CASE REPORT

Pneumocystis pneumonia in a non-HIV patient on chronic corticosteroid therapy: a question of prophylaxis

Michael J Plakke, Leena Jalota, Benjamin J Lloyd

Department of Internal Medicine, The Reading Hospital and Medical Center, West Reading, Pennsylvania, USA

Correspondence to
Dr Michael J Plakke,
mjplakke@gmail.com

SUMMARY

A man in his late 50s with a history of membranoproliferative glomerulonephritis presented with fever and mild dyspnoea. He was HIV-negative and had been on corticosteroids as immunosuppression for 6 months prior to tapering them off 1 week before presentation. He was not taking prophylaxis for *Pneumocystis jirovecii* pneumonia. After unsuccessful treatment for community-acquired pneumonia, his condition worsened and he required intubation and mechanical ventilation. Full respiratory workup including bronchoscopy revealed *P jirovecii* as a source for the patient's infection. He was treated successfully with a 21-day course of trimethoprim-sulfamethoxazole and eventually weaned off the ventilator. He has had no complications to date. In our review of this case and the existing literature, we believe that proper utilisation of prophylaxis for pneumocystis pneumonia may have prevented our patient's transfer to intensive care unit. In our article, we discuss this issue and explore current evidence for prophylaxis.

BACKGROUND

Pneumocystis pneumonia (PCP) is a developing issue among non-HIV patients receiving chronic immunosuppression. Corticosteroids appear to be the most commonly implicated agents in this regard, particularly when used with other immunosuppressants. This case serves as a reminder that it is important to consider the diagnosis of PCP because the morbidity and mortality of this infection is significantly worse in this population compared to patients who are HIV-positive. PCP prophylaxis should also be considered in select patients, especially those on corticosteroids for extended periods of time.

CASE PRESENTATION

A man in his late 50s presented with fever and mild dyspnoea. He had a history of chronic renal failure secondary to membranoproliferative glomerulonephritis (MPGN) diagnosed 6 months prior to admission. He had been treated with 60 mg of prednisone daily for 6 months and mycophenolate mofetil for 4 months without improvement of his renal function. He had poor follow-up and was never placed on prophylaxis for PCP. His corticosteroids were tapered off 1 week prior to admission with the plan to initiate haemodialysis in the near future, but he became ill in the interim.

On admission, the patient appeared ill but was not in respiratory distress. He was febrile at 39.3°C,

tachycardic at 94 bpm, tachypneic at 24 bpm, and had a blood pressure of 179/95. He had bilateral fine crackles on pulmonary examination and bilateral pitting oedema of his lower extremities. There was an infiltrate noted on chest radiography; therefore, he was admitted for sepsis owing to pneumonia and started on empiric antibiotic coverage for the most common bacterial pathogens.

Despite extension to broad-spectrum antibiotics including vancomycin and piperacillin-tazobactam, there was no improvement. The patient had daily fever spikes, no new lung findings on chest radiography, and cultures remained negative. A high-resolution CT scan of the thorax was obtained. Following this, he underwent a series of laboratory tests, including broad serological studies, to establish a diagnosis. Subsequent testing revealed no positive findings. On the seventh day of hospital admission, the patient's respiratory status rapidly declined; arterial partial pressure of oxygen was low at 57 mm Hg (75–90 mmHg). After minimal improvement using bi-level positive airway pressure, endotracheal intubation was performed and the patient was admitted to the intensive care unit (ICU) for progressive hypoxemic respiratory failure.

While being mechanically ventilated in the ICU, bronchoscopy was performed and bronchoalveolar lavage (BAL) revealed the presence of *Pneumocystis jirovecii*. The patient was initially started on high-dose intravenous trimethoprim-sulfamethoxazole (TMP-SMX) and intravenous corticosteroids. He required mechanical ventilation and vasopressor support for two additional days owing to septic shock. On his third day in the ICU, he was successfully weaned off mechanical ventilation and vasopressor support. The antibiotics and corticosteroids were converted to oral dosing, and he required decreasing amounts of oxygen. After achieving respiratory and hemodynamic stability, he was transferred to an intermediate level of care. He spent a total of 6 days in the ICU. After gradual return to his baseline level of respiratory function, he was discharged on hospital day 17.

