Original Article

Computed tomography imaging characteristics of paradoxical reactions in perihepatic and hepatic tuberculosis

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Background: Hepatic and perihepatic tuberculosis (TB) are rare forms of extrapulmonary TB. Paradoxical reactions, characterized by the enlargement of existing lesions or the appearance of new lesions during anti-TB treatment, are uncommon in hepatic TB. This study aimed to retrospectively analyze the computed tomography (CT) imaging characteristics of paradoxical reactions in hepatic and perihepatic TB to enhance the understanding of this condition.

Methods: We conducted a retrospective review of the data of patients diagnosed with perihepatic and hepatic TB at the Kunming Third People's Hospital from January 2020 to June 2024. We selected patients with follow-up CT imaging showing paradoxical reactions, and we summarized their initial CT findings, paradoxical reaction CT manifestations, and follow-up CT presentations.

Results: The data of 37 patients with perihepatic and hepatic TB and CT follow-up imaging were collected. Of the 37 patients, 14 (37.8%) exhibited paradoxical reactions characterized by an enlargement of existing lesions or the appearance of new lesions on review. Among these 14 patients, 7 were male, 7 were female, with ages ranging from 17 to 46 years (median age: 23 years). Twelve patients had concurrent pulmonary TB, and 13 patients had other extrapulmonary TB. Thirteen patients tested positive for TB infection by interferon-gamma release assay, and eight had positive etiological results. Twelve patients showed a decrease in CD4+ T-cell counts. The time to the paradoxical reaction onset after initial diagnosis ranged from 13 to 183 days (median time: 82 days). The initial CT presentations of these 14 patients included 11 cases of perihepatic peritoneum/hepatic capsule linear or nodular thickening (capsular type), and three cases of combined perihepatic peritoneum/hepatic capsule linear or nodular thickening with hepatic parenchymal lesions (mixed type). Capsular-type paradoxical reactions manifested as new or enlarged nodules of the perihepatic peritoneum/hepatic capsule and intrahepatic lesions, with marked ring enhancement on enhanced scans. Mixed-type paradoxical reactions showed significant enlargement of perihepatic peritoneum/hepatic capsule lesions and intrahepatic lesions, with the enhanced scans showing higher ring enhancement than that in the initial presentation. Among the 12 patients with long-term follow-up data, lesion improvement began at 6 to 20 months (median time: 12 months). CT imaging showed gradual lesion size reduction, decreased ring enhancement density, an absence of ring enhancement, and lesion calcification.

Conclusions: During anti-TB treatment, perihepatic and hepatic TB patients can show paradoxical reactions, which often present as ring enhancement. After treatment, these paradoxical reaction lesions can show improvement. CT-enhanced scans have diagnostic value in the occurrence and progression of perihepatic and hepatic TB.

Keywords: Liver; peritoneal cavity; tomography; tuberculosis (TB); X-ray computed tomography

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Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) infection, remains a significant global public health concern. According to the 2023 Global Tuberculosis Report of the World Health Organization, there were 10.6 million new cases of TB worldwide in 2022, resulting in 1.3 million deaths (1). It was estimated that China, a country with a high TB burden, had 748,000 new cases and 30,000 deaths (1). TB primarily affects the lungs, but it can involve multiple systems and organs throughout the body (2). When the infection occurs outside the lungs, it is referred to as extrapulmonary TB. Extrapulmonary TB is associated with a lower risk of person-to-person transmission than pulmonary TB; however, its incidence remains significant (3). In developed countries, it accounts for approximately 20% to 50% of all TB cases (4-6). In China, where the prevalence of TB is high, extrapulmonary TB without pulmonary involvement constitutes 32% of all reported TB cases (7).

Hepatic TB, a rare form of extrapulmonary TB, accounts for approximately 0.3% of extrapulmonary cases (8). More than half of patients with hepatic TB exhibit no obvious clinical symptoms, making the condition prone to misdiagnosis (9). A paradoxical reaction refers to the worsening of existing lesions or the development of new lesions during anti-TB therapy (10). Reports of paradoxical reactions in hepatic TB are rare (11-13). The pathogenesis of hepatic TB is generally thought to involve the formation of lesions in the hepatic parenchyma when *M. tuberculosis* spreads to the liver through intrahepatic blood vessels (14). In terms of imaging, hepatic TB is classified into various types, including miliary, macronodular, hepatic capsular, and tuberculous cholangitis (15). However, research on imaging changes in hepatic TB during anti-TB therapy is limited.

