Scientific Research Publishing

Open Journal of Gastroenterology, 2022, 12, 153-160
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Unusual Case of Miliary Tuberculosis with Hepatic Involvement

Michael Agyekum Adu-Darko

Department of Acute Internal Medicine, Milton Keynes University Hospital, Milton Keynes, United Kingdom
Email: agyekum64@gmail.com

How to cite this paper: Adu-Darko, M.A. (2022) Unusual Case of Miliary Tuberculosis with Hepatic Involvement. *Open Journal of Gastroenterology*, **12**, 153-160.
https://doi.org/10.4236/ojgas.2022.127015

Received: June 18, 2022
Accepted: July 23, 2022
Published: July 26, 2022

Abstract

Miliary tuberculosis (*MTB*) of the liver can present non-specifically, which often leads to a diagnostic delay. The objective of this clinical case report is to highlight an unusual presentation of miliary TB in a young female patient, who was admitted to hospital with right upper quadrant tenderness and constitutional symptoms. Most of her investigations yielded little to support the diagnosis until a subsequent positive TB Elispot test and CT chest, abdomen and pelvis with contrast were done. Features of this case are discussed, together with anti-tubercular treatment (ATT) strategy utilized for miliary TB with hepatic involvement.

Keywords

Miliary TB, Constitutional Symptoms, Anti-Tubercular Treatment (ATT)

1. Introduction

Mycobacterium tuberculosis (TB) infection of the liver, known as hepatic TB, is an extrapulmonary manifestation of TB. The first recorded case of hepatic TB was reported in 1858 by Dr. John Syer Bristowe, an English physician [1]. In 1905, more than 20 years after Koch's discovery of the TB bacillus, Drs. Rolleston and McNee had classified hepatic TB into miliary (disseminated) and local (isolated) forms [2]. Among reported hepatic TB cases, miliary form accounted for 79% of cases, while local hepatic TB accounted for 21% of cases [3]. If left untreated, miliary TB has a mortality approaching nearly 100% [4], reducing to 7.1% - 30% with treatment [5]. Clinical features of hepatic TB are nonspecific, which often leads to a delay in diagnosis with high morbidity and mortality [6]. The objective of this case report is to emphasize how unusual miliary TB can present and the importance of considering it early as a differential diagnosis.

Hepatic TB has become more prevalent, believed to be due to the immuno-

suppression caused by HIV leading to a reactivation of latent TB [7]. Over 50% of HIV and TB co-infected people present with extrapulmonary involvement, which includes hepatic TB [8].

Tuberculous bacilli can reach the liver via hematogenous dissemination, from the lungs, or by local spread from the gastrointestinal tract [9]. In miliary hepatic TB, bacilli reach the liver via the hepatic artery [10]. Miliary hepatic TB is characterized by diffuse seeding of the liver with tubercles ranging from 0.6 to 2.0 mm in diameter situated in the lobules of the liver [11].

Symptoms include abdominal/flank pain, decreased appetite, fever and chills, malaise and weight loss. Patients often have leukocytosis, elevated inflammatory & liver markers and creatinine. Local hepatic TB and military TB may differ in presentation. Local hepatic TB may present primarily as diffuse abdominal pain, while patients with miliary hepatic TB may present with acuterespiratory symptoms such as a cough, with or without sputum production [12].

Liver biopsy with mycobacterial culture is considered the most specific diagnostic test for hepatic TB [11] [12]. Ultrasound guided liver biopsy is generally preferred to improve the sampling and increase the diagnostic accuracy [13].

A clearer understanding of hepatic TB will help clinicians with diagnostic and management decisions to improve patient outcomes.

The World Health Organization (WHO) recommendation for the treatment of drug susceptible pulmonary TB (rifampin, isoniazid, ethambutol, and pyrazinamide for two months, followed by 4 months of rifampin and isoniazid) has been applied to hepatic TB with positive outcomes [14].

Although the optimal duration of treatment of hepatic TB is controversial, usually a duration of 6 - 12 months appears to be effective for most patients [14].

