



# CASE REPORT

## Two Cases of Autoimmune Hepatitis Presenting with *Pneumocystis jiroveci* Pneumonia

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### INTRODUCTION

*Pneumocystis jiroveci* pneumonia (PJP) is a respiratory disease that causes high morbidity and mortality among immunocompromised and HIV patients.<sup>1</sup> In the United States, it remains the most common Acquired Immunodeficiency Syndrome (AIDS) defining illness. Though PJP can be life threatening, it is a treatable infection, so a rapid and accurate diagnosis is essential. Clinically, these patients present with nonspecific respiratory symptoms and signs suggestive of pulmonary infection such as cough, fever, dyspnea, hypoxemia, and an abnormal chest x-ray. PJP prophylaxis is considered the standard of care for patients with CD4 counts of less than 200 cells/mm.<sup>2</sup> PJP formerly occurred in 70 - 80% of HIV patients; however with prophylaxis and PJP treatment, the associated mortality has decreased to 20 - 40%.<sup>2-3</sup>

Approximately 90% of PJP cases occurred in patients with CD4+ counts of less than 200 cells/mm.<sup>2</sup> Other factors that are associated with increased risk for PJP include previous episodes of PJP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, or higher plasma HIV RNA.<sup>4-5</sup> Patients with a history of oropharyngeal candidiasis should receive chemoprophylaxis against PJP.<sup>3,4</sup> Trimethoprim-sulfamethoxazole is the recommended prophylactic agent and one double-strength tablet (160 mg - 800 mg) daily is the preferred regimen.<sup>2</sup> The diagnostic test of choice for PJP pneumonia is fiberoptic bronchoscopy with bronchoalveolar lavage and identifying the organism either by direct visualization with stains or by polymerase chain reaction (PCR). Prognosis for the patient depends on underlying comorbidities and immunological status.<sup>6</sup>

Autoimmune hepatitis is a chronic disease that can occur in patients of all ages and all ethnicities.<sup>7</sup> However, it is seen most commonly in females between 40 - 50 years old. A diagnosis of autoimmune hepatitis usually is made and characterized

by clinical signs and symptoms, laboratory abnormalities, the presence of antibodies, and the concentration of serum globulin. Some of the most common symptoms include fatigue, icterus, abdominal discomfort, abdominal distension, dark urine, pale stools, and pruritus. Physical exam findings may include splenomegaly, ascites, hepatomegaly and epigastric tenderness.<sup>8</sup>

Characteristic laboratory findings in patients with autoimmune hepatitis can include an increase in bilirubin and abnormal liver enzyme levels.<sup>8</sup> Patients with autoimmune hepatitis also may have circulating serum antibodies, which can include anti-nuclear antibodies (ANA) and anti-smooth-muscle antibody (ASMA). It is also possible to see other antibodies such as anti-liver/kidney microsomal antibodies (ALKM-1), anti-liver cytosol antibodies (ALC-1), anti-double-stranded DNA (anti-dsDNA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). On occasion, anti-mitochondrial antibodies also may be found in association with all of the above.<sup>8-9</sup> The clinical manifestations range from asymptomatic to fulminant hepatic failure. Symptomatic patients with autoimmune hepatitis who are untreated have high mortality rates. The initial treatment for autoimmune hepatitis usually consists of immunosuppression with steroids sometimes combined with azathioprine.<sup>10</sup> The 10-year survival for treated patients is 90% and includes patients with advanced cirrhosis.<sup>9</sup>

Two separate cases of documented autoimmune hepatitis are presented. Both patients were admitted to the hospital with severe upper respiratory infectious symptoms and were diagnosed with *pneumocystis jiroveci* pneumonia. PJP is most common in patients with HIV/AIDS and patients diagnosed with cancer, but it is rare to find it in patients with autoimmune hepatitis.<sup>11</sup>

A literature search using PubMed revealed an article discussing PJP pneumonia and alcoholic liver disease.<sup>12</sup> A literature search on PJP pneumonia patients with severe liver disease revealed one article about liver transplant patients who developed PJP, suggesting possible prophylaxis for such patients.<sup>13</sup>

### CASE REPORT

Table 1 discusses two patients with PJP pneumonia.

