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Case report

Pulmonary cannonballs in a patient with Acquired Immunodeficiency Syndrome (AIDS)

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ABSTRACT

Pneumocystis jirovecii pneumonia (PJP) remains one of the most common and life-threatening complications in patients with AIDS. PJP typically presents subacutely with a dry cough, shortness of breath with exertion, fever, and bilateral ground-glass opacities on imaging. However, atypical imaging findings have been reported including cysts, isolated lymphadenopathy, and small to large nodules. This case highlights the importance of considering unusual presentations of a relatively common entity in order to prevent delays in diagnosis and treatment.

Introduction

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection cause by the unicellular fungus, *Pneumocystis jirovecii*. It gained global recognition in the early 1980s as one of the most common and the first defining-illness associated with acquired immunodeficiency syndrome (AIDS) in Europe and the Americas. The introduction of highly active antiretroviral therapy in the mid 1990s coupled with the implementation of effective, affordable, and safe prophylactic measures for those at risk resulted in a substantial decline in cases [1]. Despite the effectiveness of chemoprophylaxis and antiretroviral therapy, PJP remains one of the most common human immunodeficiency virus (HIV)-related opportunistic infections.

Pneumocystis spp. exists in 3 different morphological forms: cyst, trophozoite, and sporozoite. The organism is transmitted from human to human via the airborne route, with those with asymptomatic colonization serving as reservoirs [1,2]. In patients with HIV, PJP typically presents subacutely with a dry cough, shortness of breath with exertion, fever, and bilateral ground-glass opacities on imaging. However, unusual imaging findings have been reported including cysts, isolated lymphadenopathy, and small to large nodules [3]. This case highlights the importance of considering atypical presentations of a relatively common entity in order to prevent delays in diagnosis and treatment.

Case

A 50-year-old female with a history of HIV/AIDS (CD4 + 0 cells/uL, viral load 9,840 copies/mL) diagnosed in 2007 and not on antiretroviral therapy for the last 18 months presented to the hospital for the evaluation of a one-week history of dry cough and one-day history of hemoptysis. Trimethoprim-sulfamethoxazole (TMP/SMX) had been provided by an urgent care clinic three days before admission without improvement. The patient also had history of Pneumocystis pneumonia and progressive disseminated histoplasmosis diagnosed in 2007. She denied having other opportunistic infections in the past or other medical problems since stopping antiretroviral therapy 18 months ago. The day she first presented to the hospital with these symptoms will be defined as “day 0” in this report.

On exam, blood pressure was 116/65 mmHg, pulse was 123 beats per minute, temperature 36.9 °C and respiratory rate of 24 breaths per minute. She appeared malnourished and chronically ill. She had a healed tracheostomy scar and the lung exam was significant for bibasilar rales (worse on the right) with hemoptysis on a tissue at bedside. A complete blood count was normal with the exception of microcytic anemia with a hemoglobin of 10 g/dL. A complete metabolic panel was within normal limits. Venous blood gas analysis showed respiratory alkalosis with low partial pressure of carbon dioxide at 38 mm Hg (reference range 41–47 mm Hg). The urinalysis was normal and the urine drug screen was negative.

The initial microbiologic evaluation consisted of a sputum culture which showed normal respiratory flora. BioFire Film Array showed *Chlamydophila pneumoniae*. A chest x-ray noted “multiple large lung masses in bilateral lower lobes.” A computed

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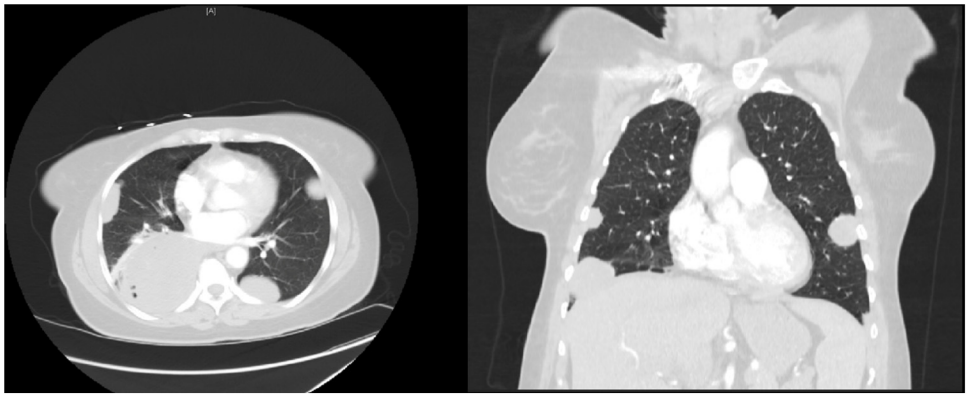