To date, he has not experienced any complications from PCP or his ICU stay. He is currently receiving thrice weekly haemodialysis owing to end-stage renal disease from MPGN. He is no longer taking corticosteroids or TMP-SMX.

INVESTIGATIONS

On admission, pulse oximetry revealed an oxygen saturation of 96% on room air. A white blood

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count was decreased at 3700 ($4.8\text{--}10.8 \times 10^3$) with slight eosinophilia of 6.2% (0–6%). Radiography of the chest demonstrated a dense infiltrate in the right lung apex concerning for possible early pneumonia. Blood and sputum cultures were negative.

A high-resolution CT scan of the thorax on day 4 of the admission demonstrated small bilateral pleural effusions with passive atelectasis and diffuse ground-glass opacification (figure 1).

BAL washings sent for culture showed cyst forms of *P jirovecii* stained with Grocott-Gomori methenamine-silver nitrate (GMS) (figure 2).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for fever and dyspnoea in an immunocompromised patient is broad. While infectious causes are most common, inflammatory causes, pulmonary oedema, acute respiratory distress syndrome, neoplastic processes, and drug-related causes should be considered.

Atypical pneumonia often presents with dry cough, fever, myalgia, and malaise; it may be extremely difficult to identify specific pathogens in immunocompromised patients based on clinical findings. Aside from more common community-acquired bacteria, opportunistic bacterial pathogens of the lung such as *Mycobacterium tuberculosis* and *Nocardia* should be strongly considered. Viral aetiologies of pneumonia include cytomegalovirus, herpes simplex virus, and severe influenza. Fungal organisms such as *Aspergillus* and *Cryptococcus* may also present with non-specific pulmonary symptoms similar to those brought on by *Pneumocystis*. Parasitic lung infections are even more rare and include the helminths *Strongyloides* and *Ascaris* and the protozoan *Toxoplasma*. Löffler's syndrome includes pulmonary infiltrates and peripheral blood eosinophilia associated with helminthic infections, which may also present with concurrent gastrointestinal symptoms.¹ Toxoplasmosis is rare in non-HIV immunocompromised patients but may present with pulmonary symptoms and neurological findings.

Inflammatory lung processes that may present as fever and dyspnoea include acute eosinophilic pneumonia, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, and connective tissue diseases. These disorders may also present

with vague respiratory symptoms, eosinophilia, and lack of response to empiric antibiotic therapy.

Underlying neoplastic processes should be ruled out in patients with a history of weight loss and the presence of other risk factors such as smoking, exposure to asbestosis, and history of local radiation therapy.

Methotrexate, bleomycin, and cyclophosphamide are known to cause pulmonary toxicity and should also be discussed as possible causes of fever and dyspnoea in immunocompromised patients taking these drugs.^{2–4} Amiodarone and nitrofurantoin are also commonly used drugs that are known to cause pulmonary toxicity and should be identified in patients with refractory dyspnoea.^{5,6}

TREATMENT

Treatment with TMP-SMX and adjunctive corticosteroids resulted in rapid clinical improvement and successful weaning off mechanical ventilation. Upon discharge, TMP-SMX was continued for a 21-day course and the corticosteroids were tapered off.

OUTCOME AND FOLLOW-UP

The patient completed his course of antibiotic treatment and corticosteroid taper for PCP and has not had any respiratory complications since his hospitalisation.

He is no longer on chronic immunosuppression for MPGN, but receives haemodialysis thrice weekly.

