

## **Case study**

### **An unusual detected cause of abnormal liver enzymes in an aircrew member periodical visit: case report**

#### **Abstract**

**Background:** Hepatic tuberculosis is a rare entity, poorly described in the literature. It presents with nonspecific clinical manifestation and imaging findings mimicking other liver disease making diagnosis challenge. We report a case of isolated hepatic tuberculosis in asymptomatic cabin crew member diagnosed accidentally by investigating a liver chemistry test disorder.

**Case report:** a 28 year-old Moroccan cabin crew attendant came to the aeromedical expertise center to perform her periodical medical assessment. She had no medical history. Physical examination was unremarkable. Liver chemistry test values were elevated. Imaging studies of the liver suggested malignant disease. Histological examination showed isolated hepatic tuberculosis.

**Discussion:** isolated hepatic tuberculosis is very uncommon, lacks typical clinical manifestation and radiological features, but remains an important differential diagnosis of hepatic nodules especially in endemic areas. This observation highlights the benefit of liver chemistry test evaluation realized systematically for periodical aeromedical fitness to diagnose some pathology in asymptomatic stage avoiding complications. Hepatic tuberculosis is a cause of temporarily unfitness because it's not compatible with flight safety conditions. Aircrew with hepatic tuberculosis will need to be assessed for both complete

disease control and full resolution of any iatrogenic side effect of antituberculous drugs before returning to fly under some restrictions.

**Keywords: liver tuberculosis, extrapulmonary tuberculosis, flight safety, aptitude management.**

### **Introduction:**

Tuberculosis (TB) is a worldwide public health problem with considerable morbidity and mortality in both developed and developing countries [1]. In Morocco it's still endemic with more than 30000 new cases per year [2]. Pulmonary involvement remains the most frequent form of tuberculosis with 80-90% of cases but there is an increasing interest in extrapulmonary forms of tuberculosis as its relative frequency increases [3].

Hepatic tuberculosis is a rare pattern, particularly in the absence of miliary TB; it is poorly described in literature and represents less than 1% of all cases of TB [4]. Clinical symptoms vary widely; they are nonspecific like right upper quadrant pain, jaundice, ascites, nausea hepatosplenomegaly, fever, weight loss or night sweats, etc. [5]

Comment [lp1]: TB

Imaging findings are nonspecific and can mimic other liver diseases such as hepatic tumors or metastases which lead to a diagnostic challenging [6]. Sometimes Hepatic tuberculosis may be asymptomatic leading directly to several complications like miliary, fulminant hepatic failure and death if not early diagnosed and properly managed [4-6].

Comment [lp2]: TB

We report a case of hepatic tuberculosis in a cabin crew member diagnosed accidentally by investigating perturbation of liver's chemistry tests performed in a systematic aeromedical fitness. Through this case we reveal the interest of liver chemistry tests (realized for pilot and crew members every one and two years respectively) in leading to early diagnosis for some rare pathology, avoiding complications and preserving life and flight safety.

The diagnosis of hepatic tuberculosis leads to unfitness to fly and requires rationally specific fitness assessments.

### Case presentation:

We report a case of a 28-year-old woman Moroccan cabin crew member who came to the aeromedical expertise center at the military hospital of Rabat for her periodic medical assessment. She has no medical history, no smoking, no alcohol or drugs consumption. She was declared to be asymptomatic.

Physical examination was normal. Liver and spleen were not palpable with any jaundice and there was no palpable lymphadenopathy.

Chest X-ray was normal within opacities.

Systematic chemistry liver tests showed abnormalities:  $\gamma$ -glutamyltransferase (up to three times the upper limit of normal (ULN)), elevation of aminotransferases (up to two to three times the ULN).

**Comment [Ip3]:**  
Liver function tests

**Comment [Ip4]:**  
Write the data in a Table

Erythrocytes sedimentation rate (ESR) was elevated at 50 mm in the first hour (ULM < 10 mm).

Complete blood count was normal.

**Comment [Ip5]:**  
Write the data

Abdominal ultrasonography revealed nodular hepatomegaly.

Abdominal computed tomography (CT) showed low-density multiple liver nodules without bile duct dilatation (cf. figure1).

