Fatal Sepsis in an AIDS Patient during Therapy for *Pneumocystis carinii* Pneumonia

R.J. Piso, M. Rossi, T. Oehler, X.M. Nguyen, M.G. Täuber

Abstract

The case of a patient with a newly diagnosed HIV infection and *Pneumocystis carinii* pneumonia is presented. Despite treatment with high-dose trimethoprim/sulfamethoxazole (TMP/SMX) and prednisone with initial improvement, the patient acutely deteriorated with severe acidosis and died on the 4th day of hospitalization. *Cryptococcus neoformans* grew the next day in broncheoalveolar lavage (BAL) and blood culture. As simultaneous presence of more than one opportunistic infection can occur in these patients, systematic workup for other common opportunistic infections must be performed.

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Introduction

Since the introduction of new antiretroviral drugs, the incidence of AIDS-defining illnesses in HIV-positive patients has declined dramatically [1, 2]. Currently, patients who are admitted to a hospital with an opportunistic infection (OI) often suffer from a previously undiagnosed HIV infection; these events are relatively rare in areas with well-developed health care systems such as in Switzerland. Usually, little information on previous medical history is available for patients admitted for an acute OI whose HIV-positive status was not known. Also, the experience in dealing with these patients may not be as developed as it was before the introduction of effective antiretroviral therapy. We describe here a patient with a newly diagnosed HIV infection who presented with typical signs of *Pneumocystis carinii* pneumonia and who acutely deteriorated under therapy with trimethoprim/sulfamethoxazole (TMP/SMX) and prednisone because of a second opportunistic infection.

Case Report

A 35-year-old male with unknown HIV status, who was living with an HIV-positive female partner, presented with a history of 1 month of cough, shortness of breath and weight loss of 6 kg. His temperature was 38.5 °C, blood pressure 110/70 mmHg, heart rate 120/min and respiratory rate 30/min. The clinical examination showed a thin white male (body mass index 18.5) in moderate respiratory distress with hepatosplenomegaly, oral thrush and generalized lymphadenopathy. There were fine crackles at the base of the lungs bilaterally, no cardiac murmurs and the patient was hemodynamically stable. Neurologic examination showed no abnormalities. Chest radiographs revealed diffuse fine interstitial infiltrates in both lungs. Because of persistent hypoxemia despite oxygen supply, the patient was transferred to our tertiary care hospital. Suspecting *P. carinii* pneumonia, treatment with TMP/SMX (5 mg TMP/kg iv tid) and prednisone (50 mg po bid) was initiated and subsequent broncheoalveolar lavage (BAL) confirmed the diagnosis. During the 1st and 2nd days of hospitalization, symptoms improved, but on the 3rd day the patient reported sudden onset of impaired vision in the left eye without local pain or headaches. Ophthalmologic examination was normal and the neck was supple. 12 h later the patient had to be transferred to the intensive care unit because of sudden deterioration with progressive hypoxemia requiring intubation and mechanical ventilation. Shortly thereafter, cardiopulmonary resuscitation (CPR) was performed because of hemodynamic failure. Circulation could be stabilized by catecholamines. Frank metabolic acidosis with elevated lactic acid levels was documented (Table 1). During the 4th day of hospitalization, the pulmonary and hemodynamic situation again worsened with renewed need for catecholamines and increasing ventilatory support. Pulmonary emboli were ruled out by angiography. Transesophageal echocardiography documented severe right ventricular dysfunction, but no evidence of endocarditis. 12 h after admission to the intensive care unit, the patient died in circulatory failure despite efforts to resuscitate him. The next day, blood cultures and BAL fluid grew *Cryptococcus neoformans*. The antibody test for HIV was positive and the CD4 cell count was 16 cells/ml.

Discussion

In this patient, *P. carinii* pneumonia was correctly suspected upon clinical presentation and subsequently confirmed in

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BAL. Following published guidelines, the patient was treated with TMP/SMX combined with corticosteroids to prevent further deterioration of his hypoxemia in the first days after initiation of therapy [3]. Despite the combined therapy, the patient experienced pulmonary and hemodynamic deterioration on the 4th day, a time point compatible with immune-mediated increase in pulmonary capillary leakage during the treatment of *P. carinii* pneumonia. However, unexplained by the pulmonary process, respiratory deterioration was accompanied by pronounced metabolic acidosis with increased serum lactate concentrations. Nosocomial pneumonia was ruled out by chest X-ray and negative sputum examination. Unexpectedly, fungemia with *C. neoformans* was documented in lysis-centrifugation blood cultures (Isolator™), but not on standard blood culture media.