In clinical practice, it has been observed that during treatment, some patients with tuberculous peritonitis may experience paradoxical reactions, involving both the hepatic capsule and, in some cases, the hepatic parenchyma. However, the precise pathological processes and disease progression remain unclear. Due to the anatomical proximity of the perihepatic peritoneum and hepatic capsule, distinguishing between these structures on imaging when lesions are present can be challenging. Therefore, this study conducted an analysis of the perihepatic peritoneum and hepatic capsule and presented the clinical features and computed tomography (CT) imaging changes of 14 cases of perihepatic and hepatic TB paradoxical reactions during anti-TB therapy to improve the understanding of this condition. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2265/rc).

Methods

Study participants

A total of 75 patients initially diagnosed with perihepatic and hepatic TB through etiology, pathology, and clinical treatment improvement were consecutively identified between January 2020 and June 2024 at Kunming Third People's Hospital. Following the exclusion of 38 patients without follow-up CT imaging data, 37 patients with available follow-up CT imaging data were included in the study. Among them, 14 patients (37.8%) exhibited either an enlargement of existing lesions or the emergence of new lesions indicative of a paradoxical reaction during follow-up imaging. Of the 14 patients, 7 were male and 7 were female, with ages ranging from 17 to 46 years (median age: 23 years). Twelve patients had concurrent pulmonary TB, and 13 patients had other extrapulmonary TB. Thirteen patients tested positive for TB infection by interferon-gamma release assay, and eight had positive etiological results.

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by the Ethics Committee of the Kunming Third People's Hospital (No. KSLL20230711001). All participants provided written informed consent for their involvement in the study. If participants were under the age of 18 years, informed consent was also obtained from their parents or legal guardians.

CT imaging examination

The multi-slice spiral CT scanners were applied in the scanning process, with a tube voltage of 120 kV and the tube current adjusted using an automatic milliampere technique. The scanning range for the abdomen extended from the diaphragm apex to the pubic symphysis. Both plain and contrast-enhanced abdominal scans were conducted. For enhanced scanning, the contrast agent was administered as a bolus injection through the median cubital vein at a rate of 2.5–3.0 mL/s, with a contrast dose of 390 mgI/kg. The enhanced scanning included arterial, portal venous, and delayed phases. The arterial phase occurred 25–30 seconds after contrast administration, the portal venous phase 60–70 seconds after injection, and the delayed phase 120–150 seconds post-injection. The slice thickness for both the plain and enhanced scans was 5 mm, with a reconstructed slice thickness of 0.5–0.625 mm.

CT imaging analysis

The initial abdominal CT examinations and follow-up scans of 14 patients were analyzed, focusing on hepatic capsule or adjacent peritoneal thickening, perihepatic space lesions, and intrahepatic parenchymal lesions. Both the initial CT imaging features and changes observed in the follow-up imaging were recorded. Patient imaging data were retrieved from the hospital's Picture Archiving and Communication System (PACS) software platform, and the CT images were reviewed using Radiant Digital Imaging and Communications in Medicine (DICOM) Viewer for detailed analysis. The imaging manifestations were independently reviewed by two physicians with intermediate or higher professional titles and extensive experience in infectious disease imaging diagnosis, using a blinded method. In cases of disagreement between the interpretations of the two physicians, a third physician reviewed the images, and consensus was reached through joint consultation.

Results

For the 14 patients, the time from the initial CT imaging presentation to the appearance of a paradoxical reaction, characterized by the enlargement of perihepatic or intrahepatic lesions or the development of new lesions, ranged from 13 to 183 days (median time: 82 days). Among these patients, 12 had decreased $CD3^+$, $CD4^+$, and $CD8^+$ T cell counts.

The initial CT imaging findings included 11 cases of perihepatic peritoneum or hepatic capsule lesions (capsular type), and three cases of both perihepatic peritoneum or hepatic capsule lesions and hepatic parenchyma lesions (mixed type). Among the capsular-type cases, nine exhibited linear thickening with mild enhancement on enhanced scanning, while two exhibited linear thickening combined with nodular thickening, with ring enhancement of the nodular thickening on enhanced imaging. In the mixed-type cases, the perihepatic peritoneum or hepatic capsule lesions were similar to those observed in the capsular-type cases, while the intrahepatic lesions appeared as round, low-density shadows, demonstrating either no enhancement or mild ring enhancement on enhanced scanning.