**Table 1. Two cases of PJP pneumonia.**

	Patient 1	Patient 2
<b>Gender</b>	Female	Male
<b>Age</b>	58 years old	31 years old
<b>Admitted for:</b>	Hypoxemic respiratory failure, syncope, right pleural effusion, productive cough for 1 week	Recurrent jaundice, extreme fatigue, fever, dry cough, progressive abdominal distension, 20 lb weight gain since last discharge 3 weeks prior
<b>Past medical history:</b>	Breast cancer, hepatic encephalopathy, obesity, autoimmune hepatitis diagnosed 4 months prior	Alpha-1 antitrypsin deficiency (diagnosed 2 weeks prior), esophageal varices, hypertension
<b>Past surgical history:</b>	Multiple paracenteses and thoracenteses; bilateral breast reduction	
<b>Social history:</b>	Former smoker	Former alcohol drinker; stopped 3 weeks prior

	Patient 1	Patient 2
<b>Home medications</b>	Prednisone 20 mg daily for 4 months Azathioprine 100 mg daily for 4 months Furosemide Lactulose Rifaximin	Prednisone for 16 days
<b>Vital signs upon admission:</b>	99.1F, 83/49 mmHg, 94 bpm, 30 rpm on mechanical ventilation	100.4F, 129/73 mmHg, 110 bpm, 16 rpm on room air
<b>Physical exam:</b>	Lungs: Diffuse crackles and rhonchi Abdomen: soft, mildly distended, decreased bowel sounds	Scleral icterus Lungs: clear to auscultation bilaterally Abdomen: soft, distended with ascites, diminished bowel sounds Extremities: anasarca Integument: jaundice Neurological: mild asterixis
<b>Pertinent laboratory work:</b>	WBC: 15,840 $\mu$ L INR: 1.9 PTT: 32 seconds AST 89 U/L ALT: 43 U/L Alkaline phosphatase: 179 UL Albumin: 2.7 g/dL Total bilirubin: 7.1 mg/dL	WBC: 35,000 $\mu$ L INR: 3.2 PTT: 49 seconds AST 192 U/L ALT: 167 U/L Alkaline phosphatase: 320 UL Albumin: 2.7 g/dL Total bilirubin: 15.8 mg/dL Antinuclear antibody titer: 1:80 Anti-smooth muscle antibody: 30 Liver biopsy: PAS diastase-resistant droplets Alpha-1 antitrypsin phenotype: SZ
<b>Model for End-Stage Liver Disease Score</b>	26	30
<b>Child-Pugh Classification</b>	Class C	Class C
<b>(1-3)-<math>\beta</math>-d-glucan (BG) assay:</b>	Positive with > 500 pg/mL	Positive with > 500 pg/mL
<b>Pneumocystis by PCR:</b>	Positive x 2 376 DNA copies/mL and 208 DNA copies/mL	Positive > 1000 DN copies/mL
<b>Procalcitonin on admission:</b>	4.64 $\mu$ g/L	
<b>Outcome:</b>	Expired due to multiorgan failure	Stabled, discharged home

Patient 1 was transferred to our facility and required mechanical ventilator support for worsening hypoxemic respiratory failure. She was started on broad spectrum antibiotics and norepinephrine secondary to shock. She had a near complete opacification of the right lung from a pleural effusion (Figure 1). Fiberoptic bronchoscopy of the left upper and lower lobes showed purulent secretions in the left main stem and trachea. Thoracentesis showed straw-colored fluid.

She remained thrombocytopenic and coagulopathic. Throughout her hospitalization, she required transfusions of platelets and cryoprecipitate. Her (1-3)- $\beta$ -d-glucan (BG) assay, performed



Figure 1. Chest radiograph demonstrated a right pleural effusion.

on two different occasions, was positive with > 500 pg/mL. Her pneumocystis by PCR was positive on two different occasions. The first sample, obtained from a bronchoalveolar lavage in the left upper lobe, was positive with 376 DNA copies/mL. The second sample was taken from the left lower lobe of the bronchoalveolar lavage and was positive for 208 DNA copies/mL. Organisms were seen on cytology preparation. She also grew candida albicans in her lavage. All other cultures were negative. Despite all supportive efforts, she expired due to multi-organ failure.

