



Case report

Gallbladder tuberculosis mimicking carcinoma: A case report of a rare entity

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ABSTRACT

Introduction: Gallbladder TB (GBTB) is a rare disease with a non-specific presentation, simulating cholecystitis and gallbladder malignancies. We describe a rare case of infiltrative GBTB with biliary strictures in a young female who was initially diagnosed with metastatic gallbladder carcinoma.

Case presentation: A 33-year-old female presented with recurrent episodes of obstructive jaundice, significant weight loss, fatigue, and oligomenorrhoea. Imaging studies revealed features of locally advanced gallbladder carcinoma with proximal and distal common bile duct strictures. However, biopsy of the liver tissue surrounding the gallbladder mass confirmed necrotizing granulomatous inflammation with similar findings from fine needle aspiration of the cervical lymph node. Along with the histopathological findings, radiological evidence of pulmonary tuberculosis confirmed the diagnosis of infiltrative GBTB. The patient was successfully managed with anti-tubercular drugs along with biliary decompression.

Discussion: The rarity of GBTB is attributed to the high alkalinity of bile and bile acids, which afford protection against tubercle bacilli. Patients commonly present with abdominal pain, fever, abdominal lump, anorexia, and weight loss. Biliary strictures, though rare, have been described in GBTB and simulate cholangiocarcinoma. Due to the non-specific findings of pre-operative laboratory and radiological investigations, most patients are taken up for surgery and diagnosed with TB on post-operative histological analysis.

Conclusion: Gallbladder TB is a rare disease which poses a diagnostic challenge because it lacks any pathognomonic features. A tissue diagnosis must be carried out before confirming gallbladder and biliary tract malignancies. Physicians in TB-endemic regions should possess a high index of suspicion for diagnosing GBTB.

1. Introduction

Tuberculosis (TB), an infectious disease that mainly affects the lungs, can involve any part of the body, either as a primary or disseminated disease. Gallbladder TB (GBTB) is a rare entity, even in areas of endemicity, on account of the gallbladder's high resistance to tubercular infection [1]. It commonly presents with non-specific symptoms such as abdominal pain, fever, abdominal lump, weight loss, and anorexia [1]. Due to its vague presentation, it is often misdiagnosed as gallbladder carcinoma [1]. We describe a rare case of infiltrative GBTB in a young female who was initially diagnosed with metastatic gallbladder

carcinoma. Our patient also had biliary strictures; these are uncommon but have been reported in cases of GBTB. This work has been reported in line with the Surgical Case Report (SCARE) criteria [2].

2. Case presentation

A 33-year-old female with no known comorbidities presented with recurrent jaundice for the last 7 years, with each episode of jaundice being of the cholestatic type (indicated by direct hyperbilirubinaemia and significantly elevated alkaline phosphatase levels) and resolving spontaneously. She admits to taking alternative medicine on multiple

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occasions to alleviate her jaundice. She also complained of significant weight loss, fatigue, and oligomenorrhoea since the last 2 years. Physical examination revealed cervical lymphadenopathy. Routine laboratory investigations showed disproportionately raised alkaline phosphatase (508 IU/mL). The viral and autoimmune hepatitis panels, anti-mitochondrial and anti-nuclear antibody profiles, and HIV serology were all negative.

A triphasic contrast-enhanced computed tomography (CECT) scan of the abdomen [Fig. 1A, B] done 5 years ago showed a distended gallbladder (GB) with thick walls containing calculus in the lumen and a dilated common bile duct (CBD) with distal abrupt tapering indicative of distal CBD stricture. As part of her current workup, a magnetic resonance cholangiopancreatography (MRCP) was done, which showed a mass-like irregular GB wall thickening with infiltration of the adjacent liver parenchyma with bilobar moderate intra-hepatic biliary dilatation, splenomegaly, and dilated CBD with multiple intraluminal filling defects indicative of choledocholithiasis [Fig. 1C, D]. Serum CA 19-9 and Carcinoembryonic Antigen (CEA) were within normal limits. Given the clinical and radiological findings, it raised suspicions of an aggressive disease, possibly gallbladder carcinoma with local invasion affecting the liver and distal CBD.

