Lesson of the month 1: Lobar pulmonary consolidation in an immunocompromised host

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A 19-year-old male with a history of idiopathic panuveitis, currently taking methotrexate and infliximab, presented to our institution with 6 weeks of cough, dyspnoea and fevers. He had failed outpatient antimicrobial therapy. Computerised tomography (CT) of the chest revealed the presence of a lobar pneumonia and he was treated with broad spectrum antibiotics, which did not improve his symptoms. Bronchoalveolar lavage was performed with a transbronchial lung biopsy because of the diagnostic uncertainty of the patient’s presentation. Pathology revealed non-budding yeasts, consistent with Pneumocystis. Serological and urine studies were positive for both Histoplasma and Blastomyces. The diagnosis of Histoplasma pneumonia was made because of the presentation being inconsistent with Pneumocystis pneumonia, and serology, urine and pathology testing being more consistent with Histoplasma. The patient was treated with oral itraconazole and was doing well at follow-up 12 weeks after hospitalisation.

KEYWORDS: Blastomyces, fungi, Histoplasma, immunosuppression, Pneumocystis, pneumonia

Case presentation

A 19-year-old male with idiopathic panuveitis diagnosed 5 years previously, which was initially treated with prednisone and then with infliximab along with topical therapy, presented to the clinic with 6 weeks of cough, greenish sputum, left-sided chest pain, haemoptysis, exertional dyspnoea, fevers, chills and night sweats. His primary doctor initially treated him with amoxicillin-clavulanate but his symptoms persisted and he was referred to our institution for admission.

Assessment

At admission, the patient was febrile (38.4°C) and tachycardic (109 bpm). Other than bilateral scattered crackles, the physical examination was normal. Laboratory testing showed a normal leukocyte count (7,100/µL), mildly elevated C-reactive protein (8.2 mg/L) and an elevated angiotensin converting enzyme (ACE) level (120 U/L; normal 8–53 U/L). The patient was a college student living in a dormitory. He denied using recreational drugs, alcohol or tobacco. He had lived in Iowa for his entire life. He denied travel to a tuberculosis-endemic region, camping or hiking. He often visited a friend who had a pet dog and cat. He was not receiving Pneumocystis pneumonia prophylaxis.

A computerised tomography (CT) scan of the chest revealed consolidation in the lingula with additional bilateral micronodularity and hilar/mediastinal lymphadenopathy (Fig 1). Broad-spectrum coverage was provided with vancomycin and levofloxacin. An extensive diagnostic work-up was pursued, including serum and urine studies, bronchoalveolar lavage (BAL) and transbronchial lung biopsy (Table 1). BAL cell differential revealed lymphocytosis (42%) with no malignant cells. Serological and urine antigen studies demonstrated reactivity for Blastomyces and Histoplasma. The lung biopsy showed necrotising granulomatous inflammation with scattered, non-budding degenerative yeasts (2–4 µm), suggestive of Pneumocystis species (Fig 2).

Diagnosis

There was considerable diagnostic uncertainty with evidence for several infectious causes, including Pneumocystis, Blastomyces and Histoplasma. Furthermore, lymphocytic alveolitis (BAL lymphocytes >20%) can be present in various non-infectious conditions, including sarcoidosis, hypersensitivity pneumonitis, drug-induced lung disease, pulmonary lymphomas and lymphoproliferative disorders.

The possibility of sarcoidosis was entertained, as it would explain the panuveitis, and may also be manifesting in the lungs. Further, sarcoid-like granulomatous reactions have been reported with infliximab and other anti-tumour necrosis factor agents. Although granulomatous inflammation was seen on biopsy, the presence of fungal elements suggested infection. Lobar consolidation is unusual for sarcoidosis, which usually presents as hilar/mediastinal lymphadenopathy and/or multiple nodules in a perilymphatic distribution. ACE elevation lacks specificity as it can also be seen in fungal or
Mycobacterial infection, diabetes, hypothyroidism, and other conditions.

