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Case Report

Internal Medicine Section

Atypical Presentation of Alcoholic Liver Disease as Isolated Direct Hyperbilirubinaemia with Non Resolving Pneumonia Secondary to Multidrug Resistant *Escherichia coli* and *Aspergillus* Co-infection: A Case Report

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ABSTRACT

It is uncommon for a patient with Alcoholic Liver Disease (ALD) to present with isolated hyperbilirubinaemia that is not accompanied by substantial hepatic abnormalities. Patients with ALD are more likely to develop bacterial and Invasive Fungal Infections (IFI) early in the course of their disease, and both are linked with more severe systemic inflammation, a poorer clinical prognosis, and a higher mortality rate. Due to escalating antibiotic usage, lengthy hospital stays, and intensive medical procedures, hospitalised cirrhotic patients are increasingly at risk of acquiring IFI. In patients with alcoholic liver failure, persistent IFI is a primary cause of death and treatment resistance. This case involved a 34-year-old male with an unusual combination of worsening sepsis and jaundice without any other significant abnormalities in liver function. He was given adequate antibiotics to treat the isolated organism *Escherichia coli (E. coli)*, but his pneumonia persisted. After positive tests for an IFI, he was given antifungal medications as well. However, he failed to improve and eventually succumbed to his illness.

Keywords: Cirrhosis, Jaundice, Non-resolving pneumonia, Tuberculosis

CASE REPORT

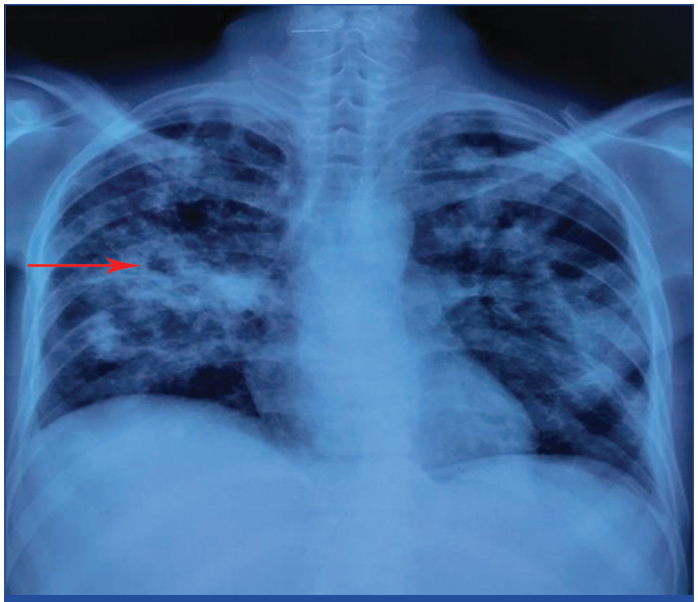
A 34-year-old male presented to the emergency department with complaints of fever for one and a half months- continuous and low-grade-along with cough and expectoration. It was associated with shortness of breath or haemoptysis. He had abdominal distension for one month. He developed yellowish discoloration of the skin and dark urine for 15 days. He noticed bilateral pedal oedema for 10 days. The patient also had decreased appetite, nausea, and vomiting for the last one month. He did not have associated abdominal pain, passage of black tarry stool, bloody vomit, generalised itchiness, alteration of sleep-wake cycle, or decreased urine output. There was no history of any chronic drug intake or IV drug abuse. He has been drinking alcohol for the last 15 years (about one and a half pints of vodka daily). He also had a history of smoking 8-10 cigarettes daily for the last 15 years. He never had such jaundice before, nor did his family members have such jaundice or any known liver diseases.