Liver MRI showed a well defined liver round mass, with different size hypo-intense on T1 hyper-intense on T2 moderated with intermediate B-value diffusion enhanced in portal time with late homogenization (cf. Figure 2).

This aspect was highly suspected of malignancy.

An ultrasonography-guided percutaneous liver biopsy was performed, and histopathological examination of the specimen showed caseating granulomas with epithelioid histiocytes and giant cells. Acid-fast bacilli (AFB) were detected on a smear examination.

Pulmonary tuberculosis was excluded by realizing chest CT and searching for AFB in expectorated sputum for 3 consecutive days. Ultrasound scanning and CT of the abdomen didn't identify ascites, abdominal or retroperitoneal lymph nodes or specific tissue involvement which characterizes other localization of intra-abdominal tuberculosis.

Comment [lp6]: TB

The diagnosis of isolated hepatic tuberculosis was confirmed and anti tuberculosis drugs were prescribed for 9 months. The cabin crew was declared unfit to flying.

Comment [lp7]: TB

After 3 months of treatment without any adverse effect, chemistry liver tests and ESR were normal with total disappearance of liver lesions (cf. Figure 3). Therefore, the patient was declared fit to fly by derogation.

Comment [lp8]: liver function tests

### Discussion:

There are several forms of hepatic involvement of TB described in the literature, but the most common form of hepatic involvement is the miliary form. Hepatic involvement of TB in the absence of miliary or pulmonary/extrapulmonary TB is a rare entity and constitutes less than 1% of all cases [1, 4]. Because low oxygen tension in the liver is unfavorable for

mycobacteria growth [7]. It is believed that the route of transmission is different in miliary TB from primary hepatic TB. In the miliary form of TB the route of dissemination is similar to other forms of extrapulmonary TB which results from hematogenous dissemination of the infection through the hepatic artery [5]. While in primary hepatic TB, the tubercle bacillus reaches the liver through the portal vein from primary intestinal tuberculosis [8], the infection may also reach the liver by lymphatic spread [9].

**Comment [lp9]:**

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Re-write

**Comment [lp10]:** TB

A variety of diseases and conditions favor the development of active tuberculosis such as tobacco smoking, intravenous drug use, malnutrition and severe underweight, diabetes, HIV infection, immunosuppressive treatment, chronic renal failure, silicosis, gastrectomy and jejunoileal bypass. [10]. In the case presented, we don't recognize any risk factor presented by our flight attendant, she was HIV negative without a history of smoking or drug use.

**Comment [lp11]:**

Jejuno-ileal

The most frequently encountered clinical and laboratory findings described in literature are fever with chills, weight loss, abdominal pain, jaundice splenomegaly, hepatomegaly in 94-100% of cases in nodular form simulating cancer of the liver or tender form simulating liver abscess [1,4,7,9]. Elevated alkaline phosphatase level was observed in 25% of cases [1]. In this case report, the patient was asymptomatic; no hepatomegaly was detected in physical examination with only an elevated aminotransferases and  $\gamma$ -glutamyltransferase level.

Hepatic tuberculosis has no characteristic imaging features and can closely mimic primary liver malignancy or metastases [4,7,9], or other liver diseases like sarcoidosis and lymphoma [9]. Computed tomography is superior to ultrasound scanning for identification of hepatic disease; it can show intrahepatic hypodense lesions or liver calcifications and can be used to guide liver biopsy which is the most useful tool to confirm the diagnosis.

MRI of hepatic TB shows a hypointense nodule with a hypointense rim on T1-weighted imaging. A hypo-intense, iso-intense or hyper-intense nodule with a less intense rim on T2-weighted imaging [8]. Hepatic TB also shows FDG-avidity on F-18 FDG PET/ CT similar to other malignant tumors [11].

Comment [Ip12]: The MRI

Comment [Ip13]: Hyper-intense

Our patient had multiple nodules expanded to both lobes of the liver on CT-scan and MRI; this aspect was highly suspected of malignancy. PET /CT was not performed in our case.

Once the diagnosis of hepatic tuberculosis has been made and other localizations or a military were excluded, tuberculostatic treatment will be started for a minimum of 6 months, rifampicin and isoniazid for the duration of treatment with additional pyrazinamide and ethambutol during the induction as usual for 3 months. Some clinicians use an extended antibiotic course to reduce the risk of relapse [5,9], although some recent publications indicate that at least 1 year of medical therapy is required [4,6]. Our patient was treated for 9 months.

