



Hepatic nontuberculous mycobacterial granulomas in patients with cancer mimicking metastases: an analysis of three cases

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Abstract: Hepatic granulomas caused by nontuberculous mycobacteria (NTM) are an uncommon, insidious, and indolent disease. Making an accurate diagnosis of a hepatic nontuberculous granuloma is challenging because of nonspecific clinical presentations and radiological appearances, especially in patients with a history of malignant tumors, as these lesions may mimic metastases and make a dilemma for decision-making in treatment. Herein, we report three cases of hepatic nontuberculous granulomas following operations for malignant tumors, including colon cancer, ovarian adenocarcinoma, and both rectal and renal carcinoma, respectively. Two patients presented with multiple hepatic lesions and the third had a solitary nodule in the liver. Computed tomography (CT) showed low attenuating nodules without early enhancement in the arterial phase but a slight peripheral enhancement in the portal venous phase after the intravenous administration of contrast agent. Magnetic resonance imaging (MRI) showed high signal intensity on T2-weighted image, rim enhancement in the venous phase and no contrast agent of Gd-EOB-DTPA uptake in the hepatobiliary phase. The biopsy was performed, and histopathological examinations revealed the chronic granulomas composed of epithelioid histiocytes, inflammatory cells, and Langhans giant cells. The results of nested polymerase chain reaction (PCR) were positive for NTM.

Keywords: Liver; granuloma; nontuberculous mycobacteria (NTM); *Mycobacterium tuberculosis* (MTB); malignant tumor

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Introduction

Hepatic granulomas can be observed in a variety of conditions, and the detection may indicate the first clue to an ongoing systemic disease. A hepatic granuloma is usually caused by *Mycobacterium tuberculosis* (MTB), rarely by nontuberculous mycobacteria (NTM) (1). The

term “nontuberculous mycobacteria” (NTM) generally refers to mycobacteria other than MTB complex and *M. Leprae* (2). NTM are emerging pathogens that can affect both immunocompromised and immunocompetent people (3). Like MTB infections, NTM infections can occur anywhere in the body. It is classified into four clinical syndromes: chronic pulmonary disease, lymphadenitis,

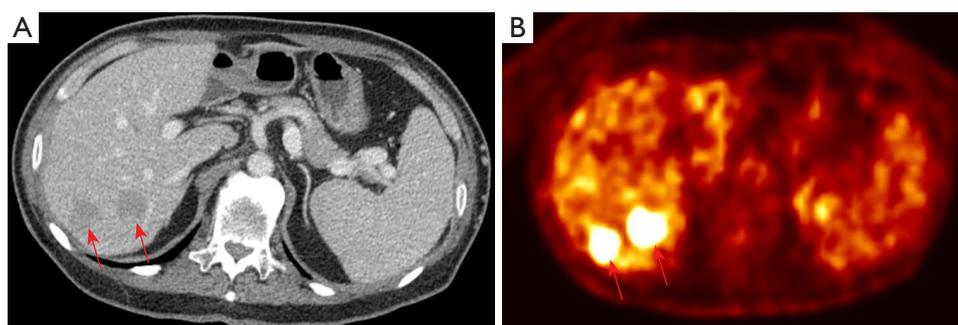


Figure 1 A 49-year-old male with a history of hemicolectomy for right ascending colon cancer. (A) Axial contrast-enhanced CT image in the portal venous phase shows two low attenuating nodules with slightly peripheral enhancement in the right lobe of the liver (arrows); (B) axial F-18 FDG PET-CT image shows two FDG avid lesions in the right lobe of the liver (arrows).

cutaneous disease, and disseminated disease (3,4). Hepatic nontuberculous infection can be a disseminated extrapulmonary expression of active NTM disease, with a tendency towards an increased incidence among people with underlying malignancy. Both tuberculous and nontuberculous infections of the liver in immunocompetent hosts are relatively rare, especially when they present as solitary or multiple nodules on imaging examinations, they are difficult to differentiate, frequently with misdiagnosis causing inappropriate therapy or delay in treatment (5-8). Herein, we describe three cases of hepatic granulomas caused by NTM infection occurring in patients with cancer, mimicking hepatic metastases on computed tomography (CT) and magnetic resonance imaging (MRI).

Case presentation

Case 1

A 49-year-old male reported to the hospital with multiple and various sizes of hypoechoic nodules in the right lobe of the liver during regular follow-up ultrasound surveillance after the operation. He had a personal history of ascending colon cancer and underwent right hemicolectomy half a year ago. The laboratory results of serum carbohydrate antigen-199 (2.7 ng/mL) and carcinoembryonic antigen (1.2 ng/mL) were all within normal limits. The other biochemical tests were nonspecific. Due to the findings of multiple hepatic nodules, subsequent CT examination was performed and demonstrated multiple, low attenuating nodules measuring 20–45 mm in size in S4–8 of the liver, no early enhancement in the arterial phase but slight peripheral enhancement in the portal venous phase (*Figure 1A*) after the administration of intravenous contrast agent. Fluorine-18 fluorodeoxyglucose

positron emission tomography/CT (F-18 FDG PET-CT) revealed hepatic nodules are hypermetabolic (*Figure 1B*), highly suspecting metastases in the right lobe of the liver, considering personal colon cancer history. The patient received an ultrasound-guided fine needle biopsy (FNA) for tissue proof. Histopathological findings revealed granulomas with Langhans giant cells and infiltration of epithelioid and inflammatory cells, and the final diagnosis was a chronic inflammatory granuloma, while Ziehl-Neelsen staining and acid-Schiff staining showed negative for acid-fast bacilli and fungi. The polymerase chain reaction (PCR) for formalin-fixed paraffin-embedded tissue revealed NTM infection. The follow-up CT examination after three months showed no significant changes in previous hepatic granuloma and no newly appeared lesions.

