

Septic Shock Due To Pneumocystis Pneumonia In HIV Infected Patients- Is The Virulence Of Pneumocystis Jiroveci Changing?

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Citation

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Abstract

Pneumocystis jiroveci pneumonia is the most common pulmonary opportunistic infection in patients with human immunodeficiency virus. The mortality for those patients that develop acute respiratory failure requiring mechanical ventilation is as high as 50%. The development of septic shock in those patients is usually due to a superimposed bacterial infection or the presence of other opportunistic infection like Aspergillus, Cryptococcus, systemic Candidiasis or toxoplasmosis. We report a unique case series of four patients with Pneumocystis jiroveci pneumonia with acute respiratory failure and hemodynamic consistent with septic shock. Despite extensive investigation, the sole etiology for the shock was Pneumocystis jiroveci. The mortality for those patients was higher than the reported for a similar population with shock due to bacterial infections. We speculate that this could reflect increasing virulence of Pneumocystis jiroveci, which induce a greater derangement of the pro and inflammatory system.

INTRODUCTION

Pneumocystis jiroveci (formerly Pneumocystis carinii) pneumonia (PCP) is the commonest pulmonary opportunistic infection in patients with human immunodeficiency virus (HIV). It is a major cause of morbidity and mortality in the immunocompromised patient. There is an increased mortality of up to 56 to 60% for patients with PCP related acute respiratory failure requiring mechanical ventilation. Hemodynamic compromise and shock in those patients is usually a consequence of superimposed infections. To our knowledge, PCP as a sole cause of shock has not been reported in the literature.

We present a series of four cases of HIV/AIDS patients with PCP pneumonia presenting with acute respiratory failure and septic shock.

CASE 1

A 47 year-old man with AIDS, not on HAART, CD4 count 38cells/UL presented with cough and dyspnea of two-week duration. He denied fever, weight loss or hemoptysis. His past medical history includes CVA and CNS toxoplasmosis.

On examination, he was tachycardic (110beats/min) and tachypneic (22breaths/min) with an oxygen saturation of

98% on ambient air. Physical exam was significant for crackles in the right lung base. The remaining of the exam was unremarkable.

Laboratory was remarkable for anemia-hematocrit 27% and platelet of 212cells/mm³. Serum creatinine and lactate dehydrogenase (LDH) were elevated with a normal liver function test. Arterial blood gases (ABG) showed hypoxemia with increased alveolar-arterial (Aa) gradient. Chest-x-ray (CXR) initially revealed a right lower lobe infiltrate. He was admitted to the hospital with the presumptive diagnosis of community acquired pneumonia versus an opportunistic infection with PCP.

Treatment with ceftriaxone, azithromycin, oral corticosteroids and trimethoprim-sulfamethoxazole (TMP-SMX) was initiated.

In view that hypoxia was out of proportion to radiological findings, a ventilation-perfusion scan and an echocardiogram were performed, both of them were normal.

The patient clinical condition deteriorated rapidly in the following 24 hours, with the development of acute respiratory failure and shock (MAP 45mmHg). He was

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transferred to the Intensive Care Unit (ICU) where he was intubated and resuscitated. The initial PAO₂/FIO₂ ratio was 200. Fluids and norepinephrine were given and a central venous catheter inserted. Central venous pressure (CVP) was maintained between 10 to 12 mmHg. His mixed venous saturation was 78%. The CXR revealed bilateral infiltrates.

Flexible fiberoptic bronchoscopy (FFB) was performed on the third day of admission to the hospital and bronchoalveolar lavage (BAL) was positive for PCP. Rest of the septic work up that included blood, respiratory, stool, urine cultures as well as abdominal/renal ultrasound were all negative. Ceftriaxone and azithromycin were discontinued on day fourth of admission and the patient was weaned off vasopressors in the following 48-72 hours. The renal function returned to normal, the LDH decreased to 180 unit/l and the PAO₂/FIO₂ ratio increased to 416.

Subsequently the patient developed TMP-SMX induced thrombocytopenia and treatment was changed to pentamidine on day eight of admission. Due to pentamidine induced pancreatitis he completed treatment with clindamycin and primaquine. The patient's clinical-radiologic condition improved but due to metabolic encephalopathy he required tracheostomy for long term airway management.