On general physical examination, the patient was conscious, oriented to time, place, and person. His Body Mass Index (BMI) was 19.03 kg/m^2. He was hypotensive (BP 80/50 mm Hg) and had a feeble pulse, tachycardia, and tachypnoea. There was pallor, deep icterus, and bilateral pitting type pedal oedema. The abdomen was distended, non-tender, and shifting dullness was present. Hepatosplenomegaly was noted on palpation. Bilateral coarse crepitations were found in the mammary and infra-axillary areas. Laboratory investigations on the day of presentation showed macrocytic anaemia, neutrophilic leukocytosis with a normal platelet count and renal function tests. He had direct hyperbilirubinaemia with normal transaminases [Table/Fig-1]. Arterial blood gas analysis was suggestive of respiratory alkalosis. Electrocardiogram (ECG) was normal. Chest X-ray showed homogenous opacity in the right upper zone, right middle zone, and left middle zone with right-sided pleural effusion as shown in [Table/Fig-2]. Pleural fluid analysis showed 80 cells with 50% lymphocytes and an exudative picture with an Adenosine Deaminase (ADA) level of 19 IU/L. Ascitic fluid showed 10 cells with 100% lymphocytes and a low Serum Ascites Albumin Gradient (SAAG) (0.9) with ADA of 21 IU/L. Ultrasound (USG) Abdomen showed hepatomegaly (20 cm) with Grade-I fatty liver (as per ultrasonography grading) [1] with no features of intra and extra-hepatic biliary obstruction, splenomegaly (18 cm), normal portal vein caliber, and gross ascites.

Tests	Value obtained	Normal value
Haemoglobin (g/dL)	6.9	12-16
TLC (/mm^3)	17000	4000-11000
DLC	P85L14M1	-
Platelets (lacs/µL)	1.87	1.5-4.5
Blood Urea (g/dL)	42	5-20
Serum creatinine (g/dL)	0.8	0.7-1.3
Total Bilirubin (mg/dL)	18.3	0-1
Direct bilirubin (mg/dL)	15.5	0-0.3
Serum Glutamic Oxaloacetic Transaminase (SGOT)	19	28-36
Serum Glutamic Pyruvic Transaminase (SGPT) (IU/L)	16	28-36
Alkaline Phosphatase (ALP) (IU/L)	132	50-110
Total Protein (g/dL)	4.9	6-8
Albumin (g/dL)	1.9	3.5-5.5
INR	1.64	1.1

[Table/Fig-1]: Investigations done on admission.

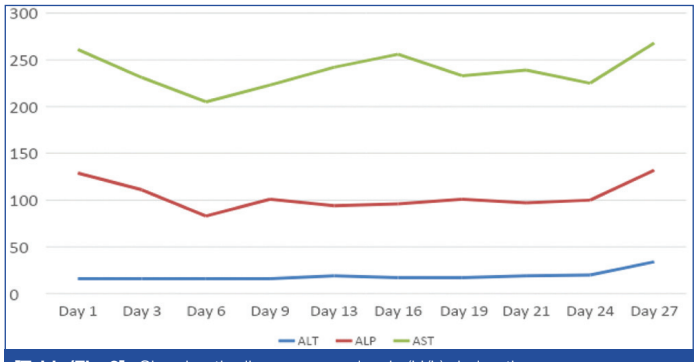
On admission, the diagnosis of ALD, ascites, severe anaemia, sepsis with septic shock, bilateral lower respiratory tract infection was made for which the following two differentials were kept- Pulmonary Koch's or Bacterial pneumonia. The patient was started on oxygen therapy in view of respiratory distress. Broad-spectrum antibiotics (piperacillin-tazobactam 4.5 grams eight hourly, metronidazole 500 milligrams eight hourly) hepatic modified anti-tuberculous treatment



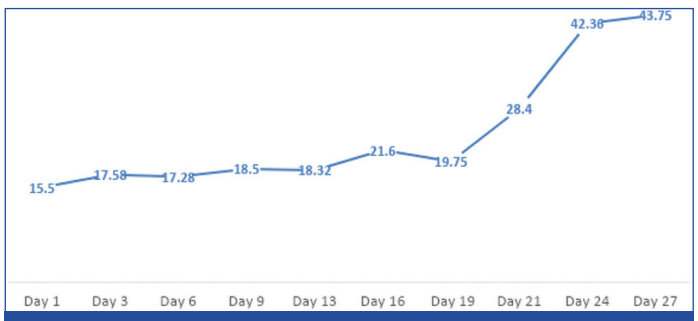
[Table/Fig-2]: Showing chest X-ray done on day 1.
Homogenous opacities in right upper zone, right middle zone and left middle zone (arrow)

(levofloxacin 500 milligrams, ethambutol 800 milligrams, and injection streptomycin 750 milligrams once daily) and inotropic support (noradrenaline) were added. Packed Cell Volume (PCV) transfusion and medical management (diuretics for ascites, inotropes for shock) of complications of liver disease was done.

