Case report

Pulmonary coinfection by *Pneumocystis jirovecii* and *Cryptococcus* species in a patient with undiagnosed advanced HIV

Benjamin Valente-Acosta ,[1] José Padua-Garcia,[1] Andrés Tame-Elorduy[2]

[1]Internal Medicine Department, Centro Medico ABC, Ciudad de México, Mexico
[2]Escuela de Medicina, Instituto Tecnologico y de Estudios Superiores de Monterrey Campus Ciudad de Mexico, Tlalpan, Mexico

Correspondence to
Dr Benjamin Valente-Acosta; benjamin.valente-acosta1@alumni.lshtm.ac.uk

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SUMMARY

Pneumocystis jirovecii is a common cause of pneumonia in patients with advanced HIV. In a lot of cases, there is a concomitant pulmonary infection. Cryptococcosis presents as a common complication for people with advanced HIV. However, it usually presents as meningitis rather than pneumonia. We present a case of a patient with coinfection by *P. jirovecii* and *Cryptococcus* spp without neurological involvement and a single nodular pulmonary lesion.

BACKGROUND

Patients with HIV can have multiple infections at the same time. Pulmonary infection due to *Pneumocystis jirovecii* is a classic presentation of patients with advanced HIV infection. Multiple coinfections have been reported in association with *P. jirovecii*. However, *Cryptococcus* spp lung infection has seldom been reported. We report a case of a *Cryptococcus* spp pulmonary infection presenting as a solitary lung cavitated nodule after completed resolution of a *P. jirovecii* pneumonia in a patient with recent HIV diagnosis.

CASE PRESENTATION

A 35-year-old Hispanic man without any relevant medical history presented with a productive cough and dyspnoea that had progressed from only during heavy exertion to mild to resting dyspnoea over the course of 4 weeks. He mentioned that he had nocturnal diaphoresis. He began treatment at home with amantadine, chlorphenamine and paracetamol without significant improvement.

At the initial evaluation, his breathing was laboured with the use of accessory muscles. Acrocyanosis and central cyanosis were observed. Fine rales with hypoventilation were heard on thoracic auscultation. The O_2 saturation was at 64%–70% without supplemental oxygen. The respirations were 30/min, the heart rate was 110 beats/min and the blood pressure was 140/90 mm Hg. White plaques were seen in the pharynx and palate.

INVESTIGATIONS

Bloodwork was ordered and a thoracic X-ray and CT scan were taken, which showed alveolar occupation on both hemithoraxes (figure 1).

Giemsa staining was conducted on the sputum, and it showed cysts with *P. jirovecii*. Additionally, cultures for aerobes, mycobacterium and fungi were ordered and were all negative. The cryptococcal antigen was negative in the bloodwork and beta-D-glucan levels were >500 pg/mL.

An HIV test was ordered and the result was positive. The CD4 count was 4/µL and the viral count was 816 000 copies/mL.

TREATMENT

The patient was hospitalised in the intensive care unit, and treatment began with cotrimoxazol, prednisone, ceftriaxone, clarithromycin and caspofungin while the test results came back. After a diagnostic bronchoscopy was performed on the day after his hospitalisation, his condition deteriorated, resulting in intubation with mechanical ventilation.

Infection by *P. jirovecii* was confirmed by pathology and PCR. The patient improved slowly, and by the 12th day, antiretroviral treatment was initialised (dolutegravir, emtricitabine and tenofovir). We took another chest CT scan on day 14 (figure 2) that showed improvement of the alveolar occupation. He was extubated on the 20th day and released on the 35th day.

OUTCOME AND FOLLOW-UP

As part of his HIV follow-up, a thoracic X-ray was taken after 14 days of his discharge. It showed a cavitated nodule in the right middle lobe. So, a CT scan (figure 3), was conducted. It showed complete improvement of the alveolar occupation but a larger cavitated nodule. Consequently, another bronchoscopy was performed. Infection by *Cryptococcus* spp was confirmed by Masson's trichrome stain (figure 4). The bronchoalveolar lavage was negative for bacteria, mycobacteria and fungi. In the bloodwork, the cryptococcal antigen became positive (1:640) and the beta-D-glucan was negative, so a lumbar puncture was performed in order to rule out meningitis. The histoplasmosis antigen was not found in the urine. At this point, the patient had 71 copies/mL of HIV-1 RNA and the CD4 count was 88/µL. Because the patient was asymptomatic, 400 mg of fluconazole per day was indicated. The CT scan after 4 weeks showed a reduction in the size of the nodule (figure 5), the HIV-1 RNA was 72 copies/mL and the CD4 count was 155/µL. He continued with fluconazole to complete the 6 months treatment. After 36 weeks of the initial *P.*