CASE 2

A 37 year-old African-American man with HIV/AIDS, CD4 count less than 20 cells/UL on HAART and PCP prophylaxis presented with a three week history of shortness of breath, fever, and cough. On admission to the hospital, he was febrile (T° 36.7°C) and he had a respiratory rate of 19 breaths/min, pulse rate 139/min and blood pressure of 100/60mmHg. Physical examination revealed bilateral basal crackles and oxygen saturation of 86% on ambient air. Laboratory was remarkable for an increased serum LDH. An ABG analysis showed a PAO₂ of 61 mm Hg on 4L of oxygen by nasal canula (Aa=115). The CXR showed bilateral interstitial infiltrates more prominent in the left side. He was admitted to medical floor with the impression of PCP pneumonia and was empirically treated with TMP-SMX and oral prednisone. In the following 24 hours, he developed hypoxic respiratory failure, a spontaneous pneumothorax was found that required chest tube drainage and intubation and mechanical ventilation due to persistent hypoxemia. After 24 hrs in the ICU, the patient developed shock requiring vasopressors and fluids. A FFB with BAL and transbronchial biopsy (TBBX) revealed Pneumocystis

pneumonia. Respiratory cultures from BAL for bacterial, viral and fungal organisms did not reveal any pathogens. Blood and urine cultures as well as repeated laboratory and detailed physical exam did not reveal any other focus of infection causing shock. He was empirically started on broad spectrum antibiotics (Vancomycin and Imipenem) for presumptive health care associated pneumonia (HCAP). The patient condition continued to deteriorate and he died on day 14 of hospital admission.

CASE 3

A 58 year-old female with HIV/AIDS, CD4 counts of 38cells/UL, and not compliant with HAART was admitted with worsening of shortness of breath, nonproductive cough and fevers and chills of two-week duration. She also complained of oral thrush and non-bloody diarrhea of one-week duration. She recently signed against medical advice from another emergency room (ER) where she was there for similar complaints. She was found hypotensive with BP of 90/60mmHg, pulse rate of 106/min, respiratory rate of 18/min, temperature of 39°C and oxygen saturation of 84% on ambient air. Physical examination revealed respiratory distress with use of accessory muscle and bilateral lung crackles and oral thrush. Arterial blood gas on 40% venturi mask showed a PAO₂ of 60mmHg and an Aa of 195. Hemoglobin was 8.1gm/dl, serum LDH 771unit/L, and cortisol level of 38ug/dl.

The CXR showed diffuse interstitial infiltrates. A CT chest revealed bilateral ground glass opacities (GGO) and no evidence of pulmonary embolism. Patient was resuscitated with intravenous normal saline and she was started on TMP-SMX and intravenous steroids for PCP pneumonia and Vancomycin and piperacillin - tazobactam for empiric coverage of a presumed hospital acquired pneumonia. Patient was admitted to the ICU where she required endotracheal intubation with mechanical ventilation. Blood pressure did not improve with fluids and she required norepinephrine to keep a MAP >65 mmHg. A mixed venous saturation was 73% and the CVP was 12. A FFB with BAL performed on day of admission revealed Pneumocystis pneumonia. All the septic work up including respiratory cultures from BAL for bacterial, viral, fungal and AFB and blood, urine and stool cultures did not reveal any pathogenic organisms. Echocardiogram was normal. Vancomycin and piperacillin-tazobactam were discontinued on day 3. Her hemodynamic status improved in first 48 hours and the vasopressors were discontinued. On day 5, the patient was

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extubated and later discharged home to complete PCP treatment.

CASE 4

59 yr-old female with chronic obstructive pulmonary disease (COPD), nicotine and alcohol dependence presented with worsening shortness of breath of three-week duration. She also had history of latent TB at the age of 40 and completed treatment.

In the ER her vitals were: blood pressure of 117/82mmhg, pulse rate of 111/min, respiratory rate of 20/min, temperature of 36.7°C and oxygen saturation of 85% on ambient air. On physical examination, patient was in respiratory distress, unable to talk in full sentences and she had bilateral rhonchi on lung exam. A CXR revealed bilateral diffuse interstitial infiltrates. Arterial blood gas revealed PAO₂ of 50 with an Aa gradient of 57. The patient was transferred to ICU with the impression of COPD exacerbation secondary to atypical pneumonia. She was started on steroids for COPD exacerbation and Azithromycin and ceftriaxone for atypical pneumonia. Enzyme immunoassay (EIA) done on day 2 for HIV was positive. CD4 count was less than 20cells/UL and LDH was 575unit/L. Sulfamethoxazole-trimethoprim for Pneumocystis pneumonia was added. In the following 24 hours her condition rapidly deteriorated and she was intubated for hypoxic respiratory failure and vasopressors were started for shock. Two units of packed red blood cells were transfused for an Hb of 7mg/dl. Fiberoptic bronchoscopy with BAL confirmed PCP pneumonia. All the septic work including urine for legionella, sputum for gram stain, respiratory, blood and urine cultures were negative. ICU course was later complicated by multi organ failure and family decided to transfer the patient to palliative care.