Paradoxical reaction CT imaging findings: in the capsular type, paradoxical reaction was characterized by newly developed or enlarged nodules in the perihepatic peritoneum or hepatic capsule, as well as intrahepatic lesions, which displayed significant ring enhancement on contrast-enhanced scans. In the mixed type, there was significant enlargement of the perihepatic peritoneum or hepatic capsule lesions, along with the intrahepatic lesions, with a higher intensity of ring enhancement on the enhanced scanning compared to that on the initial imaging presentation.

CT imaging findings of improvement: among the 14 patients, 12 underwent abdominal follow-up CT imaging for over a year. The median time for lesion improvement was 12 months (range, 6–20 months). Follow-up CT scans revealed a gradual reduction in lesion size, reduced ring enhancement density, an absence of ring enhancement, or the appearance of lesion calcification (see *Figures 1-3*, and *Figure 4* for a depiction of the progression).

Discussion

Hepatic TB is classified as a component of disseminated TB. Its pathogenesis is generally understood to involve the dissemination of *M. tuberculosis*, which typically originates

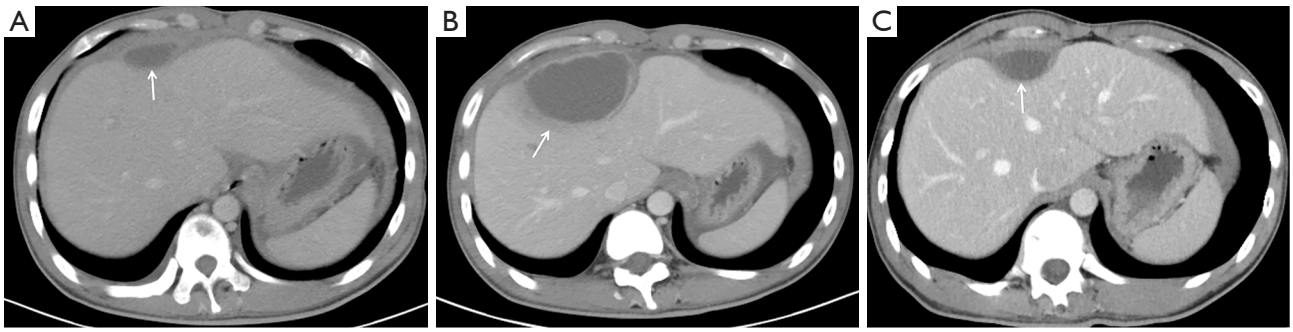

Figure 1 A 19-year-old male patient diagnosed with pulmonary, peritoneal, and hepatic tuberculosis, confirmed by a positive sputum culture for *Mycobacterium tuberculosis*. (A) An abdominal contrast-enhanced computed tomography scan in the portal venous phase, conducted on January 19, 2021, revealed substantial thickening of the perihepatic peritoneum and hepatic capsule, along with visible fusiform ring-enhancing lesions (as indicated by the white arrow), indicative of a capsular pattern. (B) A follow-up computed tomography scan, conducted on May 11, 2021, revealed further thickening and enhancement of the perihepatic peritoneum and hepatic capsule. The fusiform ring-enhancing lesions had enlarged significantly, with indistinct boundaries between the hepatic parenchyma and the lesions (as indicated by the white arrow), which was consistent with a paradoxical reaction. (C) A subsequent computed tomography scan, conducted on February 18, 2022, demonstrated a reduction in the size of the fusiform ring-enhancing lesions in the perihepatic peritoneum and hepatic capsule (as indicated by the white arrow).

