Apical Pneumocystis jiroveci as an AIDS defining illness: A case report illustrating a change in the paradigm

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ABSTRACT

Pneumocystis jiroveci pneumonia is a common acquired immune deficiency syndrome defining illness. Pneumocystis jiroveci pneumonia is classically described as having symmetrical bilateral perihilar ground-glass opacities on chest radiographs. We present an "atypical" case of Pneumocystis jiroveci pneumonia presenting as symmetric biapical cystic spaces with relative sparing of the remainder of the lungs in a 22 year-old male, previously undiagnosed with acquired immune deficiency syndrome. Our case illustrates that formerly unusual presentations of Pneumocystis jiroveci pneumonia are becoming more common as acquired immune deficiency syndrome defining illnesses as more patients are being imaged with further imaging such as high resolution computed tomography.

CASE REPORT

A 22-year-old man with no past medical history presented with acute onset chest pain. Over the prior four weeks, he complained of heart palpitations with lightheadedness. He then developed a dry cough which was not relieved with over-the-counter medications. The cough became productive with green sputum and he also began to have mild diarrhea and fever, with no weight loss or chills. Upon presentation, he had a temperature of 100.1°F (37°C) (normal 97.3-99.1°F; 36-38°C), mild tachycardia, and mild hypotension.

Imaging findings

Initial chest radiographs demonstrate multiple large biapical cavitary opacities with air-fluid levels (Figure 1 and Figure 2) with sparing of the lower lobes. Subsequent computed tomography (CT) images demonstrate multiple cavitory lesions with air-fluid levels at both apices and relative sparing of the remainder of the lungs (Figure 3). Based on this imaging presentation and the clinical history, the differential diagnosis included pneumatoceles, tuberculosis, blebs and bullae, neurofibromatosis type 1, cystic metastasis, and pulmonary sarcoidosis.

Management

Since the imaging findings were nonspecific, the patient was started on broad spectrum antibiotics including piperacillin/tazobactam and vancomycin. Bronchoscopy was performed and was negative for acid fast bacilli and Pneumocystis jiroveci. Further workup revealed a cluster of differentiation 4 (CD4) count of 38 (normal >500) and a viral load of approximately 250,000 (normal =0). Due to the concern for an opportunistic infection, a second bronchoscopy was performed with bronchoalveolar lavage. This yielded Pneumocystis jiroveci organisms by Gömöri methenamine silver staining (Figure 4). The previous antibiotics were discontinued and treatment with double strength trimethoprim-sulfamethoxazole was initiated.
Follow-up

The patient was discharged two weeks later with near complete resolution of his symptoms. A repeat chest radiograph was obtained at the time of discharge, and demonstrated interval improvement of the bilateral cystic opacities, with only a small residual opacity in the right lung apex (Figure 5). He was discharged with a seven-day prescription of trimethoprim-sulfamethoxazole for Pneumocystis jiroveci pneumonia (PJP). He was to follow up with his primary care physician to begin highly active antiretroviral therapy (HAART).

DISCUSSION

Etiology and Demographics

Pneumocystis jiroveci (previously called Pneumocystis carinii) is a complex organism best classified as a fungus. Exposure to this organism is ubiquitous, with most children being exposed by 3 or 4 years of age. Since development of Pneumocystis pneumonia (PJP) typically involves immunocompromised patients, there is no predilection for gender or age [1, 2]. The mechanism of transmission is unclear, but clusters of outbreaks of PJP among immunocompromised populations support a person-to-person airborne transmission [3]. PJP is one of the most common acquired immune deficiency syndrome (AIDS) defining illnesses in the United States and Europe, second only to esophageal candidiasis [4]. The incidence of PJP among immunocompromised patients is approximately 40 per 1000 person years [5].

Clinical and imaging findings

Infection with Pneumocystis jiroveci pneumonia (PJP) typically becomes symptomatic when the cluster of differentiation 4 (CD4) count falls below 200 (normal >500), and results in exertional dyspnea, hypoxia, fever, chest pain, or nonproductive cough. 90% of patients also have an elevated LDH (>350) [1, 6, 7]. The gold standard for diagnosing PJP is bronchoalveolar lavage with Gomori methenamine silver or calcofluor white staining since Pneumocystis jiroveci is very difficult to culture [8]. Some patients will develop apical cyst formation. The pathogenesis of cyst formation is not well known. Proposed theories include a check-valve bronchiolar obstruction with distal cyst formation, elastase release from the macrophages with destruction of alveolar tissue, cytotoxic effect of HIV, or direct tissue destruction by Pneumocystis jiroveci. [9]

