

ORIGINAL ARTICLE

The nodular form of hepatic tuberculosis: a review with five additional new cases

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Background: Tuberculosis presenting as an isolated liver tumour, without active pulmonary or miliary tuberculosis, or other clinical evidence of tuberculosis, is distinctly rare. A greater awareness of this rare clinical entity may prevent needless surgical intervention.

Aims: To help characterise this distinctly rare presentation of tuberculosis, five new cases are presented, together with a review of the world literature. The clinical, laboratory, radiological, and pathological features of these patients are described.

Methods: Polymerase chain reaction (PCR) assay of the liver tissue was carried out in all cases to confirm an aetiological diagnosis of *Mycobacterium tuberculosis* infection.

Results: All five patients (44-71 years old; two women, three men) underwent surgery, and had a preoperative diagnosis of malignant hepatic neoplasm and a postoperative histological diagnosis of chronic granulomatous inflammation, suggestive of tuberculosis. None of them had a known previous history of tuberculosis. All of them were positive for *M tuberculosis* by PCR analysis of the liver tissue.

Conclusions: This report illustrates the difficulty in reaching a correct preoperative diagnosis. It is usually unsuspected and confused with primary or metastatic carcinoma of the liver, especially when it coexists with other malignancies. A high index of suspicion is required for diagnosis, which can be made only by histological and bacteriological studies, and PCR analysis.

Hepatic tuberculosis is usually associated with active pulmonary or miliary tuberculosis, but rarely localises as a liver tumour mass. In 1952, Eisenach *et al* reviewed the world literature and found 80 reported cases of hepatic tuberculosis, often with disseminated tuberculosis.¹ However, Oliva *et al* focused their review on 23 local hepatic tuberculomas in 1990,² and illustrated the difficulty in reaching the correct diagnosis without histology and bacteriological studies.

"Recently, the polymerase chain reaction has been used for the detection of *Mycobacterium tuberculosis* DNA"

Although tuberculosis has become less common because of the eradication of the bovine strain of mycobacterium from cattle, the pasteurisation of milk, and the advent of effective chemotherapy,³ there has been a recent increase in reported cases, and the disease is seen mainly among the elderly of the urban poor and in immunocompromised patients. Particularly in AIDS epidemic or lower socioeconomic conditions, there should be a high index of suspicion for the diagnosis of extrapulmonary tuberculosis.

In the past, histological and bacteriological evidence of tuberculosis has been the major diagnostic tool, but the frequency of positive smears and cultures is low.⁴ Recently, the polymerase chain reaction (PCR) has been used for the detection of *Mycobacterium tuberculosis* DNA, and at least 57% of hepatic granulomas caused by tuberculosis gave positive PCR test results.⁵ In our study, we have reviewed the clinical and pathological features of local hepatic tuberculosis and have carried out PCR analysis in the final diagnosis of *M tuberculosis*.

MATERIALS AND METHODS

Case selection

We identified 31 cases of hepatic granulomatous inflammation from the files of the department of pathology, Chang

Gung Memorial Hospital at Kaohsiung, Taiwan from 1987 to 2001. Among them, we identified five patients in whom a liver nodule or mass was identified on imaging studies. Clinical data were obtained from medical records that were reviewed to note the following: (1) age and sex, (2) presenting symptoms, (3) appearance of the hepatic lesion, (4) evidence of associated pulmonary disease on chest x ray, (5) sputum analysis by smear and culture for the presence of acid fast bacilli (AFB), (6) evidence of coexisting systemic diseases.

Histopathological review

The pathological reports and the haematoxylin and eosin stained histological slides of the liver tissue of these five cases were reviewed. In all patients, a Ziehl-Neelsen stain for AFB was also performed.

PCR assay

The tissue specimens previously fixed with formaldehyde and embedded in paraffin wax were cut into 5 µm sections. The tissues were immersed and digested in 1 ml of 5% Chelex (chelatin resin; Sigma, St Louis, Missouri, USA), heated to 100°C for 15-20 minutes, and then centrifuged at 20 000 ×g for five minutes. The supernatant was treated with phenol, phenol/chloroform, and chloroform and then precipitated with 10 mg/ml glycogen, 3N sodium acetate, and 1 ml 100% ethanol; after 25 minutes at -70°C, the supernatant was centrifuged at 20 000 ×g for 30 minutes at 4°C. The fluid was discarded and the DNA pellet was dried. The final extracted DNA was resuspended in 50 µl Tris buffer at 65°C for two hours and used for PCR amplification, as described below. Mock extractions of buffer were performed and amplified to ensure that no contamination occurred.