Fig. 1. Computed tomography angiogram of chest. Large posterior right lower lobe heterogeneous lesion with several foci of gas. Other bilateral pulmonary masses are also noted.

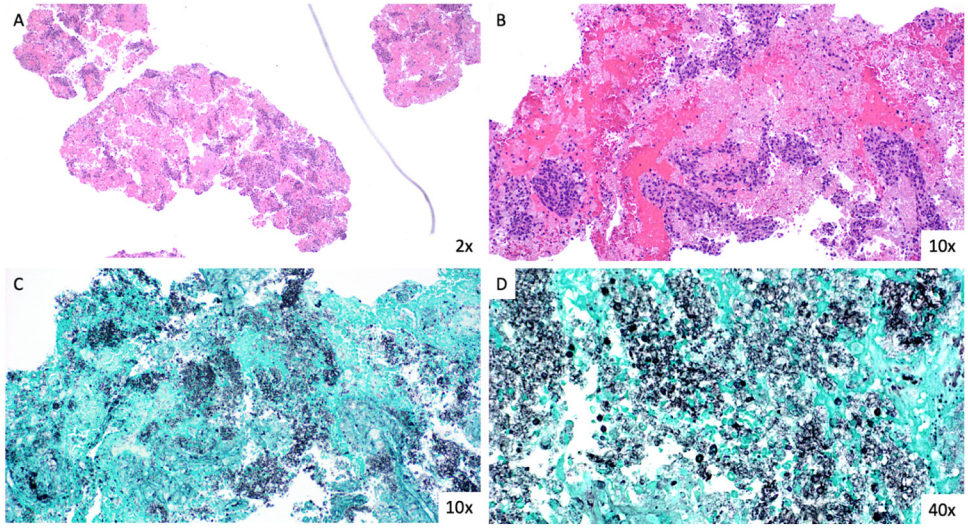

Fig. 2. Hematoxylin and Eosin staining of the lung biopsy specimen shows necrotic and hemorrhagic respiratory tissues with reactive stroma and mixed inflammatory infiltrates (A and B). Grocott-Gomori Methenamine Silver stain of the lung biopsy specimen highlight oval to round fungal elements likely represent the yeast form within the necrotic tissue (C and D).

tomography (CT) chest angiogram showed: "No evidence of pulmonary embolism. Large posterior right lower lobe heterogeneous lesion with several foci of gas. Other bilateral pulmonary masses. Enlarged subcarinal and left lower paratracheal lymph nodes" (Fig. 1). Additional testing included a negative serum cryptococcal antigen and urine *Streptococcus pneumoniae* antigen. Three sputum samples were collected and submitted for acid fast bacilli smear and cultures with negative results. The QuantiFERON gold gamma interferon release assay was also negative. A direct fluorescence antibody (DFA) staining for *P. jirovecii* in expectorated sputum was negative. Urine and serum histoplasma antigens were negative. The plasma Epstein-Barr virus DNA viral load was 5,600 IU/mL (reference range 0 IU/mL).

The patient was started on levofloxacin for presumable *Chlamydophila pneumoniae* pneumonia and prophylactic TMP/SMX. There was a lack of improvement in dry cough and associated hemoptysis on day +4 of admission.

On day +4 of hospital admission, she underwent a computed tomography guided biopsy of the large right lung mass. The Gram stain showed 2–5 white blood cells and no organisms. Acid fast bacilli smears and culture of the tissue were negative. Fungal and bacterial cultures were also negative. The pathology report was: "Positive for fungal organisms. Special stain revealed scattered individual 4–6 u m round structures consistent with yeast. No definitive budding identified. The cytomorphology of these organisms is consistent with *Pneumocystis jirovecii*" (Fig. 2).