Patient 2 was admitted to the same hospital sixteen days prior for worsening jaundice, symptoms of upper respiratory infection, fevers, fatigue, nausea, vomiting, frequent nosebleeds, and intermittent joint pain primarily in his hands, knees, ankles, and shoulders. At that visit, he was placed on prednisone and evaluated for liver disease. His laboratory evaluation showed antinuclear antibody (ANA) positive at 1:80 with anti-smooth muscle antibody positive at 30. A transjugular liver biopsy was done and the pathology demonstrated PAS diastase-resistant droplets. He also had an alpha-1 antitrypsin phenotype of SZ.

A chest radiograph (Figure 2) and a representative slice of computed tomography (CT) of his chest (Figure 3) demonstrated interval development of discrete pulmonary nodules in the mid lung zones bilaterally since his last chest x-ray from the previous admission. The pulmonary mass on the right measured 3.5 cm and the pulmonary mass on the left measured 4.0 cm. A CT of his abdomen and pelvis demonstrated a liver with a slightly nodular contour, ascites, splenomegaly, and varices (Figure 4).

He was started on broad spectrum antibiotics. A paracentesis drained 2.7 liters of ascites fluid. His (1-3)- $\beta$ -d-glucan (BG) assay test was greater than 500 and he was started on micafungin while awaiting further results. Fiberoptic bronchoscopy with bronchoalveolar lavage was positive by PCR for PJP at greater than 1000 DNA copies/mL. His antibiotics were switched to trimethoprim-sulfamethoxazole to treat the infection. He began to improve with a decreasing WBC count. Once his liver failure stabilized and his infection was resolving, he was discharged with instructions to continue trimethoprim-sulfamethoxazole treatment for 21 days then remain on a prophylactic dose for PJP.

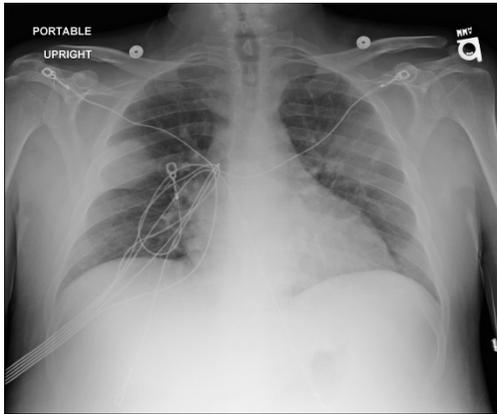


Figure 2. Chest radiograph demonstrated bilateral lung masses.



Figure 3. A representative slice of CT scan of the chest demonstrated pulmonary nodules.



Figure 4. A representative slice of the CT scan of the abdomen demonstrated a nodular contour of the liver.

## DISCUSSION

It is rare to diagnose PJP in patients with liver disease, as it is most commonly found in patients with HIV or AIDS. While patient 2 had known alpha-1 antitrypsin deficiency, his biopsy and clinical situation were more consistent with acute autoimmune hepatitis as the main driver of his current liver disease and decompensation. The occurrence of *pneumocystis jiroveci* pneumonia in cases with autoimmune hepatitis is very rare.

The incidence of PJP can be due to the administration of corticosteroids causing immunosuppression or to liver cirrhosis. Typically, shorter periods of treatment with immunosuppressive medications would not be associated with opportunistic infections. However, liver cirrhosis also is considered an immunocompromised state that can lead to a variety of infections as well and infection is directly responsible for approximately 30% of deaths in cirrhotic patients.<sup>14-15</sup> Cirrhosis will cause a systemic immune dysfunction which can decrease the ability to clear cytokines, bacteria and endotoxins from circulation. The liver contains reticuloendothelial cells which are central to clearing bacteria.<sup>14</sup> Additionally, patients with cirrhosis have decreased neutrophil mobilization and phagocytic activity. The level at which this happens can vary with the severity of liver disease.<sup>14,16</sup> Since PJP can be life-threatening, prompt diagnosis and treatment is imperative. It is felt that the “two hits” of liver failure with immunosuppression was sufficient to place these patients at risk for PJP infection with shorter periods of treatment with immunosuppression than is usually considered significant.