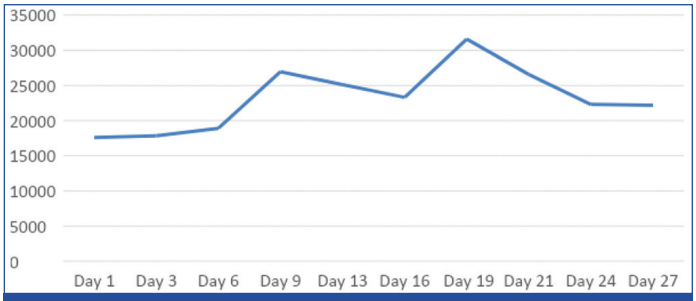
On further evaluation, sputum for acid-fast bacilli and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) was negative, sputum gram stain and fungal Potassium Hydroxide (KOH) was negative. Hepatitis viral panel (B, C) and Human Immunodeficiency Virus (HIV) tests were negative. Blood investigations showed the liver enzymes improving in the first week, followed by a plateau in the subsequent week. However, they again increased by the third week [Table/Fig-3]. The bilirubin remained stable initially but began to rise by day 19 as can be seen in the trendline shown in [Table/Fig-4]. The patient had persistently rising Total Leukocyte Count (TLC) (up to 31,000) with neutrophilic predominance however repeated blood and urine culture showed no growth and procalcitonin levels were also within normal limits (<1). [Table/Fig-5] shows trends of total leucocytes count during the course.



[Table/Fig-3]: Showing the liver enzymes levels (U/L) during the course.

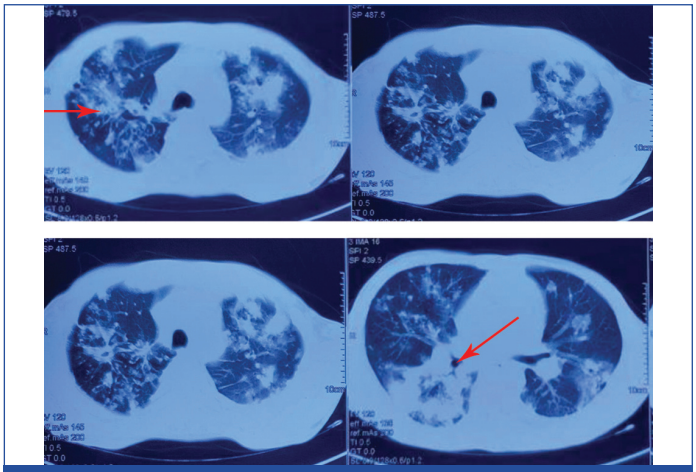


[Table/Fig-4]: Showing total bilirubin level (mg/dL) during the course.



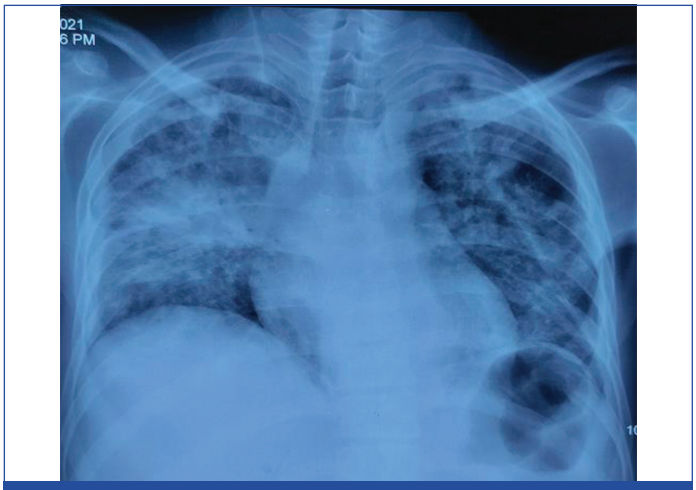
[Table/Fig-5]: Showing total leukocytes levels (cells/μL) during the course.