The patient was started on treatment dosing of TMP/SMX. A repeat DFA staining for *P. jirovecii* from induced sputum was positive. Serum test for 1–3 B-D-glucan (Fungitell) was positive at 133 pg/mL (reference range 0–80 pg/mL). Antiretroviral therapy with abacavir sulfate, lamivudine, dolutegravir, and tenofovir disoproxil fumarate was started based on previous HIV genotypes. She was seen in clinic at the end of the 21-day treatment course with TMP/SMX and reported complete resolution of cough and hemoptysis. A repeat CT of the chest was ordered but the patient has missed her follow-up appointments.

Discussion

Pneumocystis was initially considered a protozoan based on several morphologic features that included the lack of ergosterol in the cell membrane, susceptibility to anti-protozoan drugs, and lack of growth on routine laboratory media [1,4,5]. It was later classified as an ascomycetous fungi based on sequencing homology demonstrated by molecular studies [5]. Phenotypic and genetically distinct *Pneumocystis* species has been described in a number of

mammalian species. These distinct species have strict host predilections that are not transmissible to other mammalian hosts [6–8].

Three forms of the organism have been identified in humans and animals– cyst, trophozoite, and the sporozoite or intracystic form. All forms have been observed within the lungs, with the predominate morphology being the trophic form in active infection [9]. The diagnosis is based on the detection of the different forms by tinctorial staining, direct fluorescent antibody (DFA) staining, or polymerase chain reaction (PCR). DFA staining detects both trophic and cystic forms. Data comparing expectorated sputum versus induced sputum with hypertonic saline for the diagnosis of *Pneumocystis* pneumonia is limited. In those with AIDS, increasing sensitivity is noted with induced sputum, bronchoalveolar lavage, and transbronchial biopsy, respectively [10]. In those with immunocompromising conditions other than AIDS, the diagnostic yield of staining and microscopy is reduced due to decreased organism burden [11].

One distinctive feature is the presence of cholesterol in the *Pneumocystis* cell membrane, instead of ergosterol, the major binding site of amphotericin B [9]. Azoles target sterol synthesis by inhibiting the cytochrome P450 enzyme, 14α-lanosterol demethylase, which facilitates a key step in the conversion of lanosterol to ergosterol, rendering azoles an ineffective treatment for *Pneumocystis* [12]. The current first line of treatment and prophylaxis for *Pneumocystis* pneumonia is TMP-SMX. TMP-SMX inhibits the enzyme dihydropteroate synthase (DHPS) impairing folate synthesis.

Although improvements in the use of prophylactic interventions and access to antiretroviral therapy have led a decrease in its incidence, *Pneumocystis jirovecii* pneumonia remains one of the most common and life-threatening opportunistic infections in patients with AIDS [13]. The typical imaging finding is that of diffuse and bilateral infiltrates. Rare chest imaging findings include cystic pulmonary lesions, miliary nodules, larger solitary nodules, and cavitary lesions [3,14,15]. Atypical imaging presentations of *P. jirovecii* pneumonia are thought to occur in the setting of distortion of the normal lung architecture related to prior infections [16].

Pulmonary nodules or masses are infrequent, representing less than 5% of all *P. jirovecii* presentations, and typically represent granulomatous formation [15,17]. These are usually encountered early in the course of HIV infection or in those on antiretroviral therapy, when patients are able to mount a granulomatous response without the development of necrosis and cavitation [13,18–20]. Solid nodular pulmonary lesions due to PJP is an exceedingly rare presentation leading to delays in diagnosis. Granulomatous PJP should be considered in the differential diagnosis of pulmonary nodules with the appearance of cannonballs in immunocompromised individuals.

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Miranda McGhee: Writing – Original draft preparation, Visualization. Nelson Iván Agudelo Higuita: Writing – Review and Editing, Supervision. Dante Paolo Melendez-Lecca: Writing – Review and Editing.

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