Below the laboratory data for all cases and representative radiological imaging can be seen.

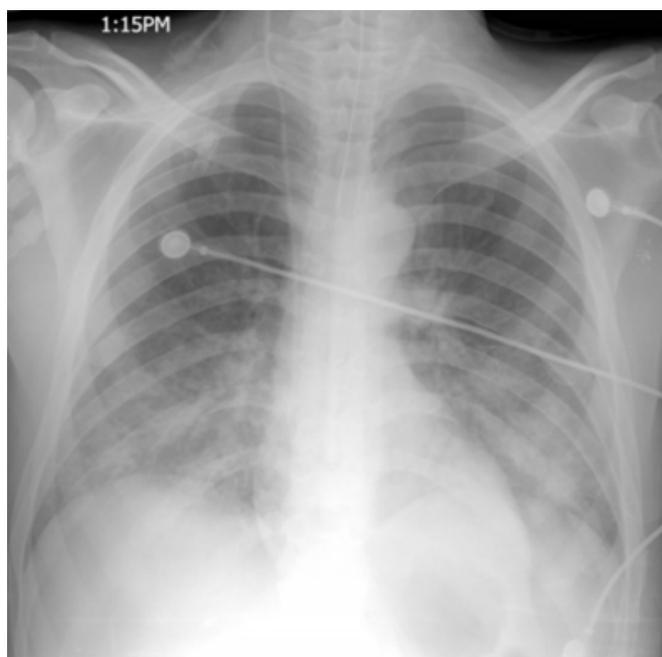
Figure 1

Table 1: Comparison of characteristics of the reported cases of PCP with septic shock

	case 1	Case 2	Case 3	Case 4
Age	47	37	58	59
Sex	M	M	F	F
CD4 count cells/UL	38	20	38	20
HAART	no	yes	no	no
PCP prophylaxis	No	yes	yes	no
PCP diagnosis	BAL	TBBX	BAL	BAL
A-a gradient	60	115	195	57
Serum LDH (unit/L)	699	568	771	557
Albumin (g/dl)	2.2	2.0	3.9	2.5
Serum Creatinine (mg/dl)	3.4	0.7	0.6	0.6
Total Bilirubin (mg/dl)	0.2	0.3	0.1	0.3
Mechanical ventilation	yes	yes	yes	Yes
Outcome	Died	Died	Survived	Died

Case 1: CXR: Bilateral alveolar infiltrates

Figure 2



Case 2: CXR: Bilateral interstitial infiltrates with left pneumothorax

Figure 3

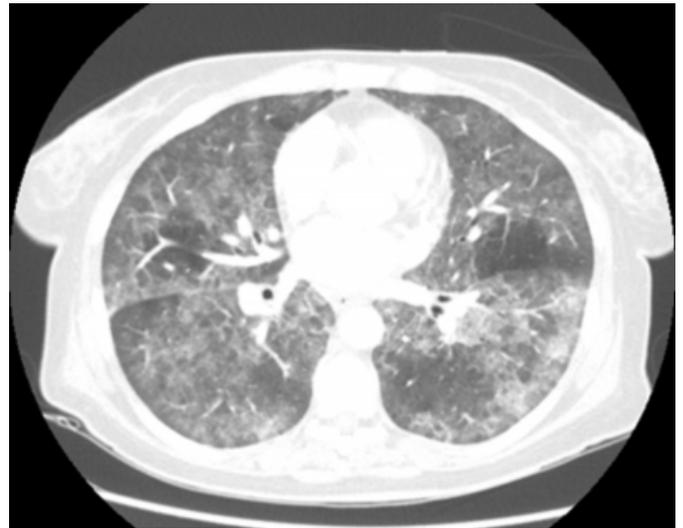


Case 3: CXR: Bilateral interstitial/alveolar infiltrates. CT: GGO plus interstitial infiltrates

Figure 4



Figure 5



Case 4: CXR: Bilateral interstitial/alveolar infiltrates

Figure 6



DISCUSSION

Pneumocystis pneumonia is caused by the fungal pathogen *Pneumocystis jirovecii*. It is the most common opportunistic infection and the leading cause of pulmonary disease and death in patients infected with HIV/AIDS. Acute respiratory failure is the leading reason for ICU admission in HIV-infected patients with PCP and bacterial pneumonia. It is estimated that 20 to 40% of patients with PCP infection will develop acute respiratory failure requiring mechanical ventilation with a mortality as high as 50%. (1, 2, 3)