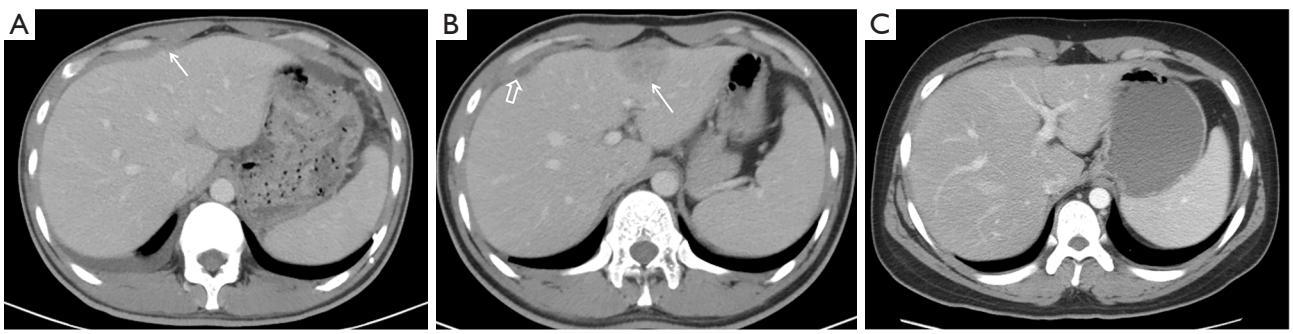

Figure 2 A 23-year-old male patient diagnosed with pulmonary, peritoneal, renal, and hepatic tuberculosis, confirmed by a positive sputum culture for *Mycobacterium tuberculosis*. (A) An abdominal contrast-enhanced computed tomography scan in the portal venous phase, conducted on August 20, 2020, revealed mild thickening of the perihepatic peritoneum and hepatic capsule (as indicated by the white arrow), indicative of a capsular pattern. (B) A follow-up computed tomography scan, conducted on November 30, 2020, revealed newly developed heterogeneously enhancing nodular lesions in the left hepatic lobe (as indicated by the white arrow) and newly-developed ring-enhancing nodules in the perihepatic peritoneum and hepatic capsule surrounding the right hepatic lobe (as indicated by the hollow white arrow), indicative of a paradoxical reaction. (C) A subsequent computed tomography scan, conducted on January 22, 2022, showed the complete resolution of the previously observed lesions.

in the lungs or gastrointestinal tract, to the liver via the hepatic artery or portal vein, resulting in the formation of lesions (14). In this study, 85.7% of the patients presented with concurrent pulmonary TB, and 92.9% with other forms of extrapulmonary TB. Isolated hepatic TB remains a rare occurrence. Notably, during the treatment of perihepatic peritoneal or hepatic capsule thickening, the appearance of intrahepatic lesions was observed, indicating that peritoneal or hepatic capsule TB may extend into the hepatic parenchyma, leading to hepatic parenchymal involvement.

Paradoxical reactions during TB treatment are reported in approximately 10–25% of human immunodeficiency virus (HIV)-negative individuals (16). The incidence