An ultrasound-guided fine needle aspiration (FNA) biopsy of the GB mass was attempted. However, histopathological examination of the tissue surrounding the GB mass showed evidence of hepatocytes with multiple areas of epithelioid granuloma containing Langhans type of giant cell and focal areas of necrosis indicative of necrotizing granulomatous inflammation [Fig. 2]. High-resolution computed tomography (HRCT) of the thorax revealed evidence of pulmonary TB in the form of tree-in bud appearance, subpleural fibroatelectatic bands, fibrotic scarring, and fibrotic nodules [Fig. 3]. However, sputum smear microscopy for acid-fast bacilli (AFB) and the GeneXpert test for

Mycobacterium tuberculosis (MTB) were negative, but the Mantoux test was positive. Lymph node FNA cytology was also done from the left group of cervical lymph nodes which revealed multiple epithelioid cell granulomas along with multinucleated giant cell clusters indicative of granulomatous lymphadenitis of the cervical lymph node [Fig. 4].

As per the guidelines of the National TB Elimination Programme of India, the patient was started on anti-tuberculosis therapy (ATT). The drug regimen consisted of a combination of Isoniazid 300 mg, Rifampicin 450 mg, Ethambutol 750 mg, and Pyrazinamide 750 mg daily for 2 months, followed by 4–7 months of Isoniazid, Rifampicin, and Ethambutol. However, 5 days after commencing ATT, the patient developed jaundice (total bilirubin jumped from 0.3 g/dL to 11 g/dL), likely due to anti-tubercular drug-induced hepatotoxicity, for which we modified the ATT regimen (Streptomycin 0.75 g + Ethambutol 750 mg + Levofloxacin 500 mg). A repeat MRCP showed a sudden cutoff of the proximal CBD at the confluence of the hilum for a distance of 1 cm, along with previous MRCP findings [Fig. 5]. An endoscopic retrograde cholangiopancreatography (ERCP) was done, which confirmed the MRCP findings, and a CBD stent was placed for biliary decompression. Her jaundice started to resolve with treatment. Anti-tubercular drug rechallenge was done with the sequential addition of Rifampicin, followed by Isoniazid, along with monitoring of her liver function. Gradually, there was improvement in the liver function tests and an increase in weight and appetite on treatment. Her symptoms started to resolve, and she was placed on an outpatient follow-up schedule with regular monitoring of her liver functions, which subsequently remained within normal limits.