2. Clinical Presentation

A 19-year-old female university student originally from Nigeria, West Africa, presented to hospital with intermittent chills, headaches, vomiting, epigastric pain of 7 day duration. She denied cough or weight loss. Physical examination was positive for right upper quadrant tenderness, pyrexia 38 degrees Celsius, hypotension and tachycardia. Murphy's sign was negative and she did not have any palpable lymphadenopathy. The patient was awake and oriented, however, ill-appearing, and complaining of marked photophobia. Her body mass index (BMI) was 18. She denied exposure to immunosuppressant drugs and was HIV negative. **Table 1** shows the lab tests done, which demonstrated liver function derangement (both hepatic and cholestatic picture) and lymphocytosis. Procalcitonin level was elevated at 0.89 nanogram/ml (reference < 0.1 nanogram/ml), suggesting likely bacterial infection. Haemoglobin, white cell count, neutrophil count, lymphocyte count, prothrombin time, partial thromboplastin time and international normalized ratio were within the normal range. At this point, she was commenced on broad-spectrum intravenous antibiotic and acyclovir to cover for possible meningoencephalitis. She had a normal brain CT scan, and

subsequent MRI brain with whole spine scan was reported as normal with no leptomeningeal enhancement or abnormal lesions. The patient had a lumbar puncture, which demonstrated normal opening cerebrospinal fluid (CSF) pressure of 16 mm Hg. Patient's CSF results are summarised in Table 2. The CSF microbiology indicated negative cultures, negative gram film, marked lymphocytosis (90%), in the context of low glucose levels and normal protein count. No fungal isolates were detected on the CSF. Her TB culture specimen and TB PCR (GeneXpert) were both negative. TB Elispot test came back positive after 10days. Subsequently, a CT thorax, abdomen and pelvis with contrast revealed numerous tiny nodules in both lungs, liver, spleen and right kidney with no collections (Figure 1 and Figure 2). She was diagnosed as a case of *miliary tuberculosis infection*, immediately commenced on anti-tubercular therapy (ATT) and transferred to a tertiary hospital for more specialist care input as well as a liver biopsy via interventional radiology. The histology of the liver biopsy did not demonstrate granuloma, but her TB culture on the specimen was positive for Acid Fast Bacillus (AFB) confirmed to be *Mycobacterium tuberculosis*. On starting ATT,

Table 1. Laboratory exams.

PARAMETERS	Value	Reference Range
Hb	132 g/L	(123 - 145 g/L)
WBC count	4.5×10^9/L	(4.0 - 11.0 × 10^9/L)
Neutrophil count	2.8×10^9/L	(1.5 - 8.0 × 10^9/L)
Lymphocyte count	1.0×10^9/L	(1.0 - 4.0 × 10^9/L)
AST	88 IU/L	(10 - 35 IU/L)
GGT	660 IU/L	(6 - 42 IU/L)
ALP	317 IU/L	(30 - 130 IU/L)
Bilirubin	14 umol/L	(<21 umol/L)
CRP	48 mg/L	(<10 mg/L)

Table 2. Cerebrospinal fluid (CSF) exam.

PARAMETERS		
Appearance	Colourless, clear	
	Value	**Reference Range**
pH	7.30	7.35 - 7.45
Glucose	1.8 mmol/L	1.6 - 2.5 mmol/L
Protein	0.25 g/L	0.1 - 0.5 g/L
WBC	2×10^6/L	0 - 5 cells/uL
Neutrophils	-	-
Lymphocytes	>10 cells/uL	0 - 5 cells/uL
Red blood cells	1/mm^3	0 - 10/mm^3

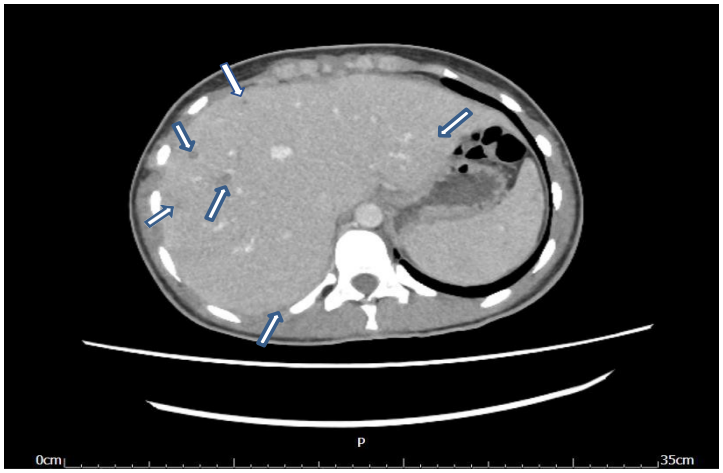

Figure 1. CT abdomen showing multiple miliary nodules (tubercules) indicated by the white arrows.

