Granulomatous hepatitis: tuberculosis or not?

Eu Jin Lim, Paul D R Johnson, Peter Crowley and Paul J Gow

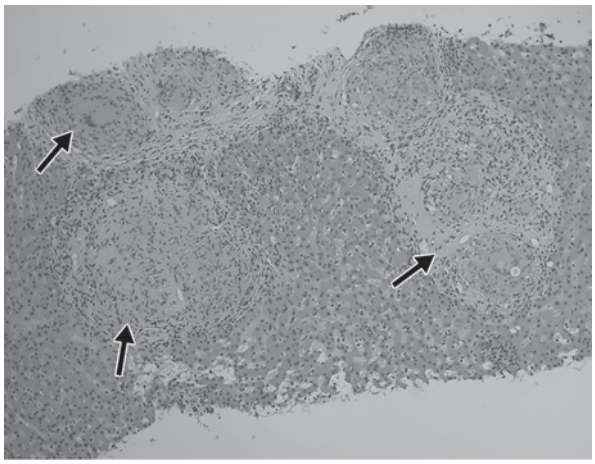
Clinical record

A 26-year-old recently married Filipino-born woman was referred to our hospital with left upper quadrant pain, vomiting and abnormal liver function test (LFT) results. There was nothing significant in her family history or past medical history. She described being unwell, and had lost 5 kg over 3 months, but had no respiratory symptoms or fever. On examination, she had slightly tender hepatomegaly palpable 3 cm below the right costal margin without any clinical stigmata of chronic liver disease. A BCG scar was noted. Her chest was clear and there were no other abnormal clinical findings. Her LFT results revealed elevated levels of alkaline phosphatase (345 U/L; normal range, 32–91 U/L) and γ-glutamyl transferase (215 U/L; normal range, < 38 U/L); other LFT results were normal. Findings of a full blood examination and urea, electrolytes and creatinine levels were all within normal limits. A triple-phase computed tomography scan of the liver was performed which showed hepatomegaly with multiple small, low-density lesions within the liver, which the reporting radiologist suggested may possibly be simple cysts. The appearance of the bowel, pancreas and lung bases were all normal. There was no intra-abdominal lymphadenopathy. Results of serological tests for hepatitis A, B and C were negative, as were results of tests for Wilson's disease and α-1-antitrypsin deficiency, and antinuclear antibody, antimitochondrial antibody and antismooth muscle antibody.

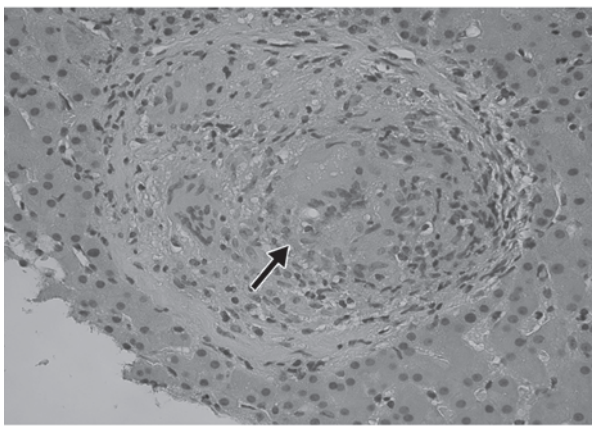
The patient subsequently underwent a liver biopsy, which revealed florid, non-caseating granulomatous reaction with aggregates of epithelioid histiocytes and Langerhans-type giant cells in a predominantly portal and periportal distribution (Figures A and B). The bile ducts were all intact and no evidence of malignancy was seen. Special stains, including Ziehl–Neelsen stain for acid-fast bacilli, were negative. The pathologist concluded that the histological appearance and distribution of granulomas was most consistent with the diagnosis of hepatic sarcoidosis.

However, because of the patient's ethnic background, further tests were undertaken to exclude tuberculosis (TB). A chest x-ray revealed clear lung fields and a normal mediastinal outline, with no indication of previous or current TB infection. A tuberculin skin test (TST) produced 12 mm of transverse induration. A QuantiFERON-TB Gold test (Cellestis International, Melbourne, Vic) was positive. As the TST and QuantiFERON-TB Gold test results were more in keeping with TB than sarcoidosis, the patient was treated for primary hepatic TB with quadruple therapy (isoniazid, rifampicin, pyrazinamide and ethambutol). Her clinical condition improved dramatically within a month of starting therapy, with a marked reduction in her hepatomegaly and normalisation of liver biochemistry.

A retrospective polymerase chain reaction on the paraffin embedded tissue from the liver biopsy confirmed the presence of active TB within the liver specimens. Five months after completing the 9-month course of antituberculosis therapy, she was well and had recently become pregnant.