3. Discussion

According to the World Health Organization, TB affected an

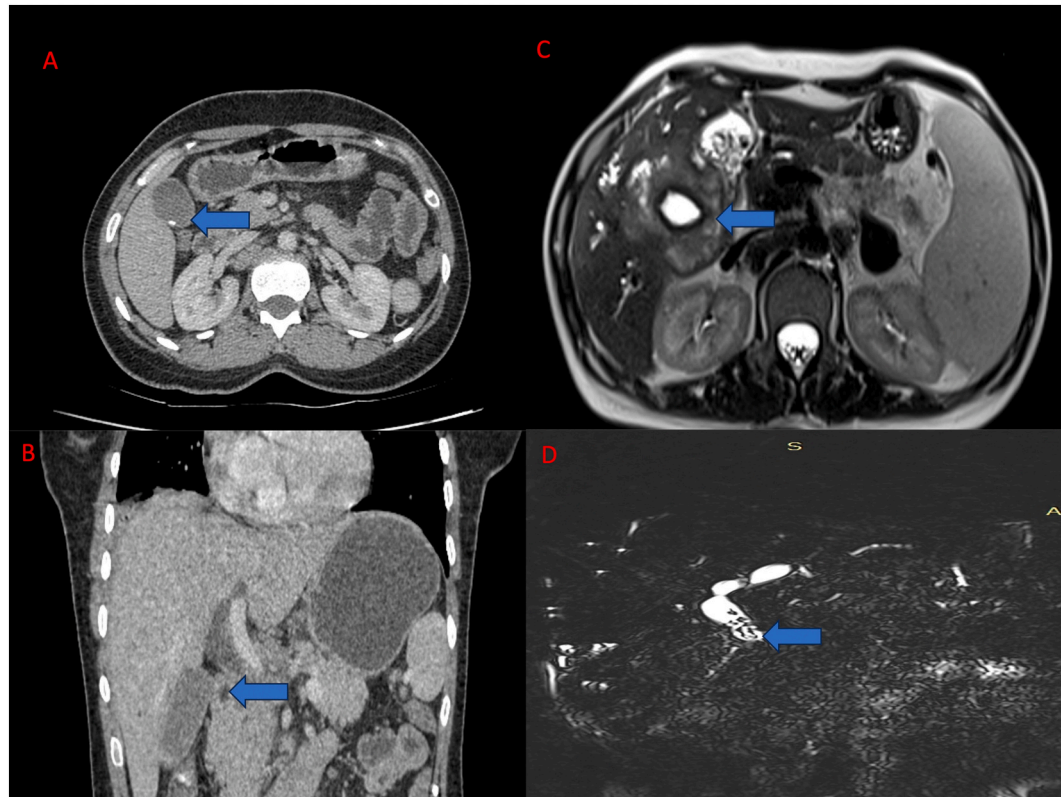


Fig. 1. A, B- triphasic contrast-enhanced computed tomography showing a distended gallbladder with thick walls containing calculus in the lumen and a dilated common bile duct with distal abrupt tapering indicative of distal CBD stricture. C, D- magnetic resonance cholangiopancreatography showing a mass-like irregular GB wall thickening with infiltration of the adjacent liver parenchyma with bilobar moderate intra-hepatic biliary dilatation, splenomegaly and dilated CBD with multiple intraluminal filling defects.

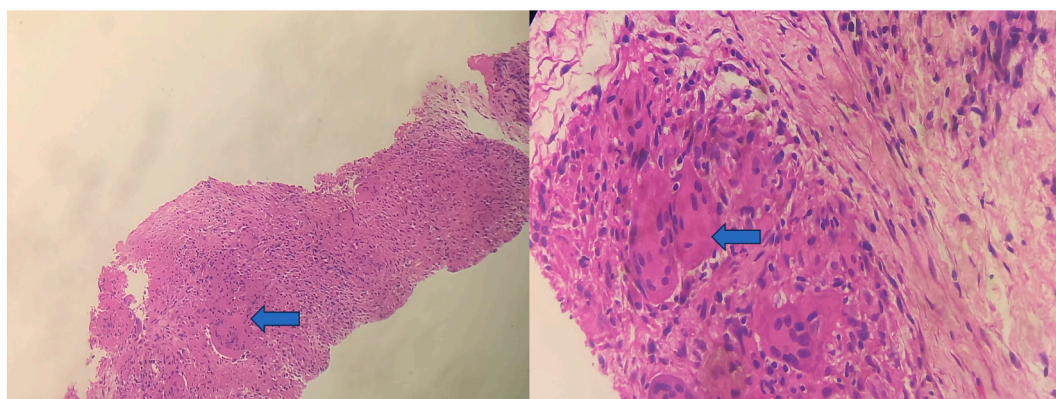


Fig. 2. 100× and 400× image of gall bladder biopsy showing multiple areas of epithelioid granuloma with Langhans type of giant cell and focal areas of caseous necrosis.



Fig. 3. High-resolution computed tomography of the thorax showing tree-in bud appearance, subpleural fibroatelectatic bands, fibrotic scarring, and fibrotic nodules.

estimated 10.6 million people worldwide in 2022, posing a major public health concern. Despite being preventable and curable, it claimed a total of 1.3 million lives in 2022, making it the second most common infectious killer after COVID-19 [3]. TB poses a threat to both developing as well as developed nations due to the impacts of globalization, migration, and the association with HIV infection [3,4].

