may also show cystic lesions and consolidation in non-HIV patients. In HIV patients ground glass opacification tends to be diffuse and inhomogeneous. In non-HIV patients this pattern is seen but there may be more sharply demarcated and lobular ground glass opacifications [11].

Light microscopy, immunofluorescent assays and polymerase chain reaction (PCR) are important diagnostic investigations in the context of non-specific clinical and radiological features. These can be performed on induced sputum, bronchoalveolar lavage (BAL) or transbronchial lung biopsy samples. For microscopic examination staining is necessary since \textit{Pneumocystis} cannot be cultured [10]. The least invasive method of investigation is testing of sputum samples induced using hypertonic saline. However microscopic diagnosis using induced sputum and BAL samples is less sensitive in non-HIV cases of \textit{Pneumocystis}, where fewer organisms tend to be present and sensitivity may be less than 50% [12]. PCR of induced sputum or BAL has been shown to be more useful with sensitivity of 87%, specificity of 92% and negative predictive value of over 98%. Samples, especially non-invasive induced sputum, should be taken prior to or soon after treatment for PCP is started to reduce the risk of false negative results. One drawback of PCR is the detection of \textit{Pneumocystis} asymptomatic colonization. However the high negative predictive value of PCR means that a negative result indicates treatment for PCP can be stopped [13]. The accuracy of PCR also means lung biopsy for diagnosis is rarely required.

The British HIV Association stratifies PCP infection by severity and this determines the recommended treatment. Severity depends on symptoms, degree of hypoxia and chest radiographic features. Mild
Pneumocystis jirovecii pneumonia in a patient with melanoma treated with infliximab and corticosteroids for ipilimumab-associated colitis


There is evidence of transmission of Pneumocystis between people including strains resistant to TMP/SMX, a first line treatment for PCP. Therefore it may be sensible to limit contact of infected individuals with other immunocompromised patients during the acute phase of the illness [16].

Pneumocystis prophylaxis is used successfully for HIV patients with low CD4 counts and for organ transplant recipients. It has been suggested prophylaxis is considered for patients receiving the equivalent of 20 mg prednisolone for more than one month and for inflammatory bowel disease patients treated with three immunosuppressive therapies including anti-TNF therapy. However there remains a lack of consensus guidelines relating to PCP prophylaxis for patients receiving immunosuppressive therapy outside of the organ transplantation setting. The reduction in risk of PCP also has to be balanced against the risk of toxicity from the commonly used drugs for prophylaxis. For example TMP/SMX can cause hypersensitivity, severe skin rashes that may progress to Stevens-Johnson syndrome or toxic epidermal necrolysis, leukopenia, renal and hepatic dysfunction. Dapsone may tend to be associated with fewer Pneumocystis organisms but larger

numbers of neutrophils and greater pulmonary inflammation, which correlates with more severe hypoxaemia and poorer outcomes [20].

Conclusion
PCP is an important opportunistic infection to consider in the differential diagnosis for patients who are immunosuppressed and have an acute respiratory presentation. Early diagnosis and treatment is important especially since mortality is high in patients with cancer. Patients with melanoma treated with immunomodulating therapies are at risk of autoimmune-related adverse events that may require powerful immunosuppression to manage with the threat of subsequent opportunistic infection. Consideration should be given to PCP prophylaxis in these patients.

Declarations
Written informed consent was obtained from the patient described in this case report.

The authors declare that there is no conflict of interest regarding the publication of this paper.

The authors declare that no specific sources of funding were sought.

The authors declare that there are no financial or non-financial competing interests.

References
   -from a commensal to pathogen: clinical and diagnostic review. Parasitol Res 114: 3577-3585. [Crossref]
Slevin F (2016) Pneumocystis jirovecii pneumonia in a patient with melanoma treated with infliximab and corticosteroids for ipilimumab-associated colitis