A: *Low-power view of a needle core biopsy of the liver showing multiple non-caseating granulomas (arrows) involving portal tracts and lobular parenchyma. (haematoxylin and eosin stain; original magnification, × 4)*



B: *High-power view of non-caseating granuloma, including a multinucleated giant cell (arrow). (haematoxylin and eosin stain; original magnification, × 20).* ◆

Granulomatous hepatitis is an uncommon condition with a lengthy list of possible causes,[1] as shown in Box 1. In our patient, the biopsy did not show bile duct destruction characteristic of primary biliary cirrhosis, or any evidence of malignancy. The patient was not taking any drugs which could cause granulomatous hepatitis. The pathology laboratory report suggested the diagnosis was sarcoidosis, and, of the infections that can cause granulomatous hepatitis, tuberculosis (TB) is the most common. Hence, although the differential diagnosis is long, the main clinical decision related to the ability to diagnose or exclude TB. If a patient with hepatic TB has corticosteroid therapy for erroneously diagnosed sarcoidosis, the consequences may be catastrophic. Active TB most typically presents with pulmonary symptoms, and the diagnosis can usually be made provided smears and cultures for mycobacteria are obtained. However, if a patient presents more atypically, as did our patient, clinicians may initially not suspect TB as the diagnosis.[2]

Tests used for the diagnosis of TB can be divided into two categories: the detection of a cell-mediated immune response to *Mycobacterium tuberculosis* (tuberculin skin test [TST] and QuantiFERON-TB Gold), and the detection of *M. tuberculosis* itself (by culture or polymerase chain reaction [PCR]).

The TST is often falsely negative in immunosuppressed patients, and can give false-positive results if the patient has had previous BCG vaccination[3] or infection with non-tuberculous types of mycobacteria. QuantiFERON-TB Gold is more specific for TB,[4] but its sensitivity is poor, especially with immunosuppression.[5] Both of these tests can be falsely negative in up to 20% of patients

1 Causes of granulomatous hepatitis

- Autoimmune
  - Sarcoidosis
  - Primary biliary cirrhosis
- Systemic infections
  - Mycobacterial — tuberculosis
  - Fungal — cryptococcosis
  - Rickettsial — Q fever
  - Zoonotic — brucellosis
- Malignancy
  - Hodgkin's disease
  - Non-Hodgkin's lymphoma
  - Renal cell carcinoma
- Drugs
  - Allopurinol
  - Sulphur drugs
  - Quinidine
  - Other drugs
- Idiopathic ◆

with active TB, and neither the TST nor the QuantiFERON-TB Gold test can distinguish between current, latent and previous (treated) infection.

The only way to definitively diagnose active TB infection is by culturing the organism, or by detecting its nucleic acid sequence by PCR amplification from tissue or fluid samples. If active disease is suspected, specimens should be cultured for *M. tuberculosis* whenever possible, as a positive result confirms the diagnosis and allows drug sensitivity tests to be performed. While the diagnosis of active TB can be confirmed by PCR, this is not necessarily as sensitive as culture, and does not allow drug sensitivity testing.[6]

In our patient, the mycobacterium was confined to the liver, which was unusual. It is far more common to have TB involvement of the liver in disseminated TB.[7] Ideally, the liver biopsy should have been sent for culture in a TB medium, but we did not suspect TB initially. Once fixed in formalin and paraffin, the tissue cannot be cultured, but PCR of *M. tuberculosis* DNA can still be performed on the specimen and may yield a diagnosis.[8]

Histological examination of liver tissue provides crucial information in the differential diagnosis of hepatic granulomas. While caseous necrosis is characteristic of TB infection, it is not always present and its absence cannot be used to exclude TB.[7] Also, as it is often difficult to detect the presence of acid-fast bacilli (AFB) within the granulomas, the absence of AFB cannot be used to exclude TB either.[9]

Lessons from practice

- It is critical to be certain that the cause of granulomatous hepatitis is not tuberculosis (TB) before commencing immunosuppressive medication.
- TB remains easy to diagnose if mycobacteria can be detected, but active TB is very difficult to exclude if cultures are negative or not performed.
- Risk of TB is determined by patient's country of birth and duration of time spent there before migration.[13]
- If TB cannot be excluded, a trial of antituberculosis therapy may be warranted. ◆

In Australia, the incidence of TB is six per 100 000 per year,[10] compared with the incidence of sarcoidosis, which is estimated at 20 per 100 000 per year worldwide;[11] sarcoidosis is thus the more likely cause of hepatic granulomas in Australian-born patients. However, the incidence of TB in the Philippines is 291 per 100 000 per year,[12] making TB the far more likely cause of hepatic granulomas in our Filipino-born patient.

We believe that if the diagnosis of TB cannot be excluded, and the patient has risk factors for TB, it is appropriate to initiate antituberculosis therapy. However, clinicians should not make this treatment decision lightly, because antituberculosis drugs have a significant side-effect profile.

Competing interests

None identified.

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