Case 2

The second patient was a 58-year-old female with a history of right ovary clear cell adenocarcinoma and total abdominal hysterectomy and salpingo-oophorectomy were performed about 6 years ago. The routine follow-up imaging examinations showed no evidence of local tumor recurrence or distant metastases. The contrast-enhanced CT demonstrated multiple low attenuating lesions with peripheral enhancement in both lobes of the liver (*Figure 2A*) 3 years ago. The follow-up Gd-EOB-DTPA contrast-enhanced MRI revealed multiple hyperintensity nodules on the T2-weighted image (*Figure 2B*) with rim enhancement in the venous phase (*Figure 2C*) and without contrast agent uptake in the hepatobiliary phase (*Figure 2D*). Hepatic metastases were suspected after examinations, and FNA was performed on the nodule in segment S6 of the liver.

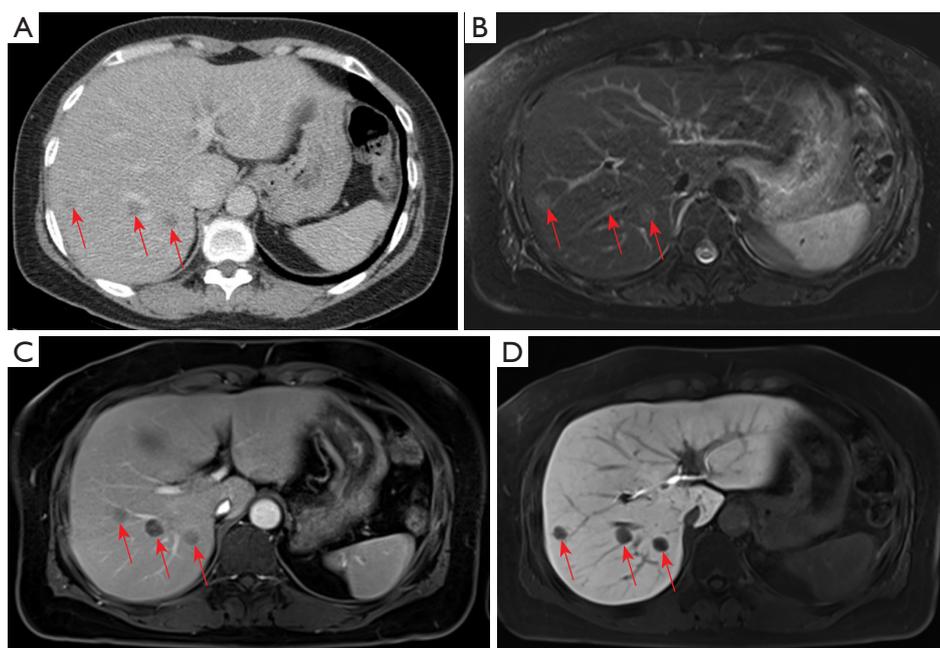


Figure 2 A 58-year-old female with a history of surgery for right ovary clear cell adenocarcinoma. (A) Axial contrast-enhanced CT image in the portal venous phase shows multiple low attenuating lesions with peripheral enhancement in the right lobe of liver (arrows); (B) axial T2-weighted image shows multiple slightly hyperintense nodules in the right lobe of liver (arrows); (C) axial contrast-enhanced T1-weighted image in the portal venous phase shows the lesions with rim enhancement (arrows); (D) axial contrast-enhanced T1-weighted image in the hepatobiliary phase shows no contrast agent uptake with the nodules (arrows).

Based on histopathology, the diagnosis was a hepatic granuloma, which was composed of epithelioid histiocytes and inflammatory cells without caseous necrosis. Then evaluation by NTM and MTB PCR kit showed positive for NTM infection and negative for MTB infection. The final diagnosis was a hepatic nontuberculous infectious granuloma, and antitubercular therapy was performed for 3 courses of treatment (21 days/1 course). In the subsequent three years of follow-up, the patient showed no significant changes of multiple hepatic granulomas and no newly developed lesions.