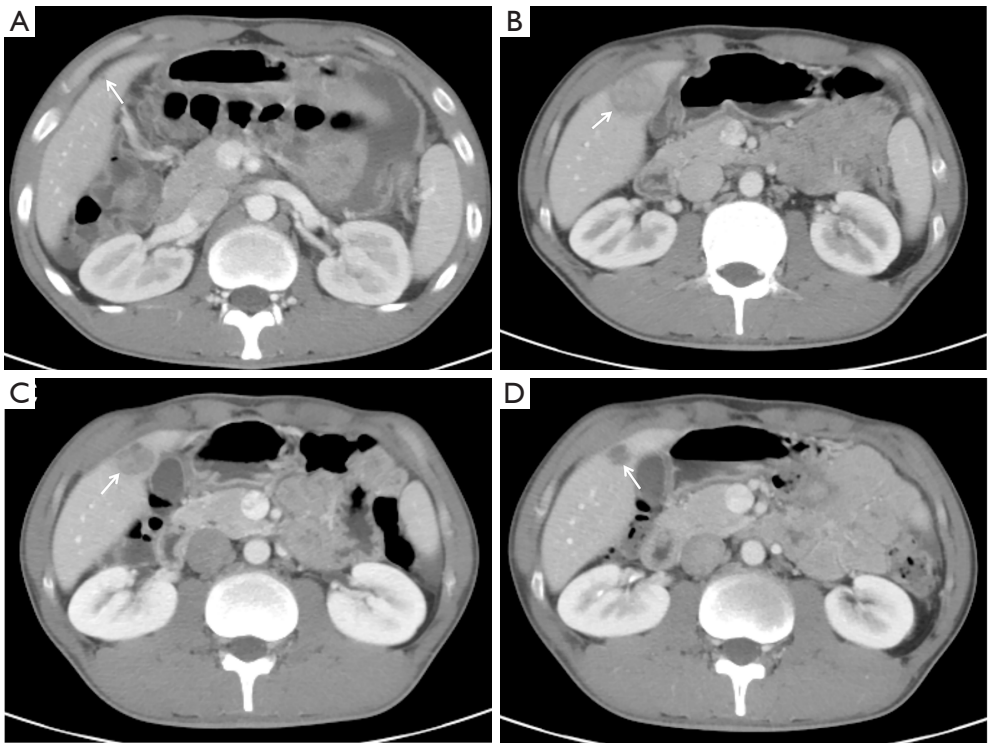

Figure 3 A 23-year-old male patient diagnosed with pulmonary and peritoneal tuberculosis. Both the *Mycobacterium tuberculosis* culture and molecular diagnostic tests were negative. A peritoneal biopsy from another hospital revealed chronic granulomatous inflammation with caseous necrosis. (A) An abdominal contrast-enhanced computed tomography scan in the portal venous phase, conducted on December 16, 2019, showed thickening and ring enhancement of the perihepatic peritoneum and hepatic capsule (not shown in the image), along with a small nodule in the lower segment of the right anterior lobe of the liver (as indicated by the white arrow). The initial computed tomography findings were classified as mixed type. (B) A follow-up computed tomography scan, conducted on March 10, 2020, revealed no significant changes in the thickening and ring enhancement of the perihepatic peritoneum and hepatic capsule (not depicted in the image), but the nodule in the lower segment of the right anterior lobe of the liver had significantly enlarged, and was accompanied by a thickening of the adjacent peritoneum and hepatic capsule (as indicated by the white arrow), indicative of a paradoxical reaction. (C) A subsequent computed tomography scan, conducted on May 26, 2020, showed a reduction in the size of the lesion in the lower segment of the right anterior lobe of the liver, but the thickening of the adjacent peritoneum and hepatic capsule persisted (as indicated by the white arrow). (D) A final follow-up computed tomography scan, conducted on December 9, 2020, showed a further reduction of the lesion in the lower segment of the right anterior lobe of the liver, and a decrease in the enhancement density (as indicated by the white arrow).

of paradoxical reaction is notably higher in cases of extrapulmonary TB (25%) than cases of pulmonary TB (2%), and the central nervous system and cervical lymph node are the most common sites affected (17). However, paradoxical reactions, specifically those involving hepatic TB, have been infrequently documented. In the current study, paradoxical reactions were observed in 37.8% of the patients, a higher proportion than previously reported (17), which may be due to the relatively small sample size of the study.

Paradoxical reactions occur within the first 1–4 months of TB treatment in over 60% of cases (18). In this study, the median time to the appearance of paradoxical reactions was 82 days. While this aligns with previous research, the accuracy of this finding might have been affected by the absence of clear abdominal symptoms in some of the patients and inconsistent follow-up imaging. A previous study noted that younger patients with TB may be at an increased risk of paradoxical reactions (19). Additionally, among patients infected with HIV, those with low $CD4^+$ T cell counts are more susceptible to such reactions (20). In the present study, the median age of the patients was