Classically, PJP has symmetric ground-glass opacities radiating from the hilum on chest radiographs [10, 16]. Computed tomography shows diffuse perihilar ground-glass opacities with peripheral subpleural sparing [11]. Although used as a screening test, the chest radiograph is negative in up to 39% of symptomatic patients who were later confirmed to have PJP by bronchoalveolar lavage [12]. This low sensitivity of chest radiographs has led clinicians to further image patients with additional imaging techniques such as computed tomography, which has shown that patients (found to be positive with PJP by bronchoalveolar lavage) may present with a variety of manifestations, including predominately apical opacities [10]. Studies have demonstrated that imaging of PJP may reveal localized opacities, thin walled cysts, multiple nodules, honeycombing, or hilar fullness. Moreover, up to 15.5% of patients with PJP may develop a spontaneous pneumothorax [13]. Gallium scans (Ga-67) may be used for detection of PJP, with diffuse lung parenchymal radiotracer uptake greater than soft tissue in equivocal cases and greater than liver or sternum in strongly positive cases. Even though gallium scans may be strongly positive despite negative chest radiographs, they are infrequently done since scintigraphy is performed 48 hours after radiotracer injection.

Our case illustrates PJP presenting with bilateral apical opacities in an immunosuppressed host. The bilateral apical distribution of PJP was first described in AIDS patients receiving inhaled pentamidine prophylaxis, which was commonly used in the late 1980s and early 1990s [14]. It was postulated that these patients were susceptible to PJP at the lung apices since the inhaled pentamidine particles settled and did not reach the apex of the lung, leaving it vulnerable to infection [15]. In 1991, PJP in an apical distribution was described in 3 patients who did not receive pentamidine prophylaxis, suggesting that this could be an independent form of presentation [16]. Inhaled pentamidine fell out of favor after trimethoprim-sulfamethoxazole was showed to be equally effective against PJP, simultaneously provide coverage against toxoplasmosis, and be more cost-effective [17]. Currently, upper lobe distributions are felt to be more common than previously thought in patients who have not had aerosolized pentamidine prophylaxis, as in our case. This is likely secondary to patients with PJP undergoing further imaging with computed tomography. For example, a study evaluating high-resolution CT in patients with suspected PJP and equivocal chest radiographs demonstrated that all patients had upper lobe predominant parenchymal opacities [18]. In addition, half of HIV-positive patients with upper lobe abnormalities on the chest radiograph were found to be positive for Pneumocystis jiroveci [19]. Pneumocystis jiroveci may also spare lung parenchyma in patients with prior radiation therapy [20, 21].

Treatment and Prognosis

Trimethoprim-sulfamethoxazole is the standard for treatment and prophylaxis of Pneumocystis jiroveci pneumonia (PJP) [22]. Only 5% of patients developed PJP while taking trimethoprim-sulfamethoxazole prophylaxis [23]. Prognosis depends on symptom severity at time of presentation, with treatment failure occurring in up to 20 percent of cases in patients with severe symptoms [25]. Second line treatment options include intravenous pentamidine, dapsone, and trimetrexate [26]. Appropriately treated PJP carries a good prognosis, with clinical improvement common within five days; imaging findings often take longer to resolve [12]. Respiratory failure requiring mechanical ventilation portends an 80% mortality rate [27]. Failure of clinical improvement after 7 days warrants repeat bronchoscopy to exclude another opportunistic infection.

Differential Diagnosis

Pneumocystis jiroveci pneumonia (PJP) can be a difficult and challenging diagnosis due its vague imaging presentations.
The differential diagnosis for apical cystic opacities is vast but can be narrowed down by clinical history, physical examination, and imaging findings. The differential diagnosis of apical cystic lesions includes blebs and bullae, neurofibromatosis type 1 (NF1), pneumatoceles, metastasis, tuberculosis, and stage 4 pulmonary sarcoidosis [29].

Blebs and bullae are top considerations in a patient presenting with incidental biapical, cystic spaces. A bleb is defined as a cystic space that measures 1 cm or less in diameter, anything larger is defined as a bulla [22]. Blebs and bullae can be differentiated from PJP primarily based on clinical presentation. Patients with blebs are typically asymptomatic, only occasionally presenting with pneumothorax [22]. In contrast, our patient presented with infectious symptoms of cough and fever.