The differential diagnosis was narrowed to the three most likely fungal infections, namely *Pneumocystis* pneumonia, blastomycosis and histoplasmosis. While imaging can raise suspicion for *Pneumocystis* infection, the diagnosis is confirmed by analysing sputum, BAL or histology. *Pneumocystis* pneumonia can produce a variety of radiographic appearances, including patchy upper-lobe-predominant ground glass opacities, and cystic lesions, but lobar consolidation is unusual. In non-HIV-infected immunocompromised patients, polymerase chain reaction (PCR) has excellent sensitivity and negative predictive value from induced sputum (100%; 100%) and BAL (84%; 98.3%) samples. However, the histologic findings suggesting *Pneumocystis* were challenging to interpret in the context of negative PCR results for this organism.

On histology, *Pneumocystis jirovecii* shares many morphologic similarities with *Histoplasma capsulatum*. Both are thin-walled yeasts measuring 2–8 µm in size, appearing collapsed or distorted in tissue sections. *Pneumocystis* often exhibits two larger intracystic bodies on silver stain and lacks budding forms. In contrast, *Histoplasma* has a smaller capsular dot and multiplies by budding. When present, budding forms can suggest *Histoplasma*; however, their absence does not exclude this possibility.

In this case, the yeasts did not show budding, a capsular dot or intracystic bodies. Although granulomatous inflammation is atypical for *Pneumocystis*, it has been reported in 4–5% of patients. Unfortunately, the degenerative nature of yeast forms,
Table 1. Summary of microbiologic data obtained by hospital day 2

| Test                          | Result               |
|-------------------------------|----------------------|
| Aspergillus antigen, serum    | Negative             |
| Blastomyces antibody, serum   | Equivocal            |
| Blastomyces antigen, urine*   | 2.78 ng/mL (positive)|
| Coccidioides IgG, serum       | Negative             |
| Coccidioides IgM, serum       | Negative             |
| Coccidioides complement fixation | Negative             |
| Cryptococcus antigen, serum   | Negative             |
| Histoplasma – mycelial, serum | 1:128 (positive)     |
| Histoplasma – yeast, serum    | 1:128 (positive)     |
| Histoplasma – immunodiffusion, serum | H and M bands noted |
| Histoplasma antigen, urine    | 0.88 ng/mL (positive)|
| Sporothrix antibody, serum    | Negative             |
| HIV 1/2 antigen and antibody screen, serum | Negative            |
| M tuberculosis QuantIFERON®; blood | Negative           |
| M pneumoniae IgG, serum       | Negative             |
| M pneumoniae IgM, serum       | Negative             |
| Q fever IgG, serum            | <1:16                |
| Q fever IgM, serum            | <1:16                |
| Coxiella burnetti PCR, serum  | Negative             |
| Cell differential, BAL        |                      |
| > Alveolar macrophages        | 57 %                 |
| > Lymphocytes                 | 42 %                 |
| > Neutrophils                 | 1 %                  |
| AFB stain, BAL                | Negative             |
| Nocardia stain, BAL           | Negative             |
| Fungal smear, BAL             | Yeast                |
| Bacterial culture, BAL        | Usual flora          |
| Adenovirus PCR, BAL           | Negative             |
| M tuberculosis PCR, BAL       | Negative             |
| Influenza A and B PCR, BAL    | Negative             |
| Respiratory syncytial virus PCR, BAL | Negative        |
| Legionella PCR, BAL           | Negative             |
| Pneumocystis PCR, BAL         | Negative             |
| Aspergillus antigen, BAL      | Negative             |
| Pneumocystis PCR, sputum      | Negative             |
| M tuberculosis PCR, sputum     | Negative             |
| AFB stain, sputum             | Negative             |
| Bacterial culture, sputum     | Usual flora          |
| S aureus PCR, nasal swab      | Negative             |

AFB = acid-fast bacillus; BAL = bronchoalveolar lavage; PCR = polymerase chain reaction
*Test performed by MiraVista Diagnostics, Indianapolis, IN, USA

and their sparse dispersion on a necrotic background, made definitive identification challenging on microscopy. Blastomyces and Histoplasma are dimorphic fungi, existing as yeasts at body temperature and hyphae at relatively cooler temperatures (<35°C). Blastomycosis and histoplasmosis are typically diagnosed by fungal stain, cytology, serology or urine/serum antigen detection. Fungal cultures take several weeks to grow and are highly specific, but are often not available early in the evaluation and, therefore, are not helpful in making the initial diagnosis. Histoplasma PCR, a recent development, has 100% specificity for BAL samples.