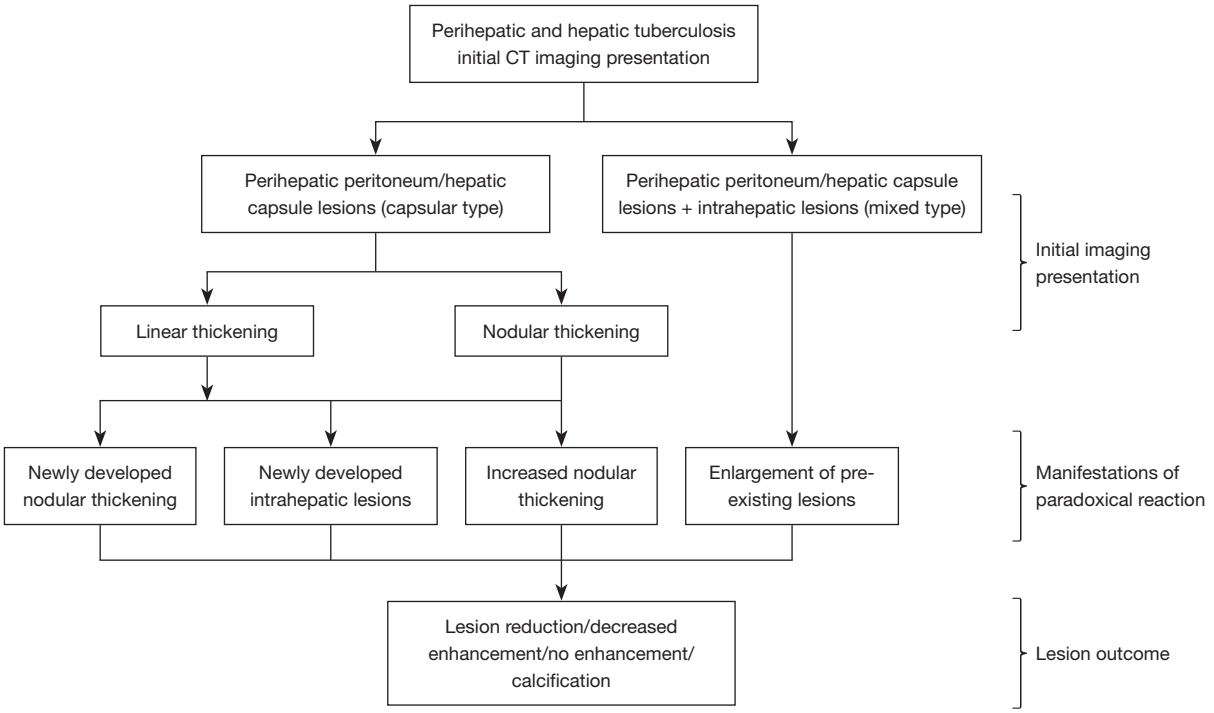

Figure 4 Computed tomography imaging manifestations of perihepatic and hepatic tuberculosis categorized based on the disease progression phase: initial presentation, paradoxical reaction, and outcome phase. CT, computed tomography.

23 years, and over 80% of the patients had decreased peripheral blood $CD4^+$ T cell counts. Thus, it is recommended that regular follow-up imaging examinations be prioritized for young patients with low $CD4^+$ T cell counts to ensure the early detection of paradoxical reactions.

The perihepatic space is anatomically situated between the perihepatic peritoneum and the hepatic capsule, and is a common site for the accumulation of intra-abdominal fluid. Previous imaging classifications of hepatic TB have not included the hepatic capsule or sub-capsular parenchymal lesions caused by paradoxical reactions associated with perihepatic peritoneal or perihepatic space lesions. Additionally, due to inflammation, distinguishing between the perihepatic peritoneum and hepatic capsule on CT imaging can be challenging. In this case series, a few patients exhibited enlargement of perihepatic peritoneal or hepatic capsule lesions that extended into the hepatic parenchyma during follow-up imaging, which provides an alternative hypothesis for the pathogenesis of hepatic TB.

CT imaging findings of hepatic TB, which may present as granulomas, granulomas with caseous necrosis, or liquefactive necrosis, are closely related to its underlying pathology (21). Tuberculous granulomas typically display mild enhancement on contrast-enhanced scans, while granulomas with caseous or liquefactive necrosis manifest as ring enhancement (15). In this study, the initial imaging findings included the thickening and mild enhancement of the perihepatic peritoneum or hepatic capsule. When paradoxical reactions occurred, they frequently manifested as the ring enhancement of lesions in the perihepatic peritoneum, hepatic capsule, or hepatic parenchyma. Presently, CT imaging cannot differentiate between caseous necrosis and liquefactive necrosis; thus, further research needs to be conducted to examine the imaging characteristics of these pathological manifestations, potentially in conjunction with surgical studies. During the follow-up, the paradoxical reaction lesions showed a gradual reduction in size and decreased enhancement with ongoing treatment, although the process was prolonged. The median time for lesion improvement in this study was 12 months, while the time to significant lesion reduction or near-disappearance was not statistically analyzed. The prolonged persistence of TB lesions presents challenges for both patients and healthcare providers. The role of interventional methods, such as surgical treatment, and the optimal timing of such interventions, remain topics that

require further examination to determine their potential benefits in the management of this disease.

In radiological differential diagnosis, hepatic TB lesions in the liver parenchyma should be distinguished from focal liver lesions. In regions with high prevalence of hepatitis B virus and hepatitis C virus infections, new parenchymal liver lesions that arise due to paradoxical reactions require careful differentiation from hepatocellular carcinoma due to their similar imaging characteristics (22). When radiological differentiation is challenging, it is necessary to integrate the patient's medical history, clinical presentation, and laboratory tests. New focal liver lesions may be indicative of hepatic TB, particularly for patients with pulmonary TB or other extrapulmonary TB.

Conclusions

Perihepatic peritoneum, hepatic capsule, and hepatic TB may undergo paradoxical reactions during TB treatment, which are characterized by the emergence of new lesions or the enlargement of pre-existing lesions. CT imaging, particularly enhanced scanning, frequently reveals ring enhancement. Following treatment, paradoxical reaction lesions may exhibit signs of improvement, such as a reduction in volume, decreased enhancement density, or the development of calcification.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-2265/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2265/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the Kunming Third People's Hospital (No. KSLL20230711001). All participants provided written informed consent for their involvement in the study. If participants were under the age of 18 years, informed consent was also obtained from their parents or legal guardians.

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