The use of corticosteroids is a risk factor for PJP.<sup>17</sup> In a large consecutive series of 116 patients without AIDS, patients with their first episode of PJP were analysed. Systemic corticosteroid therapy was administered to most of these patients the month before the onset of PJP. While it was not suggested that administration of corticosteroids is the only contributor to the development of PJP, PJP prophylaxis should be considered in patients where prolonged systemic corticosteroid therapy is prescribed.<sup>18</sup> An anti-inflammatory effect usually is obtained by administering 0.1 - 0.3 mg/kg per day of prednisone. However, higher dosages are required (ranging from 1 - 2 mg/kg/day) to produce faster immunosuppressive action.<sup>19</sup>

To treat autoimmune hepatitis, the standard therapy from clinical trials is prednisone or prednisolone at 30 - 60 mg/day alone or a lower steroid dose (20 - 30 mg/day) in combination with azathioprine (1 mg/kg/day).<sup>9</sup> Both are equally effective in the management of the patients with severe autoimmune hepatitis. Corticosteroids act rapidly on the immune system by interfering with cytokine production and inhibition of T-lymphocyte activation. The steroid dose is tapered over six-weeks to three-months to a maintenance dose of 15 mg/day or less. Most patients will have normalized aminotransferases within 6 - 12 weeks. Monitoring the response toward treatment includes serial aminotransferase and immunoglobulin measurement, and should be continued beyond normal laboratory results. A liver biopsy is recommended at the time of diagnosis because many patients have established cirrhosis at presentation.<sup>7</sup>

It may be beneficial for patients with autoimmune hepatitis who have contracted PJP to undergo prophylactic treatment for PJP with trimethoprim-sulfamethoxazole (one double strength 160 mg - 800 mg tablet daily), which is the recommended first line treatment for PJP in HIV-infected patients.<sup>20</sup> Once the prophylactic treatment is initiated, it is recommended to continue for life.<sup>2</sup> HIV-infected patients without PJP prophylaxis have a significantly higher mortality with the effect being most pronounced in those with the lowest CD4 counts. There are no studies to prove that the effect is similar to those with autoimmune hepatitis.<sup>21</sup> However, PJP unrelated to HIV can occur in immunosuppressed patients having malignancy or on immunosuppressive agents.<sup>22-23</sup>

Physicians should be aware that PJP is a possibility in patients who are receiving steroids or other immunosuppressive therapy, have a malignancy, or suffer from liver cirrhosis. The best way to decrease mortality in patients who have PJP but do not have HIV would be to identify them quickly and start prophylactic PJP therapy.<sup>22,24,25</sup> Prophylaxis for HIV patients is indicated when there is a CD4 count of less than 200 cells/mm.<sup>2,21</sup> A study performed in the UK suggested multiple steps to ensure proper treatment for PJP, including enhanced surveillance to characterize any additional groups of patients who may be at risk, increasing basic knowledge on *pneumocystis jiroveci* epidemiology, and ensuring adherence to current guidelines.<sup>26</sup>

One possibility for the increase in diagnosis of PJP is diagnostic bias, improved diagnostic methods, particularly the PCR method, which are more sensitive than previous methods.<sup>26-27</sup> There also has been an increase in number of renal transplants and hematological malignancies over the past decade; however, the increase for PJP was far greater than both of these factors combined. Thus the overall increase in PJP diagnosis cannot be explained solely on these factors.<sup>26</sup> Another reason that can explain the increase in PJP pneumonia is that patients are not receiving appropriate prophylactic therapy, which can lead to an increase in transmission.<sup>26</sup> Finally, another possibility could be that patients are living longer on immunosuppressive regimens, giving opportunistic organisms a longer period of time to infect.

For the two patients reported here, the process of their disease and the reason that they contracted with PJP are unknown. These patients most likely suffered from PJP with shorter courses of immunosuppression than usually is described, because of the second hit of immunosuppression due to cirrhosis. Perhaps the cirrhosis is a larger contributor to immunosuppression than once believed. Thus, with people living longer with cirrhosis, considerations of prophylaxis against opportunists when additional immunosuppressants are added may be warranted.

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