CASE REPORT

Fatal *Pneumocystis jirovecii* pneumonia in a HIV-negative adult

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Accepted 12 August 2015

SUMMARY

Pneumocystis jirovecii is responsible for *P. jirovecii* pneumonia (PJP) in immunocompromised individuals, with a recent rise of cases noted in non-HIV patients. A middle-aged man presented with new-onset cough, fever, hypoxia and tachypnoea. He was on a tapering course of dexamethasone for amiodarone-induced thyrotoxicosis. He developed worsening airspace disease necessitating mechanical ventilation. Bronchoalveolar lavage (BAL) fluid was positive for *P. jirovecii* and he was managed with trimethoprim/sulfamethoxazole and pentamidine, but succumbed to cardiorespiratory arrest. One-third of PJP cases occur in non-HIV patients, and have a higher morbidity and mortality. Most immunocompromised patients typically exhibit PJP during a corticosteroid taper. The accurate dose, duration or frequency of steroid use is not well established. Diagnosis of PJP in this population is more challenging due to lower BAL yield with alternate modalities such as serum/BAL β -D-glucan and PCR enhancing the yield. Further studies are needed to highlight PJP prophylaxis in patients with steroid use.

BACKGROUND

Pneumocystis jirovecii (formerly *P. carinii*) is an opportunistic pathogen that is responsible for life-threatening manifestations of *P. jirovecii* pneumonia (PJP) in immunocompromised individuals.¹ Discovered nearly 100 years ago and classified as a protozoan, it has recently been reclassified as an ascomycetous fungus.^{2,3} The scientific community had witnessed a resurgence of this pathogen in the 1980s with the onset of HIV infection. However, with the advent of effective antimicrobial prophylaxis, this entity is less commonly seen in clinical practice with HIV patients.⁴ This has paradoxically led to the emergence of this pathogen as a serious complication in other immunocompromised conditions not related to HIV.⁵ We report a rare clinical presentation of PJP in a patient with thyroiditis being treated with tapering doses of corticosteroids.

CASE PRESENTATION

A 63-year-old Caucasian man presented to our tertiary care academic medical centre reporting progressive dyspnoea of 1-week duration. This was associated with dry cough, orthopnoea and recent onset of fevers, chills and nocturnal rigours. On further review, he endorsed bilateral lower extremity swelling and recent weight gain of 20 lbs, but did not report any chest pain, nausea, emesis or diarrhoea. Medical history was significant for

hypertension, hyperlipidaemia, diabetes mellitus type II, chronic kidney disease stage III-B, obstructive sleep apnoea, sick sinus syndrome status post-permanent pacemaker and morbid obesity. He had a recent history of paroxysmal atrial fibrillation and was cardioverted to normal sinus rhythm. Subsequently, he was placed on amiodarone for maintenance therapy. However, this was complicated by hypothyroidism, likely as a side effect of the amiodarone therapy. Further work up with a thyroid ultrasound previously revealed type II toxicity, without any evidence of destructive pathology. The patient was started on dexamethasone 6 weeks prior to the current admission, at a dose of 6 mg, which was being gradually tapered. He was currently on 0.75 mg once daily during this admission. He denied any alcohol or tobacco use and family history was notable for coronary artery disease. He did not endorse any high-risk sexual behaviour or use of intravenous injections or blood products.

Physical examination revealed an alert and oriented man with fever (100.8°F), tachypnoea (32/min) and hypoxia requiring 5 L O₂ for oxygen saturations at 93%. Pulmonary examination revealed diffuse bilateral coarse crepitations and end-expiratory rhonchi. Cardiovascular examination was unremarkable except for bilateral pitting pedal oedema.

INVESTIGATIONS

Laboratory evaluation demonstrated normal leucocyte count of 6200 cells/mm³ with left shift and bandemia (14%), absolute neutrophil count 5800 cells/mm³ and absolute lymphocyte count 500 cells/mm³. Metabolic panel revealed acute kidney injury with blood urea nitrogen 66 mg/dL, creatinine 2.3 mg/dL (baseline 1.6 mg/dL) and thyroid stimulating hormone of 2.6 mIU/L. Additionally, elevated cardiac biomarkers (troponin-I 0.12 ng/mL and β -natriuretic peptide 5740 ng/L) and lactic acidosis (2.9 mmol/L) were noted. Venous blood gas was suggestive of mixed primary respiratory alkalosis with elevated anion gap metabolic acidosis.

Preliminary work up included a chest roentgenogram (CXR), which was suggestive of cardiomegaly with increase in bilateral bronchopulmonary markings (figure 1). ECG revealed ventricular paced rhythm and transthoracic echocardiogram revealed normal left ventricular function with right ventricular (RV) dilation with normal RV systolic pressures of 17 mm Hg. Lower extremity venous Doppler studies were negative for acute thrombosis.

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To cite: Mahfood Haddad T, Vallabhajosyula S, Nawaz M S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210117

Figure 1 Admission chest roentgenogram (CXR) showing bilateral airspace disease and increased bronchopulmonary markings.