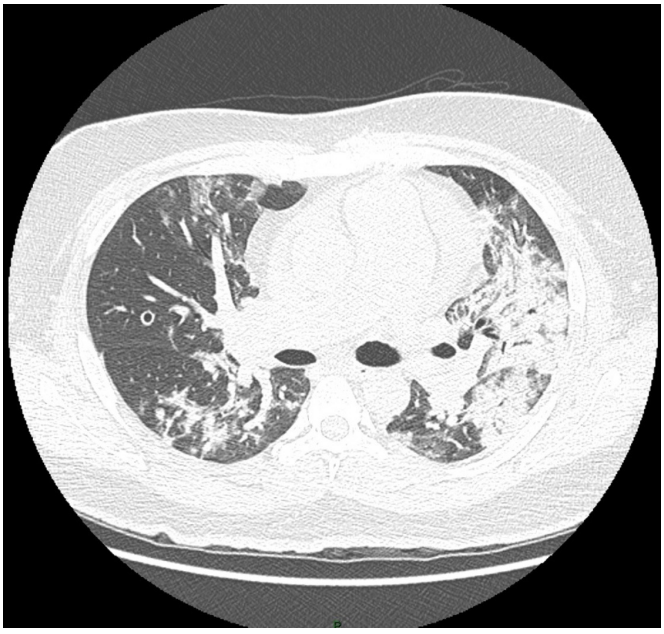

Figure 1 Admission CT scan.

jirovecii pneumonia a new CT scan showed complete resolution of the cavitated lesion (figure 6).

DISCUSSION

P. jirovecii (previously *Pneumocystis carinii*) is a common cause of pneumonia in HIV severely immunocompromised patients. The incidence has decreased in developed countries due to the early diagnosis and treatment of HIV and prophylaxis against opportunistic infections.[1] However, in low-income and middle-income countries, it continues to be one of the first manifestations of HIV.[2 3]

Conversely, cryptococcal pneumonia is rare, although it is believed to be underdiagnosed. In patients with HIV who are immunocompromised, cryptococcal meningitis is much more common. When pulmonary involvement is seen in immunocompromised patients, it is more commonly an infection by *Cryptococcus neoformans* (A serotype) than *Cryptococcus gattii* (D serotype), while *C. gattii* is the most common cause of pulmonary cryptococcosis in immunocompetent patients.[4]

In patients with HIV, *P. jirovecii* coinfection with other pulmonary pathogens, such as bacteria, mycobacteria, fungi, viruses and even parasites, has been reported. Coinfection rates with

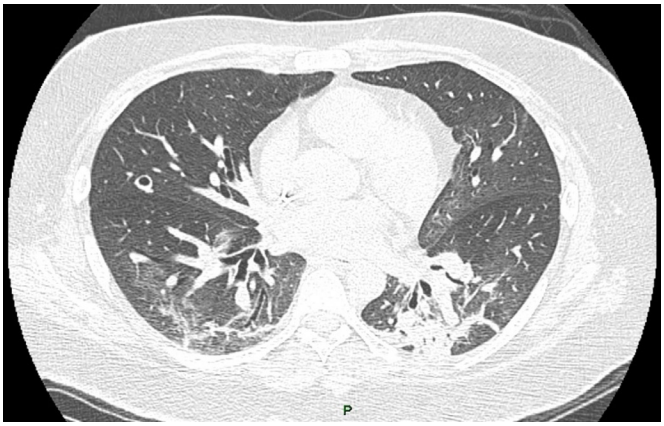

Figure 2 Chest CT scan on day 14 after admission.