NF1 is in the differential diagnosis of biapical cystic opacities. NF1 is a genetic disorder clinically presenting with a myriad of additional physical manifestations including neurofibromas, café-au-lait spots, axillary/inguinal freckling, optic nerve gliomas, Lisch nodules, and skeletal lesions. Chest manifestations include upper lobe bullae and lower lobe diffuse interstitial fibrosis. Lateral thoracic meningocoeles, posterior vertebral scalloping, rib notching, and neurofibromas are also sometimes seen on chest imaging [22].

Pneumatoceles are air filled spaces in the lung, which are typically post infectious or post traumatic. They present as thick walled structures that thin over time. Offending bacterial agents include Staphylococcus or Pneumococcal species. Pneumatoceles may be seen in patients with PJP; however, these are typically transient and much smaller than the large cystic lesions seen in our patient. Over time, pneumatoceles tend to regress and spontaneously resolve [22].

Thick walled cystic metastases are in the differential diagnosis of cystic pulmonary lesions. Neoplasms with cystic metastases include sarcoma, squamous cell carcinoma, urothelial cell carcinoma, and melanoma. Cystic metastases tend to have a basilar predominance, unlike our patient with biapical disease [22].

Stage 4 pulmonary sarcoidosis is in the differential of biapical cystic lung lesions as well. Terminal pulmonary sarcoidosis results in fibroscopic changes with upward hilar retraction with cystic and bullous changes [30]. These patients have demonstrated parenchymal volume loss from chronic cicatization and have a long standing history of sarcoidosis. Extrapulmonary manifestations include lymphadenopathy, hepatosplenomegaly, uveitis, and the skin findings of Lupus (erythema nodosum).

Pulmonary tuberculosis (TB) may appear very similar to PJP and is also prevalent in immunosuppressed patients. Primary pulmonary TB typically presents as parenchymal consolidation in any segment with associated adenopathy. Post-primary pulmonary TB presents as heterogeneous cavitory opacities in the apical and posterior segments, which may appear very similar to PJP. Acid fast staining is needed to distinguish TB from PJP [31].

REFERENCES


TEACHING POINT

Apical Pneumocystis jiroveci pneumonia was previously thought to be a rare presentation of an acquired immune deficiency syndrome defining illness. However, apical cystic Pneumocystis jiroveci pneumonia (and other atypical presentations) are encountered more often as Acquired immune deficiency syndrome patients are imaged more frequently with further imaging techniques such as high resolution computed tomography. This necessitates a shift in the paradigm of Pneumocystis jiroveci pneumonia with the radiologist needing to have increased awareness of various imaging presentations to prevent delays in diagnosis and treatment.


Thoracic Radiology:

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Figure 1: 22-year-old male with Pneumocystis jiroveci pneumonia (PJP) and bilateral apical opacities. Findings: Frontal (A) and lateral (B) chest radiographs show diffuse biapical symmetric cystic opacities (white arrows). In addition, there are multiple air fluid levels, most prominent in the left lung apex, (red arrows). There is relative sparing of the remainder of the lungs. The mediastinum and osseous structures are unremarkable. Technique: Frontal (posterior to anterior technique) and lateral chest radiographs.

Figure 2: 22-year-old male with Pneumocystis jiroveci pneumonia (PJP) and bilateral apical opacities with air fluid levels. Findings: Frontal (A) and lateral (B) magnified images of the left lung apex of Figure 1. The multiple air fluid levels in the left lung apex are more evident on this magnified image (red arrows). Technique: Frontal (posterior to anterior technique) and lateral magnified chest radiographs.
Figure 3: 22-year-old male with Pneumocystis jiroveci pneumonia (PJP) and biapical cavitating lung lesions. Findings: Non-contrast axial CT image (A) and coronal reconstructions (B) show diffuse cystic changes (black arrows) at both lung apices with surrounding ground-glass opacities and relative sparing of the lower lobes. Visualized portion of the central airways are patent. Technique: Axial CT images and coronal reconstructions from a GE Light Speed VCT 64 slice CT scanner with lung windows (center: -600 HU, range: 1600 HU), 120 KVp, 500ms, tube current modulation with mA ranging from 90-180, slice thickness 5mm, non-contrast.