Abbreviations: AFB, acid fast bacilli; ALP, alkaline phosphatase; CT, computed tomography; PCR, polymerase chain reaction

The nucleotide sequences, corresponding to the mycobacterial insertion of IS6110, previously described by Eisenach *et al*,^{6,7} was a DNA sequence of 123 bp. In brief, a 50 µl volume of PCR reaction solution was prepared containing 26.5 µl Master mixture (Taq polymerase, deoxynucleotide, triphosphate, and MgCl₂ buffer), 2 µl of each primer (5'CCTGCGGCGTAGGCGTCGG 3' and 5' CTCGTCCAGCCGCTTCGG 3'), 4.5 µl water, 10 µl specimen DNA, and 5.0 µl glycerol. The final volume was 50 µl. The amplification was carried out in a DNA thermal cycler (PCR system 9600; GeneAmp, Perkin Elmer Cetus, Wiltom, Connecticut, USA). The thermal cycling programmes comprised an initial incubation at 95°C for three minutes, followed by 30 cycles of denaturation at 94°C for one minute, annealing of primers at 68°C for one minute, and primer extension at 72°C for one minute. A final extension step was performed at 72°C for seven minutes and hold at 4°C. The product was analysed by electrophoresis on 2% agarose gels. The DNA was stained with ethidium bromide and photographed on a 312 nm ultraviolet transilluminator.

RESULTS

Clinical features

Table 1 summarises the main clinical features of these patients. The age ranged from 44 to 71 years (mean, 60.4 years). There were three men and two women. The pertinent symptoms of patients 1 and 5 were epigastralgia, with upper gastrointestinal bleeding also occurring in patient 5. Patient 2 had general malaise and body weight loss. Patients 3 and 4 were suffering from gastric cancer. Laboratory investigations showed that all patients except patient 4 showed raised alkaline phosphatase (ALP) values, with a range of 67 to 939 U/litre (normal range, 28–94 U/litre). Serum aspartate aminotransferase (normal range, 0–37 U/litre) and alanine aminotransferase (normal range, 0–40 U/litre) were normal, except in patient 3, who had mildly raised values. The chest x rays of all patients were normal, except for patient 5, in whom a 3 cm faint nodular density in the right lower lobe was noted, although this was not seen in the subsequent chest computed tomography (CT) scans. The CT scans of the hepatic lesions of patients 1 and 5 revealed left 13.0 × 8.0 × 7.0 cm and 12.0 × 8.7 × 5.5 cm tumours, respectively, with prominent calcification (fig 1). Ultrasonography revealed a hyperechoic mass, measuring 5.0 × 4.0 × 2.0 cm, over the left lobe of the liver in patient 2. In patient 4, ultrasonography showed multiple, small nodules scattered diffusely throughout the liver at post-operative follow up after gastric cancer surgery. A solitary 2 cm mass in hepatic segment IV of patient 3 was incidentally found during surgery for gastric cancer. The presumptive diagnosis of all cases was malignant or metastatic tumour. During surgery, other lesions in the lymph node, omentum, and spleen of patient 1; mesentery of patient 5; and peritoneal implantation of patient 2 were noted.

None of our five patients had a previous history of tuberculosis, diabetes, or human immunodeficiency virus infection or other causes of immunosuppression.

Gross findings

The gross photography was only available in patients 1 and 5. Both of them showed an irregularly shaped, solid, lobulated mass with yellowish to tan discolouration (fig 2). No stellate nodule was found in the liver.

Histological and PCR findings

Microscopic examination showed that all cases except patient 3 had multiple granulomas, coalesced into a conglomerate tubercle with central caseation. Many epithelioid granulomas, with Langerhans giant cells forming early non-caseation

Table 1 Hepatic tuberculosis presenting as liver tumour

Patient	Age/Sex	Gross involvement of liver	Tumour size (cm)	Site	Symptom and sign	Chest x ray	Coexisting disease	AST/ALT (U/l)	ALP (U/l)	AFB liver	AFB sputum	Surgery	Anti-TB Tx
1	44/M	Solitary	13.5	Left lobe	Epigastric pain	N	None	17/15	92	(+)	ND	Lobectomy	+
2	57/M	Solitary	5.0	Left lobe	Malaise, BW loss	N	None	43/–	185	(–)	ND	Wedge resection	+
3	63/M	Solitary	2.0	Seg. IV		N	Gastric cancer	188/124	939	(–)	ND	Wedge biopsy	Expired
4	67/F	Multiple	Small	Both lobes		N	Gastric cancer	19/–	69	(–)	(–)	Biopsy	–
5	71/F	Solitary	12.0	Left lobe	Epigastric pain	Nodular density, RLL	UGI bleeding	24/9	133	(–)	ND	Left hepatectomy	+

AFB, acid fast bacillus; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, body weight; N, negative; ND, not done; RLL, right lower lobe; TB, tuberculosis; Tx, transplant; UGI, upper gastrointestinal tract.