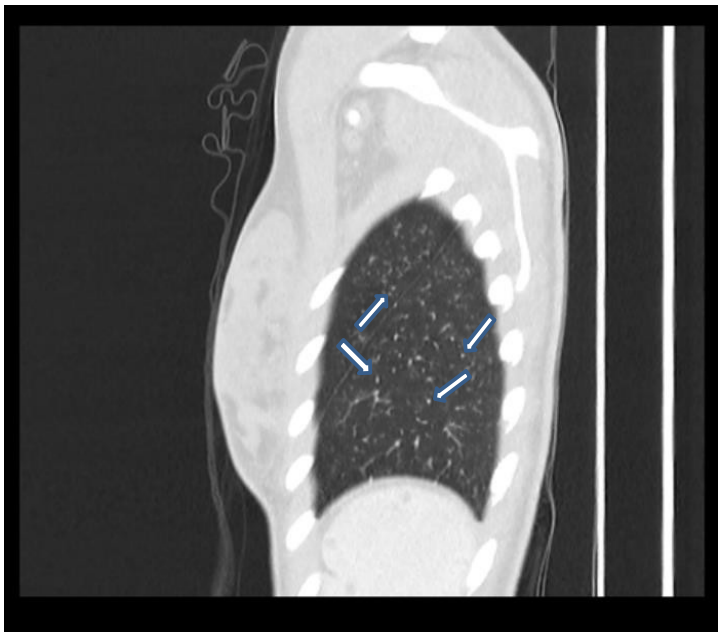

Figure 2. CT thorax (lateral view) showing multiple miliary nodules (tubercules) indicated by the white arrows.

her high-grade fevers improved in the next 24 hours, and she had initial visual assessment and daily liver function tests (LFTs) to monitor for side effects of ATT. Although she initially had worsening of her GGT and ALP, they remained stable over 72 hours of initiation therapy. Patient stayed in hospital for another 7 days before discharge with planned follow-up with the community TB nurse and Infectious Diseases outpatient reviews. She remained compliant with ATT and returned to her studies successfully.

3. Discussion

Tuberculosis (TB) is a leading cause of preventable morbidity and mortality

worldwide. The latest World Health Organization (WHO) figures indicate that total of 1.5 million people died from TB in 2020 (including 214,000 people with HIV) [15]. Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS) [15]. In 2020, an estimated 10 million people fell ill with tuberculosis (TB) worldwide [15]. The disease is characterized by high mortality, reported to be between 18% and 30% [15]. The epidemiology of military TB has been altered by the emergence of the human immunodeficiency virus (HIV) infection and widespread use of immunosuppressive drugs [15]. A TB liver abscess commonly arises from local hepatic TB but may also occur following miliary hepatic TB [16]. Local hepatic TB tends to cause more hepatocellular damage than miliary hepatic TB [17]. In contrast to miliary hepatic TB, those with local hepatic TB do not generally have evidence of active pulmonary disease [18].

Miliary TB is diagnosed by the presence of a diffuse miliary infiltrate on chest radiograph or high-resolution computed tomography (HRCT) scan, or evidence of miliary tubercles in multiple organs at laparoscopy, open surgery, or autopsy [19]. Liver biopsy with mycobacterial culture remains the most specific diagnostic test for hepatic TB [12]. The characteristic histological feature of both miliary and local forms of hepatic TB is the granuloma [11]. Hepatic granulomas are due to cell-mediated immunological responses to TB antigens and consist of focal aggregates of macrophages, including Kupffer cells that may coalesce to form Langerhans giant cells with surrounding lymphocytes and fibroblasts [17]. The clinical and morbid anatomic picture needs to be confirmed by bacteriology, histopathology, and/or a dramatic chemotherapeutic response [12]. Early risk stratification with a high index of suspicion in patients with potential risk factors, early anti-tubercular treatment, and nutritional support are key to better outcomes.

