

# Unusual Cause of Severe Jaundice in an HIV Infected Patient

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**Abstract** Lobar pneumonia as a cause of jaundice with non-obstructive conjugated hyperbilirubinemia is an uncommon complication of pneumococcus. More commonly seen in immunocompromised and elderly patients, it is believed that the offending microbe produces a toxin that directly causes hepatocellular injury and impairment of bilirubin excretion. Biopsies of patients with pneumococcal pneumonia-associated jaundice commonly depict patchy areas of hepatic necrosis and dilated biliary canaliculi without metastatic foci of infection. In the pre-antibiotic era, the prevalence of jaundice in patients with lobar pneumonia was reported to be about 14% and carried significant mortality rates. Seen less commonly today, mortality rates of invasive pneumococcal disease remain as high as 5% to 35%. We present a case of a 29 year-old-male with no medical history presented with subjective fevers, productive cough, dark urine and myalgias for three days. He was profoundly jaundiced without stigmata of chronic liver disease. Computerized tomography (CT) of the chest revealed a right lower lobe pneumonia. The patient had leukocytosis, significant elevation of transaminases, hyperbilirubinemia and was found to be influenza positive. Antibody for human immunodeficiency virus (HIV) was also positive and later confirmed with polymerase chain reaction (PCR). An extensive workup for his jaundice and hyperbilirubinemia was unrevealing and it was deemed that his clinical signs were a result of invasive pneumococcal infection from his pneumonia. The patient was treated with antimicrobials and highly active antiretroviral therapy (HAART). He ultimately had complete resolution of his jaundice and laboratory abnormalities. Although seen infrequently today, unusual manifestations of pneumococcal infection still occur and may be unrecognized in practice.

**Keywords:** *streptococcus pneumoniae, jaundice, HIV, hyperbilirubinemia*

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## 1. Introduction

Lobar pneumonia as a cause of nonobstructive conjugated hyperbilirubinemia has been reported in the literature dating back to the beginning of the 19th century [1]. It is believed that the offending microbe produces a toxin that directly causes hepatocellular injury and impairment of bilirubin excretion. This occurs more often in immunocompromised patients. Here, we present a case of a 29-year-old patient who presented with severe jaundice after newly diagnosed HIV infection and pneumococcal pneumonia.

## 2. Case Presentation

A 29-year-old male with no previously known medical history presented to the emergency room with fatigue, subjective fever, productive cough and myalgia for three days. He noted dark colored urine for one day. On examination, the patient had a temperature of 102.8 °F and

a heart rate of 117 beats per minute. He appeared ill and was profoundly jaundiced, yet stigmata of liver disease were absent. His abdomen was non-distended, soft and not tender to palpation. Laboratory studies demonstrated a white blood cell count of  $13 \times 10^9/L$  and platelet count of  $97 \times 10^3/mm^3$ . He had a total bilirubin of 14 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 101 IU/L and 165 IU/L, respectively, alkaline phosphatase (ALP) of 115 IU/L and a creatinine kinase of 757 IU/L. Lactate dehydrogenase (LDH) was 241 IU/L and haptoglobin was 229 mg/dL. Hepatitis serology for A, B and C infection were negative. Acetaminophen and salicylate serum levels were undetectable and urine drug screen was negative for illicit substances. Initial blood cultures were negative and chest x-ray did not reveal pulmonary infiltrates. Influenza A polymerase chain reaction (PCR) turned positive as well as human immunodeficiency virus (HIV) infection. His last negative HIV test was two years ago. The patient was started on oseltamivir and admitted with a diagnosis of influenza infection and painless jaundice. Workup for painless jaundice with ultrasound of the abdomen was unrevealing.