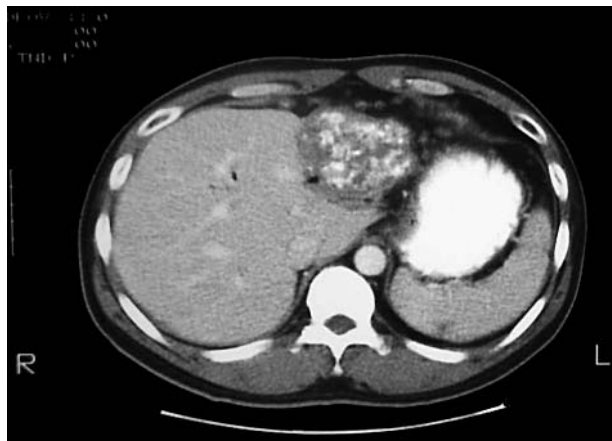


Figure 1 Abdominal computed tomography of case 1. A hypodense 13.0 × 8.0 × 7.0 cm mass in the left lobe of the liver with calcification.

tubercles, were noted around the conglomerate tubercle (fig 3). Dispersed foci of calcification in the regions of central caseous necrosis were also found in patients 1 and 5, consistent with the imaging studies. Patient 3 mainly exhibited caseation with peripheral lymphocyte, histiocyte, and Langerhans giant cell cuffing, and to a lesser extent, grouped granulomas coalescing into conglomerate tubercles. In all cases, the surrounding liver parenchyma revealed lymphocytic infiltration in the portal tracts. Ziehl-Neelsen staining of the paraffin wax embedded sections identified AFB in patient 1. In contrast, all five cases were positive for *M tuberculosis* by PCR analysis of the liver tissue, which identified a 123 bp DNA sequence, corresponding to the IS6110 insertion, in the electrophoresis agarose gel (fig 4).

DISCUSSION

Tuberculosis can affect the liver in many ways. Hepatic tuberculosis has been categorised as miliary, local, and biliary in the literature. The miliary form of spreading is the most common, and is thought to involve haematogenous dissemination via the hepatic artery.⁸⁻¹¹ In 1973, Gelb *et al* reported 30 patients who died of miliary tuberculosis; 27 had liver involvement at necropsy.¹² Some believe that hepatic tubercles are present in all cases of miliary tuberculosis.¹³⁻¹⁴ Active pulmonary tuberculosis might be present or not. Because of

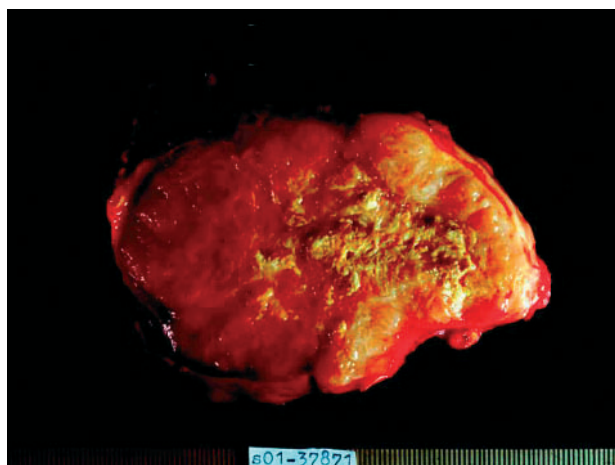


Figure 2 The cut surface of the liver in patient 5. The liver revealed a solid, lobulated mass with yellow to tan discoloration, and central calcification.

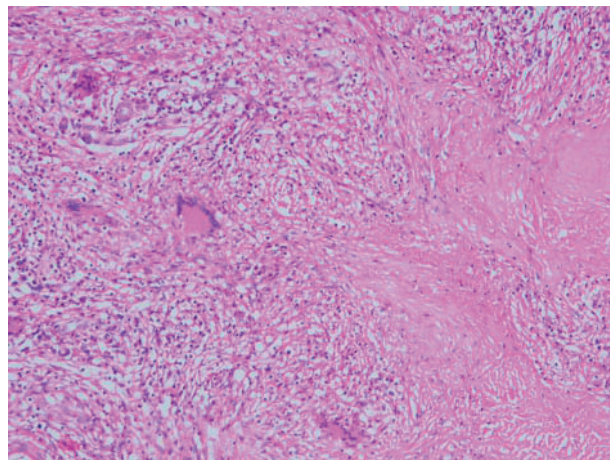


Figure 3 Photomicrograph showing the histological findings in case 5. The conglomerate tubercle comprises Langerhans giant cells, epithelioid cells, and lymphocytes.