Hepatobiliary TB (HBTB) is a rare form of abdominal TB. It is more common in males and affects individuals aged between 11 and 50 years [5]. In contrast, GBTB is more common among women, with a male-to-female ratio of 1:1.7 [1]. While abdominal TB accounts for around 12 % of all cases of extrapulmonary TB, HBTB constitutes only 1 % of

abdominal TB cases [1]. Since its discovery in 1870, only a handful of GBTB cases have been described in the literature [6]. The high alkalinity of bile and bile acids renders the gallbladder highly resistant to tubercle bacilli; hence, GBTB is extremely rare and indicates severe widespread abdominal TB [7,8]. However, the incidence of GBTB is steadily increasing [5].

In cases of abdominal TB, the primary site of infection is not always evident. The causative agent of TB, i.e., *Mycobacterium tuberculosis*, can spread to the hepatobiliary system through the following routes: hematogenous dissemination via the hepatic artery or portal venous system, canalicular infection via the biliary tracts, and contiguous spread from the adjoining viscera [1]. A history of gallstone disease, diffuse papillomatosis, or cystic duct obstruction can make the gallbladder vulnerable to tubercular infection. Comorbidities such as diabetes mellitus and HIV infection are deemed risk factors for TB. Cholelithiasis is one of the most common causes of cholecystitis and is associated with numerous cases of GBTB, as was the case with our patient [1,9].

TB of the biliary system usually causes jaundice, and its biochemical characteristics can mimic extrahepatic biliary compression [5]. Both extrinsic compression due to tuberculous lymph nodes and hypertrophy of the biliary epithelium can lead to biliary strictures, the former being more common in TB [10]. Biliary strictures due to TB are rare and can affect any part of the biliary tree, most commonly affecting the hepatic hilum [10,11]. They can even lead to upstream dilatation of the gallbladder, extra- and intrahepatic biliary trees [11]. An interesting article by Biswas et al. reported a similar case of a woman presenting with obstructive jaundice; imaging studies subsequently revealed obstruction at the liver hilum. Initially mistaken for a Klatskin tumor, the mass causing the obstruction was later identified as an inflammatory pseudotumor on histology; GeneXpert testing ultimately confirmed TB [12]. Thus, tubercular strictures are difficult to distinguish from common

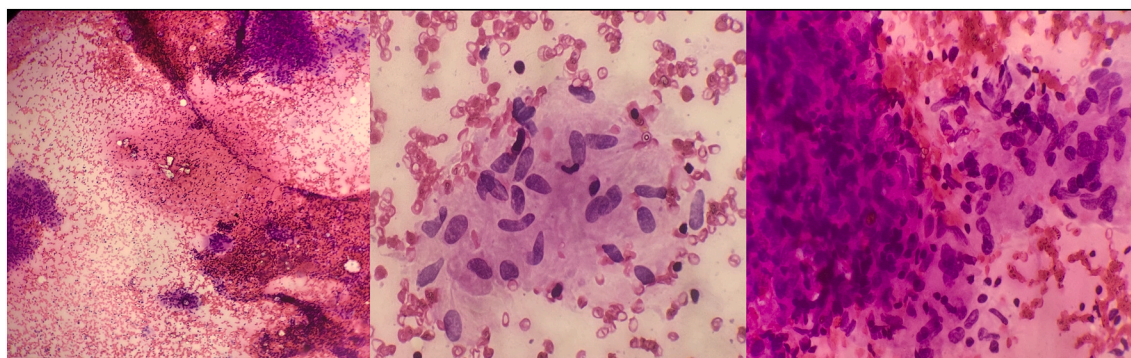


Fig. 4. FNA cytology of cervical lymph nodes showing multiple epithelioid cell granulomas along with multinucleated giant cell clusters.