DISCUSSION

PCP is a potentially fatal respiratory infection in immunocompromised hosts caused by the fungal organism *P jirovecii*. Though traditionally thought of as an AIDS-defining illness in patients with HIV, the incidence of PCP in patients without HIV is increasing, mostly owing to iatrogenic immune system defects related to chronic immunosuppressive therapy.⁷ The most commonly identifiable risk factor is corticosteroid use, and other immunosuppressive drugs may also play a role.^{8–10} It is crucial to identify immunosuppressed individuals at risk for developing PCP because several studies have shown that the morbidity and mortality in non-HIV patients is significantly worse than in patients with HIV.^{9–15}

Much research has been dedicated to identifying risk factors in non-HIV patients for developing PCP. The most common underlying conditions in these patients are haematological malignancies, organ transplantation, and chronic inflammatory

Figure 1 High-resolution CT of the thorax showing small bilateral pleural effusions with passive atelectasis and diffuse ground-glass opacification.

Figure 2 Grocott-Gomori methenamine-silver nitrate stain of *Pneumocystis jirovecii* organisms obtained from bronchoalveolar lavage fluid culture.

diseases such as Wegener's granulomatosis and polymyositis.¹¹ PCP can rarely develop in other diseases requiring long-term immunosuppression, such as asthma, chronic obstructive pulmonary disease, and glomerulonephritis.¹⁶ Among immunosuppressive drugs linked with onset of PCP, corticosteroids are the most widely culpable. A recent review of the literature implicates corticosteroid use in 55–100% of HIV-negative patients with PCP.¹¹ This is thought to be caused by defects in T-cell immunity, including a decrease in the number of circulating CD4+ lymphocytes.⁹ There is also evidence to suggest that patients are at the highest risk during corticosteroid tapering, possibly as a result of an immune reconstitution syndrome.^{8 11 17 18} The association with other immunosuppressive agents such as monoclonal antibodies, calcineurin inhibitors, and cytotoxic agents has been less well described but poses an increased risk for development of PCP as well, especially when used in conjunction with corticosteroids.^{10 19}

In patients with HIV, PCP presents with gradually worsening dyspnoea and typically has an indolent or even asymptomatic course. In contrast, HIV-negative patients with PCP have a much more rapid onset of respiratory insufficiency and may present in fulminant respiratory failure.¹⁴

Diagnosis of PCP in non-HIV patients is the same as it is in those with HIV. Chest radiography may show bilateral interstitial or alveolar infiltrates and chest CT may show ground-glass opacities.¹⁴ Pneumocystis is extremely difficult to culture, so traditionally the diagnosis of PCP is confirmed by visualisation of organisms in sputum or BAL washings stained using GMS or methanol-Giemsa solutions. It should be kept in mind that BAL has low sensitivity in community-acquired pneumonia and should be reserved for severe cases, such as immunosuppressed patients with significant respiratory compromise.²⁰ Newer methods, including PCR assays, positron emission tomography scanning, and identification of serum markers may facilitate earlier diagnosis in non-HIV-infected patients.¹⁰

Less is known about the treatment in non-HIV-related PCP compared to HIV-related PCP, but most research suggests subtle, if any, differences. The first line treatment for PCP is TMP-SMX regardless of HIV status.²¹ Patients that cannot tolerate this should be treated with primaquine plus clindamycin, atovaquone alone, or intravenous pentamidine.²¹ Adjunctive corticosteroids have shown definite clinical benefit in HIV-infected patients with moderate to severe PCP, and although there is less supporting data, guidelines recommend adding corticosteroids to the therapeutic regimen in patients without HIV as well.^{21–23} Given the fulminant course and higher death rates in non-HIV-infected patients with moderate to severe PCP, the use of glucocorticoid therapy in patients who have an arterial blood gas measurement that shows a partial pressure of oxygen ≤ 70 mmHg on room air or an alveolar-arterial (A-a) oxygen gradient ≥ 35 mmHg or hypoxaemia on pulse oximetry is recommended based on guidelines available for PCP in HIV patients.^{22 24}