Comment [Ip14]: miliary

Comment [Ip15]: months

The prognosis is usually good in most of cases after an early diagnosis and tuberculostatic treatment with a good clinical response (disappearance of symptoms, increases in appetite and weight gain) [6, 9].

The response to treatment in case of hepatic TB must be assessed by clinical findings, radiological and biological investigations. In our case, we had a normalization of liver chemistry tests after 3 months of treatment with total disappearance of liver nodules on CT-scan and MRI.

Comment [Ip16]: months

In aircrew, hepatic TB is considered as a cause of temporary disqualification because symptoms or excessive fatigue are incompatible with safe flying conditions. Moreover, anti

bacillary therapy has a significant side effect [12] of aeromedical concern mainly in the induction phase where there is a high risk of hypersensitivity reaction especially to Isoniazid. There is also a risk of convulsion, peripheral neuropathy, arthralgia, hyperuricemia with a risk of gout attack caused by Pyrazinamide. The most redoubtable and serious side effect is retrobulbar optic neuritis due to Ethambutol, it occurs within two months of starting medication and includes dyschromatopsia (red-green), decreased visual acuity, central scotoma, visual evoked potentials (VEP) alteration, and finally optic atrophy. This latest effect should be taken into account when resuming flying duties.

**Comment [lp17]:** Pyrazinamide

Hepatotoxicity must be periodically assessed for all duration of tuberculostatic treatment.

In addition to those side effects, there are another constraints which can make the aircrew unfit to fly. For instance the long missions cause problems in tuberculostatic drugs availability and in biological monitoring hardness, besides the constraints due to jet-lag in perturbing the schedules of drug taking.

Concerning our patient, she's a cabin crew member and she must be in good health to do her expected duties in managing the aircraft cabin during the trip and she must be able to take action if an in-flight or on-ground emergency occur. During her periodical aeromedical fitness, we discovered liver chemistry abnormalities related to hepatic tuberculosis in an asymptomatic phase. Tuberculostatic drugs were started for 9 months after excluding other prevalent localizations of tuberculosis and she was declared unfit to flight.

After 3months of treatment, normalization of liver chemistry values and liver MRI imaging, allow our flight attendant to get her flight duties through a waiver delivered by Moroccan expert committee of aerospace medicine, with some restrictions such as a quarterly control and unfitness for long haul flight until total recovery and end of her treatment.

Hepatic TB is a rare entity, lacks typical symptoms, signs, and laboratory data. Imaging features are various and nonspecific making the diagnosis challenging. But it should be suspected especially in endemic areas for TB.

Through this case we highlighted the role of hepatic chemistry test monitoring during periodical medical exam to diagnose some disease in initial stage before symptoms appearance, avoiding complications and preserving life and flight safety.

Hepatic TB isn't a permanent bar of flying, anti tuberculosis treatment while effective, requires a period of grounding due to adverse events with some probable potential aeromedical implications as described previously. Aircrew with hepatic TB will need to be assessed for both complete disease control and full resolution of any iatrogenic side effect of tuberculostatic drugs when resuming flying duties.

**References :**

1. Nurten TK, Ümit İ, Bahattin Ç, Haluk A, Güngör B, Nurdan T. Isolated hepatic tuberculosis: A rare cause of hepatic mass lesions. *Turk J Gastroenterol* 2014; 25: 110-
2. Ministère de la Santé, Direction de l'Epidémiologie et de Lutte Contre les Maladies Situation Epidémiologique de la Tuberculose au Maroc. 2015.
3. Ketata W, Rezik W.K, Ayadi H, Kammoun S. Extrapulmonary tuberculosis. *Revue de Pneumologie clinique* (2015) 71, 83—92
4. Mert A, Ozaras R, Tabak F, Ozturk R, Bilir M. Localized hepatic tuberculosis. *Eur J Intern Med* 2003;14:511-2.
5. Sophie R, Newsholme W, Gibson T. Diagnosis and management of intra-abdominal tuberculosis. *British Journal of Hospital Medicine*, June 2018, Vol 79, No 6.
6. Freitas M, Magalhães J, Marinho C, Cotter J. Looking beyond appearances: when liver biopsy is the key for hepatic tuberculosis diagnosis. *BMJ Case Rep* 2020; 13:e234491. Doi: 10.1136/bcr-2020-234491.
7. Levine C. Primary macronodular hepatic tuberculosis: US and CT appearances. *Gastrointest Radiol* 1990;15:307–9.
8. Jeong-Ik Park: Primary hepatic tuberculosis mimicking intrahepatic cholangiocarcinoma : report of two cases. *Annals of Surgical Treatment and Research* 2015;89(2):98-101.