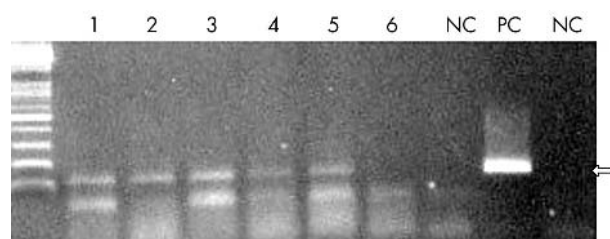


Figure 4 Polymerase chain reaction (PCR) analysis of all five cases. On electrophoresis of the PCR products a 123 bp DNA sequence (arrow), corresponding to the IS6110 insertion, was identified in the agarose gel. Lanes 1 to 5, cases 1 to 5, respectively; lane 6, normal liver; NC, negative control; PC, positive control.

low oxygen tension in the liver, which is unfavourable for mycobacterial growth,¹⁵ the local form of hepatic tuberculosis with no clinical extrapulmonary manifestations is relatively rare. It is often found in the portal areas and may reach the liver by the portal vein.² It may involve the liver diffusely or focally as space occupied nodular lesions. Terry and Gunnar reported 12 cases of diffuse hepatic involvement without evidence of tubercles elsewhere.¹⁶ The biliary form, characterised by obstructive jaundice from enlarged lymph nodes compressing the common bile hepatic duct, is the least frequently found.¹⁵⁻¹⁷ Unlike obstructive jaundice of the biliary form, the clinical presentation of local hepatic tuberculosis has no pathognomonic feature. Abdominal pain, fever, and body weight loss are most commonly found.²⁻⁸⁻¹⁸ The clinical sign also lacks consistency. Hepatomegaly is frequently found. Biochemical studies reveal no consistent findings, although a raised ALP concentration is the most frequently noted abnormality.²⁻¹⁹⁻²⁴ Other biochemical findings include variable degrees of anaemia, hypoalbuminaemia, and hyponatraemia.

Imaging studies frequently present a diagnostic challenge, especially in the nodular form. The CT appearance varies from a hypodense mass, with or without rim enhancement after contrast, to a heterogeneous density of the necrotic centre of bull's eye calcification.²⁵⁻²⁶ Ultrasonography may reveal hypoechoic or rarely hyperechoic nodules.²⁵⁻²⁷⁻²⁸ Abnormal lung lesions, identified in the chest x ray, were found in between 10% and 86% of patients.¹⁸⁻²⁹⁻³⁰ Thus, hepatic tuberculosis cannot be excluded by the absence of pulmonary

disease. Most lesions of hepatic tuberculosis are small.³¹ Giant nodular lesions greater than 3 cm in diameter are distinctly rare.^{26 32-34} So called macronodular tuberculoma was first described by Bristowe *et al* in 1858.^{29 34} The term "pseudotumour" was also used by Debray *et al*.³⁴⁻³⁶ Apart from single solitary and space occupying lesions, multiple nodules or abscesses have also been reported.^{2 34} Such polymorphous appearance mimicking primary or metastatic malignancy makes diagnosis difficult before pathological examination.

Microscopically, hepatic tuberculoma encompasses a wide spectrum of morphology. It may be a classic caseating granuloma or only appear as a non-caseous epithelial granuloma or caseous necrosis. Hersch noted that tuberculous granulomas in the miliary or diffuse form tend to be located inside the hepatic lobules, in contrast to the local forms, which predominately occur in the portal regions.³⁷ Zipser *et al* speculated that higher oxygen tension in the local form might promote conglomerate tubercle formation and subsequent caseation.³⁴ Other non-specific microscopic findings include Kupffer cell hyperplasia, focal hepatocytic necrosis with round cell infiltration, and portal inflammation. Smith *et al* divided histopathological morphology into reactive, hyporeactive, and non-reactive, according to an increasing degree of caseous necrosis and number of AFB,³⁸ which are believed to be associated with individual cellular immunity. AFB is most easily found in caseous necrosis. The absence of AFB should not detract from the diagnosis, particularly in endemic areas of tuberculosis. However, if infection with a mycobacterial bacterium cannot be proved, other diseases, such as primary biliary cirrhosis, Crohn's disease, chronic active hepatitis, drug hypersensitivity, and extrahepatic biliary obstruction, should be ruled out.³⁹