Compared to HIV-positive patients, HIV-negative patients with PCP have significantly worse outcomes. This includes higher rates of hospitalisation, respiratory failure, ICU admission, and mechanical ventilation in HIV-negative patients.¹⁹ Furthermore, published death rates in HIV-negative patients range from 35% to 50%, which may quadruple the rates of their HIV-positive counterparts.^{9 11 15 19 25} It is not known whether these statistics are skewed by the underlying diagnoses of malignancy or structural lung distortions in HIV-negative patients, but the differences are striking and warrant significant

discussion about proper management of these vulnerable patients.¹²

The use of prophylaxis for PCP in HIV-negative patients is an area of study that has garnered much attention given the increasing incidence of the infection and worse outcomes in this population. PCP prophylaxis with TMP-SMX has long been recommended in HIV-positive patients when CD4 counts drop below 200 cells/ μ l.²⁶ Guidelines have been published regarding the use of prophylaxis in HIV-negative patients on immunosuppression for cancer,^{27 28} and standards of practice exist for prophylaxis in solid organ transplant recipients. However, until very recently, no recommendations have been made concerning patients on chronic immunosuppressive therapy for other reasons. TMP-SMX has been shown to be efficacious in preventing PCP in HIV-negative immunocompromised patients, but these studies included patients with malignancies and solid organ transplants.^{29 30} There have been very few clinical trials regarding the use of PCP prophylaxis in non-HIV patients who are on chronic immunosuppression for inflammatory conditions alone. The exact subset of these patients in whom prophylaxis is warranted remains unclear. One recent meta-analysis suggests initiating prophylaxis when the risk for PCP is higher than 3.5%, which would not include patients on chronic corticosteroid therapy for mild inflammatory conditions.³⁰ Other authors suggest that a CD4 count of less than 300 cells/ μ l in HIV-negative patients may provide a general guide for who needs prophylaxis.³¹ The American Thoracic Society recently published the following recommendation.

In immune-suppressed patients without HIV, consider prophylaxis during time periods where prednisone dose exceeds 20 mg/day for greater than 1 month, especially if the patient has associated T-cell defects, or is receiving other cytotoxic drugs or antitumour necrosis factor agents.²¹

Based on these recommendations, it is probable that physicians underutilise prophylaxis for PCP in these patients.

There are certainly costs and risks associated with prophylactic treatment for PCP, but we believe that these drawbacks are outweighed by the possible benefits from providing prophylaxis to the correct patients. Life-threatening reactions to TMP-SMX include severe dermatological reactions, blood dyscrasias, and hepatotoxic reactions, but these events are rare and specific incidence rates are not known.³² A cost-benefit analysis performed on patients with Wegener's granulomatosis on immunosuppressive therapy showed increased life expectancy and reduced lifetime medical costs for patients on TMP-SMX prophylaxis.³³ This included costs incurred from adverse drug reactions resulting in the need to switch to alternate prophylactic therapy with monthly aerosolised pentamidine. We believe this analysis may be generalisable to patients with other inflammatory conditions on chronic immunosuppression.

In hindsight, our patient should have been considered for PCP prophylaxis given the dose and duration of his corticosteroid therapy for membranoproliferative glomerulonephritis and his simultaneous use of the cytotoxic agent mycophenolate mofetil. Although PCP was initially discussed, this diagnosis was not investigated until the sixth day of his hospital admission when his respiratory status began to decline rapidly. Retrospectively, questions were raised regarding the role of beginning empiric treatment for PCP in hospitalised patients in whom clinical suspicion for PCP is high. Had empiric treatment for PCP been initiated earlier, our patient's stay in the ICU likely could have been avoided. This case serves as an important reminder about how to approach similar patients.

Learning points

- Consider *Pneumocystis pneumonia* (PCP) early in patients with a history of chronic corticosteroid use presenting with pneumonia.
- Morbidity and mortality of PCP is significantly worse in HIV-negative compared to HIV-positive patients.
- Prophylaxis for PCP should be considered in all patients taking 20 mg or more of prednisone daily for a duration of greater than 1 month, based on recently published recommendations.

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