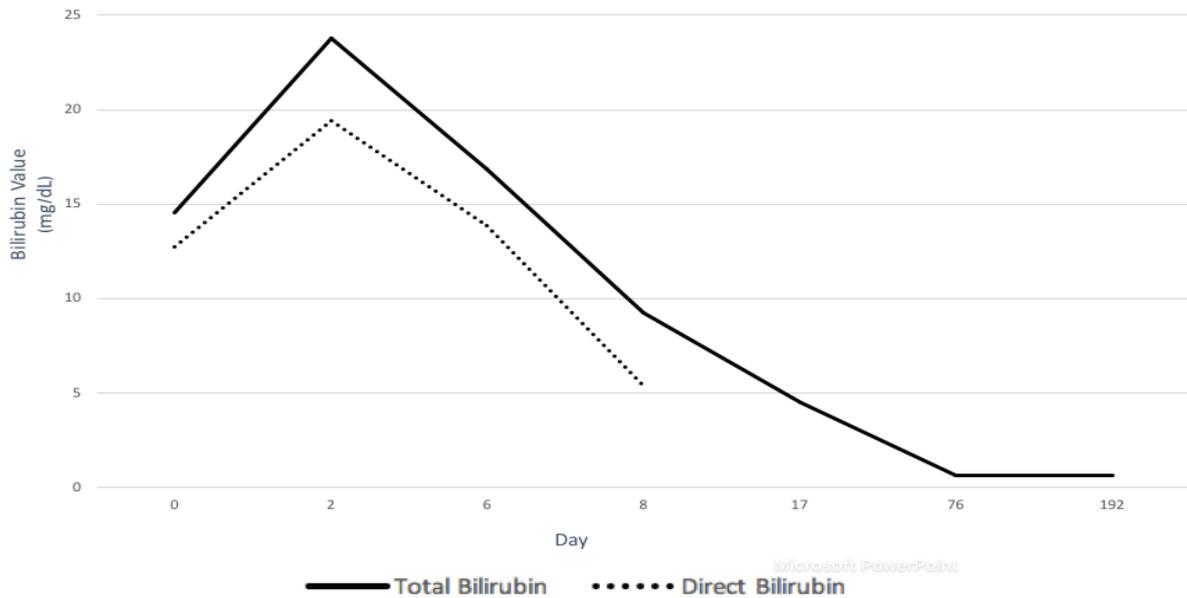
Prior to completion of workup and evaluation he signed out against medical advice but was advised to follow up at outpatient HIV clinic.

The following day, the patient returned to the hospital per the insistence of medical staff members given persistent fevers and jaundice. Repeated total bilirubin was 23 mg/dL. CD4 count was 122 cells/mm<sup>3</sup> and the HIV viral load of 56,000 copies/mL. Repeated blood cultures turned positive for *Streptococcus pneumoniae* sensitive to penicillin and ceftriaxone. Computerized tomography (CT) scan of the chest revealed a right lower lobar pneumonia. CT of the abdomen did not reveal an obstructive process that could explain hyperbilirubinemia. Workup for alternative causes of liver disease was unrevealing (see Table 1). Neither anti-smooth muscle antibody titer of 1:29 nor slight ceruloplasmin elevation as an acute phase reactant were believed to be the cause of the underlying disease process. He was treated with intravenous ceftriaxone. After thorough discussion, the patient was started on antiretroviral therapy consisting of tenofovir-emtricitabine and dolutegravir with sulfamethoxazole/trimethoprim for pneumocystis pneumonia prophylaxis.

The patient's condition improved during the hospital course. Fevers and tachycardia resolved. By hospital day 8 the patient's AST and ALT had normalized to 36 and 32, respectively. His total bilirubin and direct bilirubin had trended down to 9 and 5, respectively (see Figure 1) and the patient was discharged on oral levofloxacin with outpatient follow up.