In fact, tuberculosis is responsible for a high proportion of hepatic granulomas.^{40 41} The problem is the low frequency of positive acid fast stains and cultures, which vary from 0% to 45% and 10% to 60%, respectively.^{4 18 29 30 42} This was the case in our series, where AFB was demonstrated in only one of the five cases by acid fast stains. Many clinicians accept good clinical response to anti-tuberculosis drugs as evidence of tuberculosis. However, this approach may allow patients without tuberculosis to suffer from the toxic effects of the drug. Today, the most powerful diagnostic tool, PCR enables the rapid identification of *M tuberculosis*. PCR is a useful tool in the diagnosis of hepatic tuberculosis. Diaz *et al* found that at least 57% of hepatic granulomas caused by tuberculosis gave positive PCR test results.⁵ In the same study, they showed positive PCR results in all 11 biopsy samples from which a positive culture for *M tuberculosis* was obtained.⁵ Their result confirmed those obtained by Popper *et al* and Ghossein *et al*.^{43 44} Similarly, in our present study, positive PCR results were obtained in all five cases, whereas mycobacterial culture was not available, because the diagnosis was not suspected preoperatively. Although a relatively high rate of false negative results has been noted, this might be related to the paucity of mycobacteria in the tissue. However, the sensitivity of PCR is still much higher than that of culture.⁵ Another advantage is that PCR analysis can distinguish *M tuberculosis* from other species of mycobacterium.

"The granulomas found in patients with AIDS are microscopically different from those in patients without AIDS: they are typically small and poorly formed, without evident lymphocyte cuffing, multinucleated giant cells, caseation, or hyalinisation"

In patients with AIDS, hepatological consultation is usually requested to evaluate unexplained fever, particularly with hepatomegaly or abnormal liver biochemical tests. Because of

Take home messages

- Tuberculosis presenting as an isolated tumour without clinical evidence of tuberculosis is difficult to diagnose preoperatively, and is usually unsuspected or confused with primary or metastatic carcinoma of the liver
- Mycobacterial culture is often performed but positivity for the acid fast stain is low
- A high index of suspicion is required for diagnosis, which until recently could only be confirmed by histological and bacteriological studies
- Polymerase chain reaction analysis is a useful, additional test to confirm infection with *Mycobacterium tuberculosis* and was positive in all five patients tested

the prominent suppression of cell mediated immunity, multiple opportunistic infections may develop. The most commonly diagnosed hepatic infection in patients with AIDS is *Mycobacterium avium* intracellular, followed by *M tuberculosis*.^{1 45-52} The clinical presentation of hepatic tuberculosis in patients with and without AIDS is quite different.⁵³ ALP is also the most common biochemical abnormality in both patient groups.^{2 19 20 22-24} The granulomas found in patients with AIDS are microscopically different from those in patients without AIDS: they are typically small and poorly formed, without evident lymphocyte cuffing, multinucleated giant cells, caseation, or hyalinisation.^{1 46-52} Acid fast staining often reveals that the granulomas contain numerous bacilli that are highly suggestive of AIDS associated mycobacteria.⁵⁴ Thus, the granulomatous response may be absent in patients with AIDS, so that all tissue specimens must be acid fast stained and carefully searched.

None of our patients had AIDS, and epigastralgia, general malaise, and body weight loss were the main presenting symptoms. An incidental finding of hepatic nodule was noted in two patients (cases 3 and 4) with gastric cancer. Most of the ALP values were raised. Cases 1, 2, and 5 should be categorised as miliary hepatic tuberculosis with macronodule formation in the liver. Cases 3 and 4 revealed restricted lesions in the liver belonging to the localised form. Microscopically, the granuloma location was not useful to distinguish the miliary form from localised tuberculoma. Mycobacterial bacilli were demonstrated by the acid fast stain only in case 1, but *M tuberculosis* was later proved to be the aetiological agent in all cases by PCR.

In conclusion, our report illustrates the difficulty in reaching a correct preoperative diagnosis of nodular hepatic tuberculosis that presents as space occupying lesions. It is usually unsuspected and confused with primary or metastatic carcinoma of the liver, especially when it coexists with other malignancies, as demonstrated in two of our cases with gastric cancer. Mycobacterial culture is usually carried out but the positive rate of the acid fast stain is low. A high index of suspicion is required for diagnosis, which could be made only by histology and PCR analysis. PCR is highly sensitive and is a valuable tool for aetiological confirmation.

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