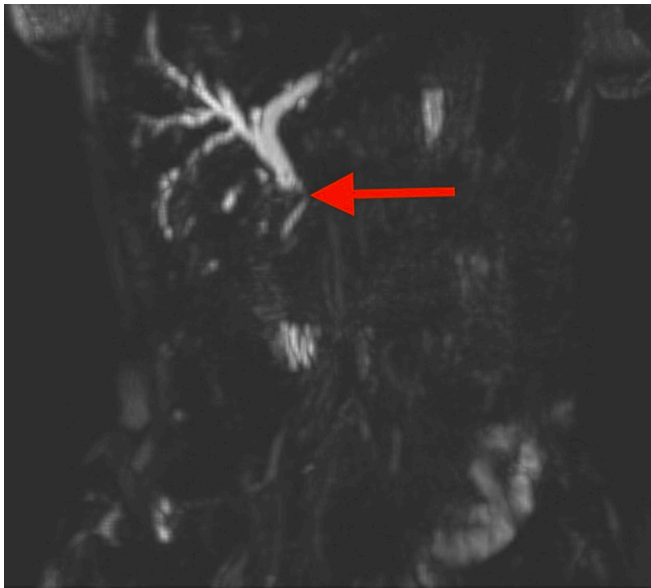


Fig. 5. Repeat MRCP showing sudden cutoff of the proximal CBD at the confluence of the hilum for a distance of 1 cm.

differentials such as primary sclerosing cholangitis and cholangiocarcinoma [10,12].

Gallbladder TB has been categorized into four distinct varieties: (1) as a component of miliary TB in children and adults; (2) as a component of disseminated abdominal TB; (3) isolated gallbladder TB without overt tuberculous foci elsewhere in the body; and (4) involvement of gallbladder in immunosuppressed and anergic states due to uraemia, cancer, or AIDS [13].

The signs and symptoms of GB TB are non-specific. The most common presentations are abdominal pain, fever, and abdominal lump, with anorexia and weight loss as constitutional symptoms. Interestingly, most patients do not have jaundice at the time of presentation [1]. TB of the gallbladder can pose a diagnostic dilemma by simulating biliary colic, acute cholecystitis, or even GB carcinoma [1,5]. Unfortunately, such patients are frequently misdiagnosed as having malignant diseases and are scheduled for surgery, only to have TB confirmed on post-operative histological analysis of the resected specimen [14].

An array of screening and diagnostic tests for TB are available thanks to technological advancements. Computer-aided detection systems, which employ artificial intelligence to read digital chest radiographs, have been approved by the WHO for TB screening in patients aged ≥ 15 years. Lateral flow urine lipoarabinomannan assay is a novel urinary antigen test that has been recommended by the WHO for TB diagnosis in HIV-coinfected patients [15]. TB antigen-based skin tests are a new class of skin tests that uses MTB-specific antigens to detect TB infection. They were found to be accurate, feasible, and cost-effective by the WHO, having a specificity higher than tuberculin skin tests and on par with Interferon-gamma release assays, especially in groups with a past history of BCG vaccination [16].

Despite advancements in diagnostic modalities, no single laboratory test or radiological investigation can accurately diagnose GBTB [1,5]. Routine laboratory tests may show a raised ESR, low hemoglobin, and a positive Mantoux tuberculin skin test [1]. Chest X-rays revealed signs of pulmonary TB in over 75 % of HBTB cases, whereas only 4 % of GBTB cases had active pulmonary TB at the time of presentation [1,5]. Ultrasonography (US) and CECT in GBTB reveal non-specific findings such as an enlarged GB, thickened GB wall, and GB mass [1,17]. Imaging modalities such as US, computed tomography, MRCP, and ERCP are useful to define the GB mass and delineate the level and extent of bile duct obstruction, but they are unable to diagnose TB in patients with gallbladder and biliary tract TB [1,18].

The definitive diagnosis of GBTB requires either histopathological evidence of a caseating granuloma or the microbiological presence of AFB on a smear or in a culture of a biopsy specimen. Both AFB stains and mycobacterial cultures have low sensitivities and therefore have a limited role in diagnosing GBTB [19]. In cases of biliary involvement, a polymerase chain reaction assay of the biliary aspirate should be carried out, as it is more sensitive than AFB staining [19]. In patients presenting with obstructive jaundice due to a GB mass, endoscopic ultrasound-guided FNA has been proven to be a safe and sensitive tool for confirming the diagnosis [20]. Nevertheless, histopathological examination of tissue samples remains the gold standard for diagnosing GBTB and ruling out other differentials such as gallbladder malignancy, lymphoproliferative disorder, cholecystitis, cholelithiasis, and granulomatous diseases like sarcoidosis [20,21]. Even in the absence of microbiological evidence, the histopathological presence of a caseating granuloma, composed of epithelioid cells surrounded by lymphocytes, with or without Langhans type multinucleated giant cells, having caseation necrosis at the center, is highly suggestive of TB and is an indication to commence anti-tubercular treatment [22].