In the last decade and as a result of early diagnosis and treatment, the frequency of PCP and PCP related acute respiratory failure has been decreasing. (4) The proportion of

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patients with PCP who require critical care has remained constant in the HAART era and approximately 10 to 15% of those patients/per year require ICU management. (5-7)

The clinical manifestations of PCP can be subtle and non specific. Fever, dyspnea, atypical chest pain, weight loss, chills, hemoptysis and nonproductive cough have been reported in over 50% of cases. However, almost all patients with PCP have at least two of the following: fever, cough, dyspnea, elevated serum LDH or an arterial partial pressure of oxygen (Pao₂) of less than 75 mm Hg. (4-6,8)

Radiological presentation are protean and they range from a normal CXR to extensive diffuse interstitial infiltrates; cavities, cyst and pleural effusion have also been reported. The typical appearance on chest CT is patchy areas of GGOs with a background of interlobular septal thickening. (9)

Serum LDH is usually elevated (>220 U/L), but the specificity for the diagnosis of PCP is low. Accurate diagnosis requires either sputum stains or FFB with BAL with/without TBBx. The diagnostic yield for FFB with BAL and TBBx has been reported in the range of 97-100%. (10)

Several poor prognostic markers reported in those patients includes decreased alveolar oxygenation, acute respiratory failure requiring mechanical ventilation, decreased serum albumin levels, increased serum LDH levels, BAL fluid neutrophilia and development of multiorgan failure. (11-15)

In a recent study looking at 451 patients with PCP, multivariate analysis identified five significant predictors of mortality: age, recent injection drug use, total bilirubin, serum albumin and A-a oxygen gradient. The in-hospital mortality was 10.3%. (16)

Patients with severe PCP manifest a hyperdynamic hemodynamic profile with an increased cardiac index and low systemic vascular resistance. The same hemodynamic profile has been reported with bacterial, fungal and viral infections. (17,18) Pneumonia and bloodstream infections have been reported to be the main sites of infections for almost all HIV infected patients with severe sepsis and shock; hospital-acquired bacteria composed the major part of the microbiology of severe infections. The development of septic shock in patients with PCP is usually due to a superimposed bacterial infection or the presence of other opportunistic infection like Aspergillus, Cryptococcus, systemic Candidiasis or toxoplasmosis. (2,18,19)

Pro-inflammatory cytokines, which control the influx of inflammatory cells in the lung in response to Pneumocystis infection, include interleukin-1 beta (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) which are also the major cytokines involved in septic shock of any infectious etiology.

Our case series is unique in that, all patients developed septic shock and despite extensive work up, PCP was presumed the culprit in the absence of any other infection. Severe sepsis and septic shock is a consequence of complex interactions between the micro organisms and host responses to infection (20). This is seen in bacterial, viral and fungal infections. The best studied are bacterial infections with gram negative pathogens. The endotoxins produced by GNB when combined with lipopolysaccharide binding protein results in activation of inflammatory and coagulation cascade. Severe sepsis and septic shock is generally believed to due to an exaggerated and maladaptive response. However newer insights have revealed an important role of microorganisms (21). Therefore the events leading to severe sepsis and septic shock can be divided to host factors and microorganism factors. Microorganism factors include virulence factors seen in both bacterial and non bacterial infections. In many parasites and fungi, primary internal transcribed spacers (ITS) genotyping, different ITS types of *P. carinii* were identified in most episodes of *P. carinii* pneumonia and ITS sequence analysis improve distinction between separate strains (22,23). This is important as clinical specimens have revealed multiple strains ranging from 23 to 77% (24,25,26). The association between these strains and morbidity is unequivocal. Some studies have revealed an association between strains and mortality (27); however others have revealed no such association (28). We hypothesize either infection by a specific ITS genotype or a specific combination of ITS strains may be responsible for worsening virulence of *P. jiroveci*, resulting in septic shock.

Interesting, in our case series, the mortality for patients with PCP-induced septic shock was higher than the reported for the same population but with shock due to bacterial infections. We can only speculate that this reflects increasing virulence of *P. jiroveci*, which induce a greater derangement of the pro and inflammatory system.

CONCLUSION

Although advances in the care of HIV-infected patients have dramatically lowered its incidence, PCP still remains a challenging clinical problem. To the best of our knowledge

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this is the first report demonstrating PCP causing septic shock without any other infection. *Pneumocystis pneumonia* should be included in the differential diagnosis of HIV infected patients in septic shock. In patients with septic shock due to *Pneumocystis*, ITS genotyping may shed light regarding the increasing virulence of *P. jiroveci*.

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