**Comment [Ip18]:**

Write References in ONE STYLE according to the Journal instructions.

**Comment [Ip19]:**

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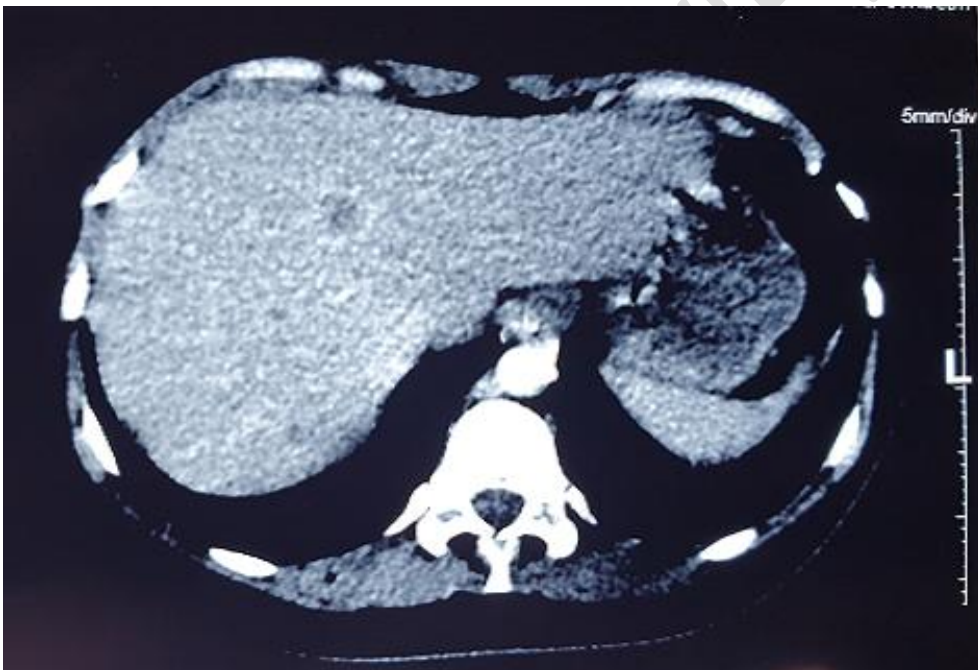
9. ALVAREZ SZ. Hepatobiliary tuberculosis. *Journal of Gastroenterology and Hepatology* (1998) 13, 833-839.
10. Kasper D, Fauci A, Hauser S, et al. *Harrison's principles of internal medicine*, 19th edition. 19th Edn. McGraw- Hill Education, 2015.
11. Wang YT, Lu F, Zhu F, Qian ZB, Xu YP, Meng T. Primary hepatic tuberculoma appears similar to hepatic malignancy on F-18 FDG PET/CT. *Clin Nucl Med* 2009; 34:528-9.
12. Aouam K, Chaabane A, Loussaïef C, Ben Romdhane F, Boughattas N.-A, Chakroun M. Adverse effects of antitubercular drugs: epidemiology, mechanisms, and patient management. *Médecine ET Maladies Infectieuses*, Volume 37, Issue 5, May 2007, Pages 253-261.

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**Captions:**

**Figure 1:** CT-scan showing multiple liver low density nodules without enhancement.

**Comment [lp20]:**  
Put the caption below Figure.



**Figure 2:** MRI T2 weighted sequence showing multiple hypersignal nodules.



**Figure 3:** Follow-up CT-scan of the abdomen 3 months under tuberculostatic therapy, showing completely regression of the liver noduli.