Figure 4 (left): 22-year-old male with Pneumocystis jiroveci pneumonia (PJP). 1000x image with Gomori methenamine silver stain demonstrates Pneumocystis jiroveci in a cup-shaped configuration with a central dark zone on a foamy proteinaceous background.
Figure 5: 22-year-old male with Pneumocystis jiroveci pneumonia (PJP) demonstrating interval improvement in biapical airspace opacities. Findings: Frontal (A) and lateral (B) chest radiographs demonstrate interval improvement in bilateral apical airspace opacities. Air-fluid levels in the left lung apex have resolved. Slight residual consolidation/scarring is evident at the right apex (blue arrows). The remainder of the lung parenchyma remains clear. Mediastinal and osseous structures remain normal. Technique: Frontal (posterior to anterior technique) and lateral chest radiographs.
### Etiology
- *Pneumocystis jiroveci*

### Incidence
- Infections in patients with competent immune systems are extremely rare.
- Exposure is typically ubiquitous by 3-4 years of age.
- Incidence in immunocompromised patients is approximately 40/1000 person-years.

### Gender Ratio
- 1:1

### Age Predelection
- None

### Risk Factors
- Immunocompromised patients with a Cluster of differentiation 4 (CD4) count <200 (normal >500) and not receiving prophylaxis are at greatest risk.

### Transmission
- Unclear, but likely airborne

### Presentation
- Nonproductive cough (75%)
- Fever (75%)
- Chest Pain
- Hypoxia

### Detection
- Difficult to culture but can be grown on Gömöri methanamine silver stain which shows “foamy bubble like areas” (see Figure 4).
- 90% have an elevated (>350) Lactate Dehydrogenase (LDH)

### Findings on Imaging:

#### Chest Radiograph
- Initial screening test, but has a low sensitivity and may be negative in up to 40% of symptomatic patients
- Diffuse symmetric hilar opacities is the classic and most common appearance
- PJP can present with a wide array of atypical patterns such as apical opacities with cavitations (as in our case), spontaneous pneumothorax, or a negative chest radiograph
  - Spontaneous pneumothorax in up to 15% of patients

#### Computed Tomography (CT)
- Essential to making the diagnosis of PJP as it is widely available and the chest radiograph has low sensitivity
- Ground glass opacities in a bilateral perihilar distribution
- Cysts- typically thin walled in an upper lobe distribution
- Multiple nodules
- Localized infiltration

#### Nuclear medicine Gallium scan (Ga-67)
- Diffuse lung parenchymal radiotracer uptake greater than in soft tissues in equivocal cases and greater than liver or sternum uptake in strongly positive cases
- May be strongly positive despite negative chest radiographs
- Infrequently used since radiotracer must be administered 48 hours before obtaining imaging

### Treatment
- Gold standard for treatment and prophylaxis in patients without sulfa allergies is trimethoprim sulfamethoxazole
- Second line treatments include:
  - Trimetrexate
  - Inhaled pentamidine
  - Dapsone

### Prognosis
- Excellent when appropriately treated
- Clinical improvement is typically seen in 5 days in 80% of cases
- Respiratory failure requiring mechanical ventilation portends an 80% mortality rate