DIFFERENTIAL DIAGNOSIS

We entertained a broad differential diagnosis including new-onset acute decompensated heart failure, acute coronary syndrome, amiodarone pulmonary toxicity, venous thromboembolism and pneumonia. Owing to the extensive cardiovascular symptoms, the patient was admitted to the cardiac critical care unit for further management of suspected acute coronary syndrome and new-onset heart failure, with intravenous heparin, intravenous diuretics, antiplatelet regimen and statin therapy. He failed to improve on this regimen and on the subsequent day, worsened clinically and developed hypotension, oliguria and worsening acute kidney injury. His cardiac biomarkers remained persistently elevated with a serial rise, making an acute coronary syndrome less likely. Additionally, his leucocyte count started rising steadily on hospital day 3 (13 500 cells/mm³ from prior 6200 cells/mm³). The clinical constellation of symptoms made a diagnosis of sepsis with developing septic shock more likely. Given the recent history of steroid use, acute adrenal insufficiency was also considered as a differential diagnosis. Repeat CXR demonstrated worsening airspace opacities, concerning for healthcare-associated pneumonia and septic shock (figure 2).

TREATMENT

The patient was subsequently started on intravenous fluids, vasopressors, vancomycin, piperacillin-tazobactam, levofloxacin and stress-dose intravenous hydrocortisone. He continued to be

Figure 2 Follow-up chest X-ray on day 2, demonstrating increasing airspace disease with worsening bilateral lower lobe opacities.

Figure 3 CT (transverse section) of the chest demonstrating bilateral ground-glass opacities worse on the right.

hypoxaemic with worsening metabolic and respiratory acidosis requiring mechanical ventilation. CT of the chest was performed to evaluate the airspace disease; the scan revealed extensive bilateral ground-glass opacities, worse on the right, suggestive of an infectious process (figures 3 and 4). Blood aerobic, anaerobic and fungal cultures revealed no growth. Bronchoalveolar lavage (BAL) performed for aetiological evaluation revealed positive β -D-glucan and negative work up for aspergillosis, herpes simplex virus, cytomegalovirus, *Legionella*, *Mycoplasma*, influenza and cryptococcal pathogens. In view of positive β -D-glucan, serum PCR for *P. jirovecii* was performed and returned positive. The patient's HIV ELISA from a prior visit was negative and was not rechecked on this hospitalisation due to the lack of a high-risk social history. The patient was transitioned to trimethoprim/sulfamethoxazole (TMP/SMX). He continued to worsen clinically with follow-up chest CT scan demonstrating continuing pathology with slight improvement in aeration (figure 5).

OUTCOME AND FOLLOW-UP

During the course of his therapy, the patient developed anuria with severe decline in renal function necessitating renal

Figure 4 CT (coronal section) of the chest demonstrating bilateral ground-glass opacities involving the bilateral lung fields with minimal sparing of left upper zone.

Figure 5 CT (coronal section) of the chest 14 days after prior CT scan demonstrating persistent bilateral opacities with slight improvement in aeration in bilateral lung fields.

replacement therapy, and was therefore transitioned to pentamidine. Owing to known issues with QT segment prolongation with pentamidine use, the patient was monitored with serial ECGs. Despite maximal medical support, he continued to decline and developed refractory metabolic and respiratory acidosis, and ultimately succumbed to cardiorespiratory arrest despite our best efforts.

DISCUSSION

PJP is a life-threatening illness. It was first noted in malnourished children during World War II, and subsequently rose to prominence during the AIDS epidemic of the 1980s.^{4 6} It is typically noted in AIDS patients with CD4+ T-lymphocyte counts <200 cells/mm³, and follows a more indolent course due to the presence of fewer inflammatory cells. PJP in AIDS patients typically has better clinical stability and survival trends in comparison to patients without HIV/AIDS.^{2 3 7} This recent emergence of non-HIV patients with PJP is due to better understanding and prophylaxis of AIDS patients, higher potency of immunosuppression in modern medicine and increased survival due to superior therapy of chronic diseases, thereby increasing the at-risk period for development of PJP.⁴ Among multiple other therapies, steroids are the mainstay of treatment of HIV-related PJP and confer short-term and long-term mortality benefits.⁵

One-third of PJP cases occur in non-HIV patients and often have high-mortality rates of 30–60%.^{2 8 9} These include patients with prior organ transplant, haematological cancers, solid organ malignancies, collagen vascular diseases, organ rejection, primary immunodeficiencies and inflammatory bowel disease.^{6 8–10} Typically, these patients are more often older, with males being more commonly affected than females.⁸ An interesting subset of these cases is those with recent or current corticosteroid use. Most of the aforementioned conditions require treatment with steroids at some stage and a significant portion of the PJP cases were noted during steroid taper.^{4 6 8} Despite the extensive literature documenting this association, the exact quantity, type and duration of steroid use is not well established in the guidelines.^{2 4 6 8 10} Although a majority of cases occur during steroid taper, about 20% occur during stable dosing.⁴