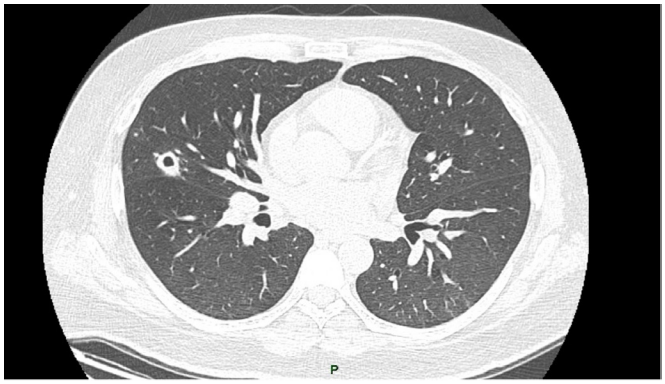

Figure 3 Chest CT scan on day 14 after discharge.

other micro-organisms range from 20% to 70%.[5] An example of bacterial coinfection was presented by Mamoudou *et al* who reported two cases of patients with HIV and *P. jirovecii* coinfection with *Pseudomonas aeruginosa* in which timely diagnosis and treatment for both conditions had a favourable outcome.[6]

Coinfection of *P. jirovecii* with *Mycobacterium tuberculosis* has also been reported in the literature.[7 8] At present, it is recognised as the most common coinfection with *P. jirovecii* in patients with HIV.[5] In a study published by Chiliza *et al*, they report that in their population of a referral hospital in South Africa, the coinfection rate was 23.6%. This coinfection was associated with a worse prognosis.[9]

Cytomegalovirus (CMV) has been reported as a coinfection agent in multiple articles.[10 11] The effect of this coinfection on the prognosis is controversial. Some studies indicate that there is no difference in morbidity and mortality between patients with *Pneumocystis* pneumonia with or without CMV coinfection,[12 13] while others report higher mortality in patients with coinfection.[14] Other viruses, such as influenza and adenovirus, have also been reported as coinfection agents.[15 16]

Strongyloides stercoralis has also been reported as a coinfection agent in a patient with HIV and *Pneumocystis* in Argentina. The patient also had *C. neoformans* meningoencephalitis and had a fatal outcome despite treatment.[17]

Coinfection by *Pneumocystis* and *Histoplasma* has previously been reported in the literature as a rare event.[18] However,

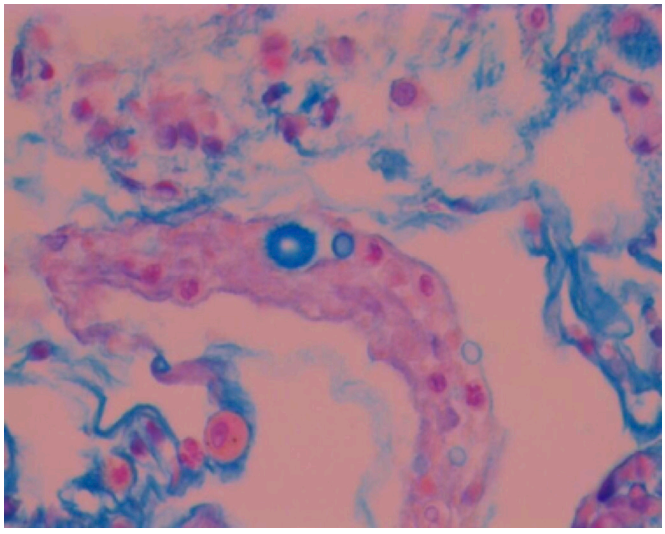

Figure 4 *Cryptococcus* spp in bronchial brushing with Masson's trichrome staining.

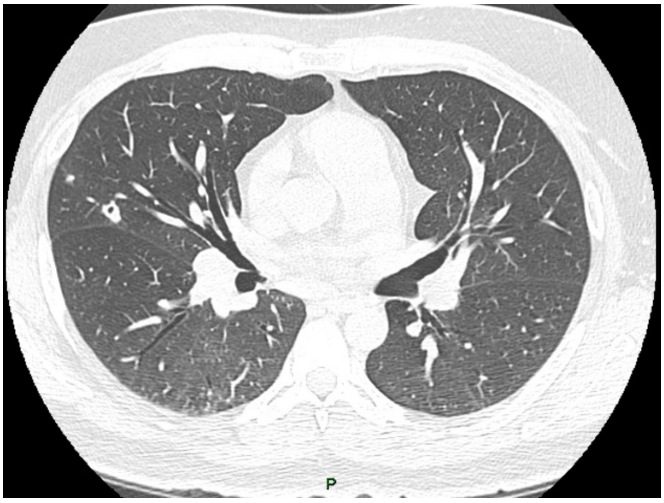

Figure 5 Chest CT scan on the 4th week of fluconazole treatment.