Contrast-Enhanced Computed Tomography (CECT) chest was suggestive of multifocal areas of consolidation with central areas of cavitation with centrilobular nodules showing tree-in-bud configuration in bilateral lung parenchyma with mediastinal lymphadenopathy with right sided pleural effusion-features suggestive of tubercular aetiology [Table/Fig-6]. CECT abdomen showed hepatosplenomegaly with dilated portal vein (15 mm) cholelithiasis with normal Common Bile Duct (CBD) and gross ascites.



[Table/Fig-6]: Showing images of CECT chest.
CECT chest showing multifocal areas of consolidation, central areas of cavitation, centrilobular nodules showing tree-in-bud configuration in bilateral lung parenchyma with mediastinal lymphadenopathy. Right minimal pleural effusion with left sided empyema. Features suggestive of tubercular aetiology

Sputum culture report was positive for *E. coli* and antibiotics (meropenem 500 milligrams eight hourly and amikacin 500 milligrams once a day) were upgraded according to culture sensitivity. Despite the above measures, patient's respiratory distress worsened. TLC continued to rise reaching up to 31000/μL and total bilirubin reaching up to 45.7 mg/dL (direct bilirubin- 42.3 mg/dL) by day 20 of illness. Repeat chest X-ray done on day 20 showed increased opacities [Table/Fig-7]. Hence, repeat sputum samples for fungal KOH and serum galactomannan assay were also sent. Patient was started on tab itraconazole 200 mg bd on day 22.



[Table/Fig-7]: Showing repeat chest X-ray (day 20) with increased opacities in bilateral lung fields.

Despite best possible efforts, the patient succumbed to his illness on day 27 of admission. Postmortem liver biopsy was taken which showed ALD with bridging necrosis and features of acute exacerbation (distortion of lobular architecture with inflammation, marked ballooning of hepatocytes with Mallory-hyaline bodies with intracellular and canalicular cholestasis, micro and macro vesicular steatosis, periportal ductal proliferation and inflammation). The serum galactomannan assay came out to be positive (3.7).

The patient had ALD, which manifested as chronic isolated direct hyperbilirubinaemia with non resolving pneumonia- pulmonary tuberculosis with superadded gram-negative bacterial and fungal pneumonia (likely pulmonary aspergillosis).

DISCUSSION

Despite widespread public awareness of its potential negative consequences, alcohol use has grown, as has morbidity and death from ALD. ALD is characterised by an array of injuries, including simple steatosis, acute alcoholic hepatitis, and cirrhosis. These pathologic processes usually overlap rather than constituting independent disease entities. Clinical jaundice or histological symptoms of intrahepatic cholestasis may be observed at various stages of ALD [2]. In cirrhosis, Acute-On-Chronic Liver Failure (ACLF) is a condition characterised by Acute Decompensation (AD), organ failure(s), and a considerable probability of mortality in the short-term [3].

The aetiology of alterations in liver function tests is multifaceted and comprehensive. Patients with non alcoholic fatty liver disease, cirrhosis of any cause, hepatitis (viral, bacterial, fungal, parasitic), ischaemic hepatitis, autoimmune hepatitis, and pregnancy-related dysfunctions have aberrant liver functions. The miscellaneous reasons include metabolic illnesses such as Wilson's, endocrinological disorders such as hypothyroidism, Addison's disease, and others, cancers, and recreational substances such as cocaine. The majority of medications are metabolised in the liver, while just a handful of them can have a substantial influence on liver function tests. Non steroidal anti-inflammatory drugs, antibiotics, HMG Co-A-reductase inhibitors, antiepileptic medication, antituberculous treatments, and herbal therapies are notable examples [4].