Co-infections with *P. carinii* and *C. neoformans* seem to be rare. Nine cases have been described in the literature [4–6], three of which were fatal. The concomitant treatment with corticosteroids may have contributed to the rapidly fatal course in this patient. Rarely, corticosteroids have been reported to lead to an exacerbation of previously undiagnosed and untreated co-infections. In particular, fulminant courses of infections with *Listeria monocytogenes*, *Mycobacterium tuberculosis* and *C. neoformans* under treatment with corticosteroids have been reported [7–9].

The clinical presentation of *C. neoformans* infections is typically a subacute meningitis accompanied by constitutional symptoms. Nevertheless, pneumonia can occur and pulmonary cryptococcosis can present like *P. carinii* pneumonia [10]. In the patient described here, BAL revealed *P. carinii* organisms by immunofluorescence, but since cryptococci also grew in the specimen, it is unclear to what extent the pulmonary symptoms in this patient were caused by cryptococci. Disseminated infection with *C. neoformans* can lead to acute respiratory deterioration with a mortality of 100%, as observed in 19/210 (9%) of patients with disseminated *C. neoformans* infections in one series [11]. Bilateral infiltrates and elevated lactate dehydrogenase levels are predictive for acute respiratory failure in disseminated cryptococcal infections, but since both findings are also typical for severe *P. carinii* pneumonia, these parameters cannot be used to differentiate between infections with either of the two organisms [11].

The etiology of the severe metabolic acidosis in this patient is not clear. No association between metabolic acidosis and cryptococcal infections has been reported. Sepsis per se can lead to acidosis, but our patient may also have had renal tubular acidosis induced by TMP/SMX. Reports of renal tubular acidosis due to TMP/SMX show a marked depletion of serum bicarbonate very similar to our case, but in the reported cases, the acidosis was compensated and did not impair pulmonary and hemodynamic functions [6, 12, 13]. Thus, in our patient a combination of fulminant cryptococcal sepsis, potentially aggravated by the concomitant use of corticosteroids, combined with renal tubular acidosis may explain the fatal course associated with severe, uncompensated acidosis.

HIV-infected patients with advanced immunodeficiency can suffer from several life-threatening infections at the same time and this must guide the initial diagnostic workup of these patients. With decreasing numbers of patients with advanced AIDS, familiarity with the complexity of these patients is not as broad as it was several years ago. When a patient presents with an OI as the first manifestation of HIV infection, a systematic workup for possible coexisting opportunistic pathogens must be performed, even if the primary diagnosis is made rapidly. This is especially important if the clinical course is atypical. Even if no routine systematic workup for all possible opportunistic infections is possible, it should be extensive upon clinical presentation. In European countries, at least *P. carinii* pneumonia, cryptococcosis, tuberculosis, toxoplasmosis and lymphoma should be ruled out in every HIV-infected patient with fever. In the present case, routine testing for cryptococcal antigen in serum or urine may have led to a more rapid diagnosis of the fungal infection and an appropriate therapeutic response. Cryptococcal antigen tests are highly sensitive (90%) and specific (100%) [14] and should be part of the workup of all patients with known or presumed HIV infection hospitalized with an acute illness, even if another diagnosis has already been established.

Even in the first world, medical care concerning HIV-infected patients is not always optimal, and approximately half of all patients infected do not receive medical care at all [15,18]. To improve the medical care for these patients, two strategies should be pursued. First, health care providers must enhance the awareness of possible HIV infection and second, the public acceptance of HIV infection must still improve. Tight collaboration between primary health care providers and HIV experts is mandatory for these patients. Fear of the diagnosis of the HIV infection still prevents many people from being tested, as illustrated

Table 1
Blood gas values during hospitalization.

	Day 1	Day 1	Day 2	Day 4		
	12:00	18:00	08:00	08:00	09:00	11:00
pH	7.45	7.48		7.355	7.02	7.32
pCO_2 mmHg	25.2	26	25	29	45	35.2
HCO_3 mmol	21.3	21.6	19.8		10.4	
Base excess	2.4	-0.5	-1.7	-8.2	-19.2	-7.2
Sa %	75	91	95	94		
Serum lactate mmol/l				8.5		

by this case. This fear is understandable albeit unfounded, as different investigators have proved that HIV infection is very well compatible with a good quality of life [16, 17]. For patients seen by medical care providers, regular measurements of CD4 count and viral loads can asses the time point to introduce antiretroviral therapy and prevent advanced immune deficiency. Patients not aware of their HIV infection are at highest risk of developing severe immune deficiency, as demonstrated by our patient. As reported by *Kaplan* et al. [18], 46 % of *P. carinii* pneumonia cases were seen in patients without medical care. Barriers for attending medical care and receiving antiretroviral therapy include lower socioeconomic status, competing subsistence needs, injecting drug abuse and affiliation with a minority group [19–21]. To diminish the number of undiagnosed HIV infections, primary care providers should mainstream HIV testing as routine clinical care, especially in high-risk groups [22].

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