a recent study in Mexico highlighted the rate of coinfection between *Pneumocystis* and *Histoplasma capsulatum* in patients with HIV (10.7%). It found that this coinfection doubles the mortality rate of patients compared with those with only a single infection.[19]

Another fungus that has been rarely reported as causing pulmonary coinfection in patients with HIV and *Pneumocystis* is *C. neoformans*.[20–22] This association has been reported in infections by other retroviruses as human T-cell leukemia virus type 1 (HTLV-1).[23]

In this case report, we present a case of a young patient with advanced HIV who presented with a pneumonic infection due to *P. jirovecii* infection. After satisfactory treatment, cavitated nodules were discovered in the lungs that were diagnosed as pulmonary cryptococcosis.

In retrospect, the patient had a CT scan on the 15th day of hospitalisation and some cavitated nodules were seen. Taking into account that the material from the first bronchoscopy did not show any yeast and the serum *Cryptococcus* antigen was negative at admission, we assumed that these nodules were by *P. jirovecii* itself. Therefore, our case highlights the need to expand the differential diagnosis of pulmonary nodules that do not improve in radiographic follow-up, even in the context of previously negative tests such as cryptococcal antigen serum test.

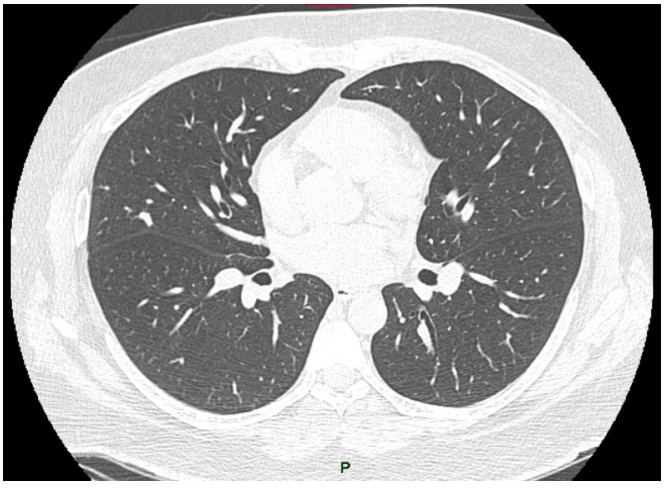

Figure 6 Chest CT scan 36 weeks after the initial *Pneumocystis jirovecii* pneumonia.

Learning points

- Patients with advanced HIV can have multiple infections at the same time due to the advanced immunosuppression. This could increase the morbidity and mortality if these infections are not diagnosed and treated effectively.
- Pneumocystis may not be the sole pathogen, but rather it may be a coinfection with other micro-organisms.
- *Cryptococcus* lung infection, although uncommon, could be a cause of cavitary lung lesions.
- A negative cryptococcal antigen test does not exclude *Cryptococcus* spp as a cause of lung cavitated nodules. Repeat testing can be valuable in cases of progression or lack of response to treatment even when a cause has been identified.

Pulmonary cavitations due to *P. jirovecii* have been reported in the literature as a form of presentation in patients with advanced HIV.[24] However, there are other infections that can be responsible for pulmonary cavitations in patients with HIV. The principal one is *C. neoformans*, although infections due to *Penicillium marneffei*, *Aspergillus* spp and *M. tuberculosis* should also be considered.[25]

These nodules were possibly made notable by improving the radiographic findings resulting from *P. jirovecii* infection, coupled with immune reconstitution syndrome, which helped so that the previously covert *Cryptococcus* spp infection could be discovered after the start of antiretroviral therapy.[26] Our patient had multiple risk factors for developing immune reconstitution syndrome, such as low T-CD4 lymphocyte count, high viral load and initiation of therapy that included integrase inhibitors.[27]

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ORCID iD
Benjamin Valente-Acosta http://orcid.org/0000-0001-9885-3594

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