**Table 1. Workup of explained liver disease**

Test	Result	Reference Range
Alpha-1 Antitrypsin	419 mg/dL	90-200 mg/dL
Babesia IgM/IgG	<1:10	<1:10
Ceruloplasmin	49 mg/dL	16-31 mg/dL
Mitochondrial Antibody	19 Units	0-20 Units
Rapid Plasma Reagin (RPR)	Non-Reactive	N/A
Smooth Muscle Antibody	29.0 Units	0-19 Units
Gonorrhea, Chlamydia Nucleic Acid Amplification in urine	Negative	N/A
Anti-nuclear antibody (ANA)	Negative	N/A
Liver Kidney Microsomal Antibody	0.7 Units	0-20 Units



**Figure 1.** Patient's bilirubin (total and direct) values trend. X-axis is hospital day number. Day 0 refers to initial presentation. Day 8 is the day of discharge with further data representing outpatient follow up



**Figure 2.** Initial chest X-ray without significant disease process



**Figure 3.** CT chest upon second admission with right lower lobar pneumonia

One month after discharge, the patient improved remarkably and his jaundice had completely resolved. After an extensive literature review and expert review, significant hyperbilirubinemia and jaundice were deemed related to the invasive *Streptococcus pneumoniae* infection.

### 3. Discussion

Jaundice with conjugated hyperbilirubinemia is an uncommon and unrecognized complication of lobar pneumonia in modern medicine. However, this association has been demonstrated in literature dating back its first description by Garvin *et al.* in 1836. [3] At the time, clinical jaundice was reported in 14% of patients with pneumococcal lobar pneumonia. [4] Blood chemistry typically reflects mild to moderate elevations in AST, ALT, and ALP with conjugated hyperbilirubinemia, which may rise from 4mg/dL to 20mg/dL. In the antibiotic era, the incidence of jaundice in patients with lobar pneumonia declined significantly. Recent publications describe pneumococcal pneumonia-associated jaundice almost exclusively in African American male patients. [4] Numerous factors have been theorized with the aim to explain the cause of jaundice including higher rates of glucose-6-phosphate dehydrogenase deficiency (G6PD) among black males with associated hemolysis. [5] However, hemolysis as the sole cause of jaundice has been largely abandoned as jaundice results from conjugated hyperbilirubinemia. [6] Nutritional deficiencies as etiologies were proposed as well, but subsequent publications discounted malnutrition as a contributing factor. [7] Non-obstructive hepatic cholestasis is thought to be due to a toxin produced by the offending organism, as in the case of our patient – *S. pneumoniae*. [4]

Although it is known that hyperpyrexia might produce jaundice, Harris *et al.* [8] demonstrated that this is not due to fever or infection themselves, but rather due to an accompanying toxemia that may have a specific affinity for the liver. [5] Non-obstructive hepatic cholestasis is thought to be due to a toxin produced by the offending organism, as in the case of our patient – *S. pneumoniae*. [4] Biopsies of patients with pneumococcal pneumonia-associated jaundice commonly depict patchy areas of hepatic necrosis and dilated biliary canaliculi without metastatic foci of infection, a finding that supports the idea of a toxin mediated process. [9] This theory may be supported by the findings of endotoxin mediated decrease in biliary excretion by inhibition of organic anion transport in rat livers. [4]

The specific toxin accountable for the hepatocellular injury observed in these patients is incompletely understood. *Streptococcus pneumoniae* consists of at least 92 distinct serotypes, each of which carries a specific risk of invasive disease. There is extensive data suggesting that the biological composition of the pneumococcal capsule is the major determinant of the serotype virulence. [10,11] Specifically, serotypes 1, 5, and 7 are the most commonly isolated serotypes from patients with invasive disease. [12,13] With the HIV epidemic and the worldwide emergence of drug-resistant pneumococci, the incidence of invasive pneumococcal disease has increased. [14] Invasive pneumococcal disease (IPD) has been described

to affect almost every organ and thus the clinical manifestations and outcomes of the disease vary tremendously. [15,16] Among risk factors, older age (65 years) and immunocompromised state are notably associated with higher incidence of the invasive disease and increased mortality rates. [5] Despite modern therapy for IPD, mortality rates of invasive pneumococcal disease remain as high as 5% to 35% and the risk of death appears to peak in the first 72 hours. [17,18]

Fortunately, our patient demonstrated complete resolution of jaundice with no residual liver dysfunction to date. Although seen infrequently today, unusual manifestations of pneumococcal infection still occur and may be unrecognized in practice. Our report highlights that direct hyperbilirubinemia may be one of the manifestations of invasive pneumococcal infection.

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