This case had risk factors including reduced BMI and possible exposure given her ethnic background. Interestingly, she did not have a BCG scar on inspection of her shoulders. She presented with non-specific systemic symptoms with markedly deranged liver function tests (LFTs), in the context of features suggestive of meningitis. Of note, majority of miliary TB cases reported were associated with immunosuppression secondary to diabetes, underlying malignancy or coinfection with HIV/AIDS, which was not seen in our case. The patient's TB Elispot test result arrived 10days into her admission, as it was usually performed by an off-site laboratory out of area of the admitting hospital. While liver biopsy may not always be necessary, microbiological and histological findings can allow for a more accurate diagnosis [11]. Occasional elevation of ALT (typical range: 0 - 200 U/L) and aspartate transaminase (AST) is often seen (typical range: 0 - 200 U/L) [19] [20]. Higher levels of ALT and AST were observed in jaundiced patients [21]. According to a systematic review by Hickey AJ *et al.* [22], the most common abnormalities associated with hepatic TB include ALP (typical range: 200 - 750 U/L) and GGT (typical range: 100 - 400 U/L). In this case report, patient did not develop jaundice. Mild hyperbilirubinemia has been reported in both miliary

and local hepatic TB cases [12], with similar trend seen in this case report's elevated bilirubin. A liver biopsy is indicated in any person with a constellation of clinical, laboratory, and radiographic suspicion of hepatic TB [19], all of which were seen in this patient. Ultrasound (US) guided liver biopsy is generally preferred to improve the sampling and increase the diagnostic accuracy [19]. Liver biopsies, when taken, should be sent for both microbiological and histological evaluation [19]. In a hepatic TB case series, AFB smear had a median sensitivity of 25% (range: 0% - 59%) [20], and unsurprisingly, this patient's AFB smear was negative. She had US guided liver biopsy subsequently, and TB culture was positive.

The duration of treatment was based on the recommendation by The National Institute for Health and Clinical Excellence (NICE) [3] guidelines from UK, American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA) [8]; all endorsing six (6) months of treatment (2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin, followed by a 4-month continuation phase with isoniazid and rifampicin).

In conclusion, miliary TB with hepatic involvementcan easily be missed due to their insidious onset and presentation, typically with vague symptoms and signs. In this case, the patient kept on deteriorating even with appropriate broad-spectrum antibiotic treatment and timely CT chest, abdomen and pelvis was key to confirming the diagnosis and starting treatment early. Prompt commencement of ATT will achieve good clinical response should the diagnosis be correct, which can be lifesaving in the setting of risk factors such as low BMI. Patients with definitive or clinically suggestive hepatic TB should be promptly initiated on 4-drug anti-TB therapy, and clinicians should observe closely for drug toxicity and complications, such as Drug Induced Liver Injury (DILI) and TB-Immune Reconstitution Inflammatory Syndrome (IRIS) [21]. Co-infection with HIV can complicate the management of hepatic TB, and clinicians must be knowledgeable of differences in pathophysiology, treatment, and disease management [22]. A high index of suspicion for hepatic TB is important if clinicians are to make an early diagnosis and initiate prompt treatment to improve clinical outcomes [22].

4. Learning Points

- A high index of suspicion should be considered in patients with risk factors for miliary TB.
- Early diagnosis with TB specimen cultures, abdominal CT is crucial to preventing long term sequalae.
- Early commencement of ATT demonstrates good rapid clinical response, should the diagnosis of TB be accurate.

Authors and Affiliations

MAD is the sole contributor in writing the manuscript, including history taking,

examination, laboratory investigations and follow up. DK was involved in the care of this patient and so was AC. JR assisted in radiology analysis and interpretation.

Ethics approval and Consent to Participate

Consent for publication was obtained from the patient.

Financial Support/Conflict of Interests

There was no funding supporting this work. The author has no relevant affiliation or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter discussed in the manuscript.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Bristowe, J.S. (1858) On the Connection between Abscess of the Liver and Gastrointestinal Ulceration. *Transactions of the Pathological Society of London*, **9**, 241-252.

[2] Chien, R.N., Lin, P.Y. and Liaw, Y.F. (1995) Hepatic Tuberculosis: Comparison of Miliary and Local Form. *Infection*, **23**, 5-8. https://doi.org/10.1007/BF01710049

[3] National Institute for Health and Clinical Excellence, National Collaborating Centre for Chronic Conditions (2006) Management of Non-Respiratory Tuberculosis. In: *Tuberculosis*: *Clinical Diagnosis and Management of Tuberculosis*, *and Measures for Its Prevention and control*, Royal College of Physicians, London, 63-76.