The mechanism of action is hypothesised to be due to lymphopenia, specifically of CD4+ lymphocytes, induced by chronic steroid use.^{5 8} Initial corticosteroid dose, total dose, hypoalbuminaemia and lymphopenia at 2 weeks were predictive of future PJP risk.^{8 10} Patients on corticosteroid doses of between 16 and 30 mg of prednisone (or equivalent) for a period of 8–10 weeks have been noted to have a significant risk of PJP.^{2 4} The median duration of occurrence of PJP is 3–4 months after steroid initiation, but rare cases within the first month have been documented.⁸

The clinical presentation of PJP in non-HIV patients is typically more acute, with hypoxaemia, cough, fever and haemodynamic instability, with a median duration of 1–2 weeks.^{2 6 8} Poor prognostic indicators at admission include tachypnoea, tachycardia, elevated inflammatory markers, elevated lactate dehydrogenase and need for mechanical ventilation.^{2 8} The typical findings are consistent with interstitial pneumonia, with the CXR showing perihilar interstitial infiltrates and/or honeycombing, which become progressively homogenous as the disease progresses.^{2 8} Alternately, a normal CXR on admission can lead to the evolution of the infiltrates on subsequent imaging.⁶ Other less common findings include solitary or multiple nodules, pneumatoceles and pneumothorax.² Classically, the diagnosis of PJP involves the visualisation of *P. jirovecii* in stains or by direct and/or indirect fluorescence. However, for patients with non-AIDS PJP, the yield from bronchoscopic or BAL fluid has low sensitivity, ranging from 38% to 53%.³ This is due to the low number of organisms in the diagnostic specimen, oftentimes leading to false-negative testing.^{1 8} The need for more sensitive testing has led to the evolution of alternate strategies such as β -D-glucan and PCR. Serum and BAL β -D-glucan have been shown to be excellent predictors of PJP in patients with an immunocompromised status.^{1 11} Further confirmation by BAL PCR primers for the gene coding for pneumocystis large subunit ribosomal RNA has served to enhance the sensitivity and specificity of diagnosis.^{2 3} In cases with strong suspicion of PJP but negative immunofluorescence and equivocal PCR, a quantitative PCR can be performed to augment the sensitivity.¹²

TMP/SMX is the mainstay of therapy for PJP but, frequently, patients have an allergy or contraindication to its use. In such cases, alternate agents such as intravenous/inhaled pentamidine, clindamycin/primaquine, atovaquone, dapsone/pyrimethamine and trimetrexate, can be used to manage PJP.^{13 14} Inhaled pentamidine has been shown to be almost as efficacious as TMP/SMX in PJP prophylaxis during multiple studies.^{15–17} However, in salvage therapy for manifested PJP, pentamidine has been shown to have marginally lower response rates and increased mortality.^{13 14} Despite these issues, it serves as an acceptable alternative to TMP/SMX when the latter is contraindicated. Additionally, adjunct high-dose corticosteroids have been shown to decrease intubation and mechanical ventilation, shorten duration of intensive care unit stay and lessen use of supplemental oxygen.⁵ Postulated mechanisms for this include anti-inflammatory effect facilitating gas exchange, suppression of host immune function and augmentation of pulmonary clearance mechanisms.⁵ Guidelines support prophylaxis for PJP among patients with cancer, transplant, graft recipients and collagen vascular disease.¹⁸ Prophylaxis is also recommended in patients receiving corticosteroids ≥ 20 mg of prednisone (or equivalent) with an additional immunosuppressive state or medication.⁴ A recent systematic review quoted the need for PJP prophylaxis in patients using steroids with a PJP risk of $>3.5\%$, however, this is only restricted to patients with rheumatological

or collagen vascular diseases.¹⁰ There are no standardised guidelines for patients receiving isolated steroid therapy and/or tapering doses of steroids. Further research is targeting alternative agents for prophylaxis and therapy, which will be greatly aided by the recent sequencing of the pneumocystis genome.^{19–21}

Our case highlights the uncommon association of PJP in a patient with corticosteroid use for thyroiditis, an association not reported before in the literature. Moreover, our patient had no disease states or therapy that would put him at an increased immunocompromised status, making this case unique and reportable.

Learning points

- ▶ *Pneumocystis jirovecii* pneumonia (PJP) presents infrequently in patients without HIV infection.
- ▶ Although the correlation of PJP with autoimmune and collagen vascular diseases is well documented, it may occasionally present in patients with steroid use, especially during steroid tapering.
- ▶ The manifestations of PJP in non-HIV patients are typically more aggressive due to a comparatively more robust immune system and thereby results in higher mortality.
- ▶ This is the first reported case of PJP in patients on steroid therapy for thyroiditis.
- ▶ Trimethoprim/sulfamethoxazole is the first line of therapy for PJP, but pentamidine serves as an efficacious alternative.

Contributors TMH was involved in patient evaluation, literature review and drafting manuscript. SV was responsible for literature review, editing manuscript and finalising manuscript. MSN was involved in literature review and drafting manuscript. RV was responsible for patient evaluation, critical review and finalising manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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