Blastomyces antigen detection in urine or serum is positive in 92% of patients with disseminated or pulmonary infections. We considered blastomycosis based on positive urine antigen testing. However, Blastomyces antigen tests are known to cross-react with Histoplasma antigen. Furthermore, Blastomyces has a large (10–15 µm) yeast form with broad-based buds and refractile walls, and was unlikely based on pathology.

Histoplasmosis was suspected in this patient with positive Histoplasma urine antigen as well as serology. Histoplasma serology is positive in 90% of subacute presentations. Serologic testing consists of complement fixation (yeast and mycelial antigens), and immunodiffusion (H and M precipitins). A single titre ≥1:32 or a fourfold rise for either yeast or mycelial antibodies is considered diagnostic.

Eventually, in our patient, histoplasmosis was confirmed on BAL and sputum culture in 4 weeks.

Management

Management recommendations for histoplasmosis are presented in Table 2. Our patient underwent treatment with itraconazole 200 mg twice daily, with plans to continue this for the duration of his immunosuppression. His symptoms resolved within 1 month of therapy and radiographic infiltrates were seen to be resolving at 6 weeks; he continued to do well at 12-week follow-up.

Azole antifungals have significant drug-drug interactions via the cytochrome P450 system so therapeutic drug monitoring is essential. Itraconazole drug level should be measured periodically.

In conclusion, it is essential to consider a broad differential diagnosis in immunosuppressed patients presenting with pulmonary disease. Aetiologies can include usual pathogens that infect immunocompetent hosts, opportunistic infections, and reactions with immunosuppressant therapy. Careful attention to the sensitivities, specificities and cross-reactivities of tests for fungal diseases is extremely important.

In immunocompromised patients from endemic regions, coinfection with Histoplasma and Pneumocystis is possible. It is important to conduct a thorough search for additional pathogens and avoid anchoring bias.

Conflicts of interest

The authors have no conflicts of interests to declare.

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Written consent was obtained from the patient to publish the clinical details and images in this article.
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Table 2. ATS recommendations for management of histoplasmosis

| Clinical situation                                      | Management recommendations |
|--------------------------------------------------------|-----------------------------|
| **Immunocompetent hosts**                              |                             |
| Asymptomatic pulmonary nodules                         | Observation alone           |
| Asymptomatic bronchiolitis                             | Observation alone           |
| Bronchiolitis causing post-obstructive pneumonia, haemoptysis, fistula or airway compromise | Bronchoscopic evaluation, bronchoscopic removal of broncholith and/or surgical intervention |
| Fibrosing mediastinitis                                | Itraconazole 200 mg BID for 12 weeks; continue for 12 months if radiographic/physiologic improvement. Consider airway or intravascular stents if tracheobronchial or vascular compromise is present. Anti-fibrotics or steroids controversial. |
| Symptomatic mild pulmonary disease                     | Observation for 3 weeks     |
| Persistently symptomatic mild or moderate pulmonary disease | Itraconazole 200 mg BID for 12 weeks |
| Severe/life-threatening pulmonary disease               | Amphotericin B (0.7 mg/kg/day) until clinical improvement or up to a cumulative dose of 2 g. Following improvement, itraconazole 200 mg BID for at least 12 weeks. Systemic steroids (prednisone 40-60 mg daily) are recommended for 1–2 weeks. |
| **Immunocompromised hosts**                            |                             |
| Mild to moderate pulmonary disease or progressive/disseminated disease | Itraconazole 200 mg TID for 3 days, followed by 200 mg BID for 12 months |
| Moderate to severe pulmonary disease or progressive/disseminated disease requiring hospitalisation | Amphotericin B (0.7–1.0 mg/kg/day) or liposomal amphotericin B (3–5 mg/kg/day) until clinical improvement or a cumulative dose of 2 g of amphotericin B. Following improvement, itraconazole 200 mg BID for 12 months. In patients with AIDS, continue itraconazole until CD4+ T-cell count is >200/μL. |
| Chronic pulmonary disease or cavitiation                | Itraconazole 200 mg BID for 1–2 years |
| Patients with AIDS who remain immunosuppressed, on lifelong maintenance therapy | Monitor urine and serum Histoplasma antigens several times per year |

ATS = American Thoracic Society; BID = two times a day; TID = three times a day.
*In patients unable to tolerate itraconazole, alternatives include fluconazole and ketoconazole.

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