[4] Falk, A. (1965) U.S. Veterans Administration-Armed Forces Cooperative Study on the Chemotherapy of Tuberculosis. Tuberculous Meningitis in Adults, with Special Reference to Survival, Neurologic Residuals, and Work Status. *American Review of Respiratory Disease*, **91**, 823-831. https://doi.org/10.1164/arrd.1965.91.1.6

[5] Venkatraman, N., King, T., Bell, D., Woltmann, G., Wiselka, M., Abubakar, I., et al. (2016) High Levels of Neurological Involvement But Low Mortality in Miliary Tuberculosis: A 6-Year Case-Series from the UK. *European Respiratory Journal*, **47**, 1578-1581. https://doi.org/10.1183/13993003.01958-2015

[6] Muray, C.J. and Lopez, A.D. (1997) Global Mortality, Disability, and the Contribution of Risk Factors: Global Burden of Disease Study. *Lancet*, **349**, 1436-1442. https://doi.org/10.1016/S0140-6736(96)07495-8

[7] Sharma, S.K. and Mohan, A. (2009) Disseminated and Miliary Tuberculosis. In: Sharma, S.K. and Mohan, A., Eds., *Tuberculosis*, 2nd Edition, Jaypee Brothers, New Delhi, 493-518. https://doi.org/10.5005/jp/books/10992_34

[8] Blumberg, H.M., Burman, W.J., Chaisson, R.E., Daley, C.L., Etkind, S.C., Friedman, L.N., et al. (2003) American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, **167**, 603-662. https://doi.org/10.1164/rccm.167.4.603

[9] Wang, J.Y., Hsueh, P.R., Wang, S.K., Jan, I.S., Lee, L.N., Liaw, Y.S., et al. (2007)

Disseminated Tuberculosis: A 10-Year Experience in a Medical Center. *Medicine*, **86**, 39-46. https://doi.org/10.1097/MD.0b013e318030b605

[10] Chong, V.H. and Lim, K.S. (2010) Hepatobiliary Tuberculosis. *Singapore Medical Journal*, **51**, 744-750

[11] Purl, A.S., Nayyar, A.K. and Vij, J.C. (1994) Hepatic Tuberculosis. *Indian Journal of Tuberculosisc*, **41**, 131-134.

[12] Hersch, C. (1964) Tuberculosis of the Liver: A Study of 200 Cases. *South African Medical Journal*, **38**, 857-863.

[13] Grant, A. and Neuberger, J. (1999) Guidelines on the Use of Liver Biopsy in Clinical Practice. *Gut*, **45**, IV1-IV11. https://doi.org/10.1136/gut.45.2008.iv1

[14] Alvarez, S.Z. (1998) Hepatobiliary Tuberculosis. *Journal of Gastroenterology and Hepatology*, **13**, 833-839. https://doi.org/10.1111/j.1440-1746.1998.tb00743.x

[15] World Health Organization (2020) WHO Report: Global Tuberculosis Control. World Health Organization, Geneva.

[16] Essop, A.R., Posen, J.A., Hodkinson, J.H. and Segal, I. (1984) Tuberculosis Hepatitis: A Clinical Review of 96 Cases. *QJM*, **53**, 465-477.

[17] Huang, W.T., Wang, C.C., Chen, W., Cheng, Y.F. and Eng, H.L. (2003) The Nodular Form of Hepatic Tuberculosis: A Review with Five Additional New Cases. *Journal of Clinical Pathology*, **56**, 835-839. https://doi.org/10.1136/jcp.56.11.835

[18] Nawaz, A., Malik, K., Alvi, A. and Ali, B. (2016) Hepatic Tuberculosis in an Immunocompetent Patient—A Diagnostic Challenge. *American Journal of Gastroenterology*, **111**, S949.

[19] Mert, A., Ozaras, R., Tabak, F. and Ozturk, B.M. (2003) Localized Hepatic Tuberculosis. *European Journal of Internal Medicine*, **14**, 511-512. https://doi.org/10.1016/j.ejim.2003.09.007

[20] Ferrari, T.C.A., Couto, C.M., Vilaca, T.S. and Xavier, M.A.P. (2006) Localized Hepatic Tuberculosis Presenting as Fever of Unknown Origin. *Brazilian Journal of Infectious Diseases*, **10**, 364-367. https://doi.org/10.1590/S1413-86702006000500013

[21] Alvarez, S.Z. and Carpio, R. (1983) Hepatobiliary Tuberculosis. *Digestive Diseases and Sciences*, **28**, 193-200. https://doi.org/10.1007/BF01295113

[22] Hickey, A.J., Gounder, L., Moosa, M.Y. and Drain, P.K. (2015) A systematic Review of Hepatic Tuberculosis with Considerations in Human Immunodeficiency Virus Co-Infection. *BMC Infectious Diseases*, **15**, Article No. 209. https://doi.org/10.1186/s12879-015-0944-6