Like any case of TB, anti-TB therapy (ATT) remains the cornerstone of treatment in GBTB. The ATT regimen usually comprises a combination of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol for a duration of 6–9 months [1]. Anti-tubercular drugs, especially Isoniazid, can cause hepatotoxicity, which may turn fatal. Monitoring liver enzymes is necessary when receiving ATT [5]. Hence, the focus is now on developing well-tolerated and efficient treatments, either by utilizing novel drug combinations or reducing the length of the treatment regimen. A recent clinical trial has shown that a 4-month regimen comprising Rifapentine (a cyclopentyl derivative of Rifampin), Isoniazid, Pyrazinamide, and Moxifloxacin was non-inferior to the standard 6-month ATT [23]. The WHO has recommended this 4-month regimen to eligible patients of drug-susceptible pulmonary TB aged ≥ 12 years [24]. A 2018 retrospective cohort study and meta-analysis of individual patient data showed significantly improved treatment outcomes for Bedaquiline-based regimens in multidrug-resistant TB (MDR TB) [25,26]. This led to a substantial shift in management strategies, with the WHO recommending an all-oral, 9-month regimen with Bedaquiline over the longer 18-month regimen in eligible patients of MDR TB [27]. In cases of biliary tract obstruction and obstructive jaundice, biliary decompression should be done by stent placement during ERCP, percutaneous transhepatic biliary drainage, or surgical decompression [5].

This case highlights the importance of a biopsy in negating a diagnosis of gallbladder carcinoma in a case of benign gallbladder mass, especially in a young patient at an uncommon age of presentation for gallbladder malignancy. Diagnosing our patient was challenging due to her non-specific presentation, lack of constitutional symptoms of TB such as fever and night sweats, lack of a past history of TB, and negative results of the AFB smear and GeneXpert assay. However, there were collaborative findings for TB, like cervical lymph node involvement and pulmonary involvement, as proven histologically and radiologically, respectively. Despite having radiological findings suggestive of metastatic gallbladder cancer, the tumor markers for gallbladder malignancy were negative. These findings pointed towards a benign etiology, i.e., tubercular infiltration of the hepatobiliary system, which was confirmed by a biopsy of the liver tissue surrounding the gallbladder mass. GBTB can present with an array of non-specific clinical, biochemical, and radiological presentations, thus requiring clinicians in TB-endemic regions to possess a high index of suspicion for diagnosing GBTB [21].

4. Conclusion

Gallbladder TB is a rare disease which poses a diagnostic challenge because it lacks any pathognomonic features and is easily confused with other diseases. GBTB closely mimics malignancy; hence, it should be considered in the differential diagnosis of biliary tract carcinomas. A

tissue diagnosis must be carried out before confirming gallbladder and biliary tract malignancies. Due to its non-specific presentation, physicians in TB-endemic regions should possess a high index of suspicion for diagnosing GBTB. Anti-TB medications are effective in treating and curing TB, but liver enzymes should be monitored during treatment due to the possibility of hepatotoxicity from these drugs.

5. Methods

The work has been reported in line with the SCARE criteria [2].

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Ethical approval is exempted for publication of anonymous case reports by the Institutional Ethics Committee.

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Author contribution

Arkadeep Dhali, Rick Maity, Jyotirmoy Biswas, Souradeep Mukherjee: Data collection, manuscript writing.

Gopal Krishna Dhali: Critical supervision, revising manuscript.

All authors agreed to the final manuscript.

Guarantor

Dr. Gopal Krishna Dhali will act as the guarantor for the manuscript.

Research registration number

Not applicable.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Data availability

The data used to support this study are included within the article.

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