Profound jaundice or cholestasis without abnormalities of liver functions, particularly a significant elevation of Aspartate Aminotransferase (AST), and signs of cirrhosis, as seen in this case, is unusual. Hossain et al., submitted a case report in which a 63-year-old gentleman with a history of heavy alcohol consumption for the previous 40 years presented with yellowish staining of the skin, black urine, severe nausea, and anorexia over the previous seven days [5]. The patient had total bilirubin of 24.8 mg/dL with direct bilirubin of 18.8 mg/dL, AST of 76 IU/L, platelets of 28000 per cu mm, and albumin of 2.7 gm/dL, while the remainder of the laboratory data, including ALT, Alkaline Phosphatase (ALP), Gamma-Glutamyltransferase (GGT), Mean Corpuscular Volume (MCV), INR, and PT, were within normal ranges. There was no sign of cirrhosis or extrahepatic duct obstruction on the abdominal ultrasound. Abdominal imaging was likewise unremarkable, including Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) of the liver with MRCP. The hepatitis virus panel was negative, as were the Anti-smooth Muscle Antibody (AMA) and sickle cell screens. A liver biopsy ruled out haemochromatosis, dysplasia, or cancer. With symptomatic care, the patient improved and was released with a bilirubin of 7.3 mg/dL. They highlighted how the specific aetiology of alcohol-induced intrahepatic cholestasis is unknown, but specialists believe that interference with basolateral uptake and intracellular transport of bile acids, as well as constriction of the intrahepatic biliary tree, are plausible reasons [6]. Alcohol also affects hepatocyte transcytosis [7].

Despite a thorough search of the literature, authors were unable to locate any other review or case report demonstrating isolated hyperbilirubinaemia in a patient with ALD. A 1968 research looked at 33 instances of alcohol-induced intrahepatic cholestasis. The research was confined to habitual alcoholic individuals with laboratory evidence of obstructive jaundice and no clear extrahepatic aetiology. The group with hepatocyte necrosis on biopsy had greater bilirubin levels than the group with normal histology [8].

Infection is highly common in people with ACLF. According to one study, the total prevalence of ACLF is 66.7%. Bacterial infection is quite frequent in the ACLF, with frequency ranging from 32 to 47% and being independently related with a significant death rate. Fungal infections are uncommon in ACLF, with a prevalence rate of 3.9%, and are linked with a poor prognosis [9,10]. In order of decreasing severity, the sources of infection include spontaneous bacterial peritonitis, pneumonia, severe sepsis, nosocomial infection, and infections caused by multiresistant organisms. Gram positive and gram-negative organisms cause 69% and 31% of infections, respectively [11]. As observed in this case, *E. coli* is the most prevalent organism producing bacteria in the gram-negative group.

Increased susceptibility to bacterial infections has been hypothesised to be caused by a number of different mechanisms, including persistent transfer of Pathogen-Associated Molecular Patterns (PAMPs) [9]. The loss of intestinal mucosal barrier integrity is another possible cause for the same. The role of chronic systemic inflammation brought on by intestinal dysbiosis has also been studied PAMPs [12]. PAMPs are produced in high quantities by infecting bacteria in persons who have bacterial illnesses; this is the root cause of ACLF [13]. PAMPs are known to trigger the innate immune system, which then results in the release of inflammatory cytokines, vasodilatory mediators, and reactive oxygen species [14].

Because of increased antibiotic usage, numerous hospitalisations, and invasive procedures, IFI are becoming more common in hospitalised cirrhotic patients. IFI is a significant source of morbidity, death, and treatment failure in ACLF patients [15]. Due to the low index of suspicion, lack of specific signs or symptoms, lack of uniform case definitions, lack of standardised diagnostic tests, low yield of fungal cultures, high turn-around times for cultures, and need for invasive tissue sampling, timely and accurate diagnosis in patients with cirrhosis is frequently challenging. Fungal colonisation is sometimes difficult to distinguish from genuine infection, especially when samples from non sterile areas are positive for fungal components. Several studies have shown that serum biomarkers such as Galactomannan Index (GMI) and 1,3-D Glucan (BDG) can be used as an adjuvant for the diagnosis of IFI in the general population [16], haematologic malignancies, and post liver transplant patients [17,18]. However, their role in ACLF patients has not been studied.

CONCLUSION(S)

Isolated hyperbilirubinaemia as a symptom of ALD with no substantial hepatic abnormalities is uncommon. Patients with ALD are more likely to develop bacterial and IFI early, and both are linked with more severe systemic inflammation, a worse clinical outcome, and greater mortality.

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