### Table 1: Summary table of Pneumocystis jiroveci pneumonia (PJP)
<table>
<thead>
<tr>
<th>Condition</th>
<th>CXR</th>
<th>CT</th>
<th>Ga-67</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumocystis jiroveci Pneumonia (PJP)</strong></td>
<td>- Diffuse symmetric hilar opacities are most common</td>
<td>- Perihilar ground glass opacities are the dominant finding</td>
<td>- Diffuse lung parenchymal radiotracer uptake greater than in soft tissues in equivocal cases and greater than liver or sternum uptake in strongly positive cases</td>
<td>- Immunosuppressed with CD4 &lt;200 (normal &gt;500)</td>
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<td>- 40% of symptomatic patients have normal CXRs</td>
<td>- Cysts- typically thin walled in an upper lobe distribution</td>
<td>- Multiple nodules</td>
<td>- Fever</td>
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<td>- Apical patterns with cystic cavitations are becoming more common</td>
<td>- Localized infiltration</td>
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<td>- Nonproductive cough</td>
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<td></td>
<td>- Spontaneous pneumothorax in 15% of patients</td>
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<td>- Chest pain</td>
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<td>- Hypoxia</td>
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<tr>
<td><strong>Blebs and bullae</strong></td>
<td>- Cystic opacities</td>
<td>- Sharply defined air-space opacities with hairline walls measuring 1 cm or less</td>
<td>- No radiotracer uptake</td>
<td>- Patients typically asymptomatic or at baseline hypoxia/shortness of breath</td>
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<td></td>
<td>- Pneumothorax</td>
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<td>- Occasionally present with pneumothorax</td>
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<td>- Not necessarily confined to the upper lobes</td>
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<tr>
<td><strong>Neurofibromatosis type 1</strong></td>
<td>- Upper lobe bullae and lower lobe diffuse interstitial fibrosis</td>
<td>- Upper lobe bullae and lower lobe diffuse interstitial fibrosis</td>
<td>- No radiotracer uptake</td>
<td>- Café-au-lait spots</td>
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<td></td>
<td></td>
<td>- Lateral thoracic meningocles, posterior vertebral scalloping, rib notching, and neurofibromas are also seen</td>
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<td>- Neurofibromas</td>
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<td>- Axillary/inguinal freckling</td>
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<td>- Scoliosis and other skeletal lesions</td>
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<td>- Lisch nodules</td>
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<td><strong>Pneumatoceles</strong></td>
<td>- May present with a normal radiograph</td>
<td>- Thin-walled air-filled spaces</td>
<td>- No radiotracer uptake</td>
<td>- Following bacterial pneumonia</td>
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<td>- May appear anywhere in the lung</td>
<td>- Resolve spontaneously or post treatment</td>
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<td>- Post traumatic</td>
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<td></td>
<td>- May be seen in Pneumocystis jiroveci pneumonia</td>
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<tr>
<td><strong>Metastases</strong></td>
<td>- Lower lobe predominance because of relative increased blood flow</td>
<td>- Lower lobe predominance because of relative increased blood flow</td>
<td>- Depending on the metastatic disease, metastases may be positive depending on the primary tumor</td>
<td>- History of sarcoma, squamous cell carcinoma, urothelial cell carcinoma, or melanoma</td>
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<td></td>
<td>- Hilar adenopathy</td>
<td>- Hilar adenopathy</td>
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<tr>
<td><strong>Stage 4 pulmonary sarcoidosis</strong></td>
<td>- Fibrocystic changes with upward hilar retraction</td>
<td>- Fibrocystic changes with upward hilar retraction</td>
<td>- Diffuse radiotracer uptake</td>
<td>- Terminal stage of long standing sarcoidosis</td>
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<td>- Parenchymal volume loss from chronic cicatization</td>
<td>- Parenchymal volume loss from chronic cicatization</td>
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<td>- Dry cough and dyspnea</td>
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<td></td>
<td></td>
<td>- Extrapulmonary lymphadenopathy and hepatosplenomegaly</td>
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<td>- Elevated angiotensin converting enzyme (ACE) levels (&gt;52)</td>
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<td>- Extra pulmonary manifestations including peripheral lymphadenopathy, uveitis, and dermatologic (Lupus pernio and erythema nodosum)</td>
</tr>
<tr>
<td><strong>Pulmonary Tuberculosis (TB)</strong></td>
<td>- Parenchymal consolidation in any pulmonary lobe or segment</td>
<td>- Consolidation in any pulmonary lobe or segment</td>
<td>- Variable radiotracer uptake</td>
<td>- Fears, night sweats, asymptomatic, cough, fatigue, chest pain</td>
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<tr>
<td></td>
<td>- Hilar adenopathy</td>
<td>- Hilar adenopathy</td>
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<td>- Differentiated from PJP by presence of acid fast bacilli</td>
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<td>- Post-pulmonary TB cavity opacities in the apical and posterior segments of the upper lobes</td>
<td>- Post-pulmonary TB cavity opacities in the apical and posterior segments of the upper lobes</td>
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<tr>
<td></td>
<td>- May have unilateral large pleural effusions</td>
<td>- Lymphadenopathy is rare in post-pulmonary TB</td>
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<td>- Military TB presents as diffuse nodules throughout the lung parenchyma</td>
<td>- May have unilateral large pleural effusions</td>
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</table>

Table 2: Differential diagnosis table of Pneumocystis jiroveci pneumonia (PJP)
ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome
CD4: Cluster of differentiation 4
CT: Computed Tomography
CXR: Chest radiograph
HAART: Highly Active Antiretroviral Therapy
LDH: Lactate dehydrogenase
MRI: Magnetic Resonance Imaging
PJP: Pneumocystis carinii pneumonia
PJP: Pneumocystis Jirovecii pneumonia

KEYWORDS

AIDS; Infection; PJP; Pneumocystis jiroveci; PCP; Pneumocystis carinii; pneumonia; Acquired immune deficiency syndrome

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