Case 3

The third patient was a 55-year-old male who had been diagnosed with rectal adenocarcinoma and bilateral renal cell carcinoma 2 years ago. Preoperative abdominal CT examination revealed an ill-defined, low attenuating lesion in segment S5 of the liver (measuring <1 cm). The laboratory examinations showed no obvious evidence of infection signs such as increased CRP level or WBC counting. Therefore, the initial diagnosis was focal fat

deposition, and metastasis is less likely. Since the lesion was very small, no interventional treatments were administered, and a close follow-up was suggested. He underwent resection and bilateral nephrectomy and sustained on long-term hemodialysis after the operation. However, the follow-up CT and MRI examinations in the half a year after the surgery revealed that the previous nodule in segment S5 of the liver increased in size from 1 to 2 cm with peripheral enhancement after administration of contrast agent (*Figure 3*). The F-18 FDG PET-CT demonstrated a hypermetabolic nodule in S5 of the liver, which indicated a high suspicion of hepatic metastasis. Finally, the successful FNA was done on this nodule of the liver. Microscopically, the nodule exhibited a caseating granuloma with a mixture of epithelioid histiocytes, inflammatory cells and Langhans giant cells in the background of fibrous tissue (*Figure 4*). Moreover, further NTM and MTB PCR kit revealed positive for NTM and negative for MTB. The patient received antitubercular treatment and was responsive to therapy. The latest follow-up CT showed the nodule decreased slightly from 2 to 1.4 cm in size and no other newly appeared lesions in the liver (*Figure 3D*).

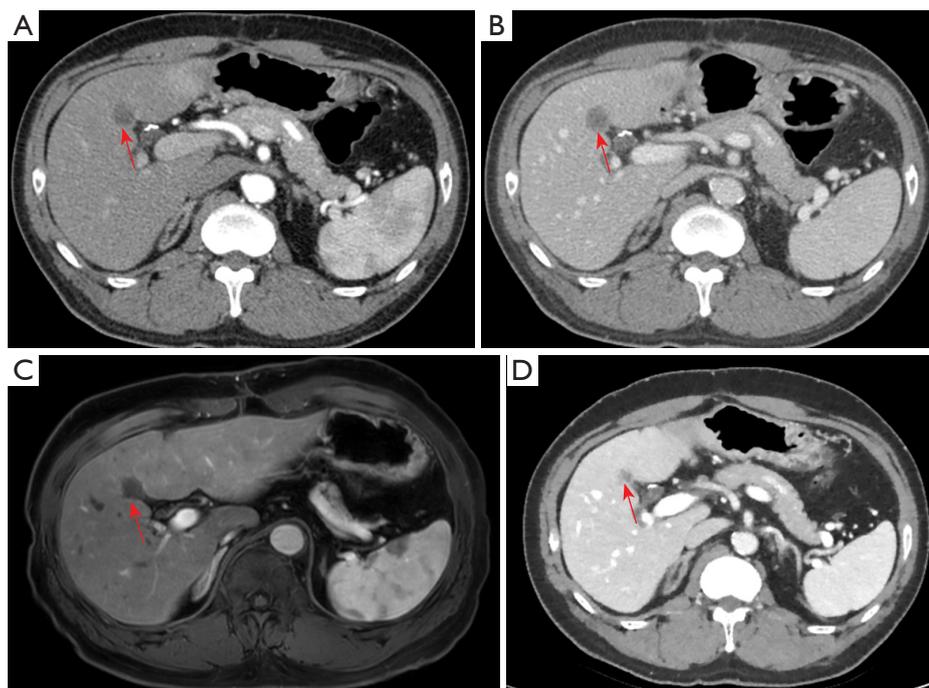


Figure 3 A 55-year-old male with a history of rectectomy and nephrectomy for rectal adenocarcinoma and bilateral renal cell carcinoma. (A) Axial contrast-enhanced CT image in the arterial phase shows an ill-defined hypoattenuating lesion with peripheral enhancement at S5 of the liver (arrow); (B) axial contrast-enhanced CT image in the venous phase shows peripheral enhancement of the nodule (arrow); (C) axial contrast-enhanced fat-suppressed T1-weighted image in the portal venous phase shows the nodule with slight rim enhancement (arrow); (D) axial contrast-enhanced CT image in the venous phase shows the nodule became smaller in size after antitubercular treatment (arrow).

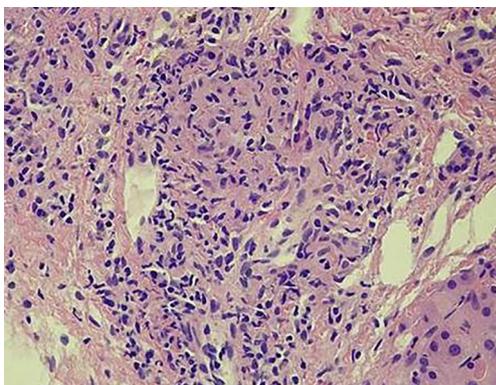


Figure 4 Microscopy of the focal lesion in segment S5 of liver from the third patient displayed granuloma comprising epithelioid histiocytes, inflammatory cells and Langhans giant cells (HE stain, $\times 400$).

Discussion

NTM are considered to be opportunistic environmental pathogens, not commonly causing diseases. However, under certain circumstances, NTM can cause a wide

variety of infectious diseases, including pulmonary NTM disease, skin and soft tissue infection, musculoskeletal infection, lymphangitis, and disseminated infection, with the pulmonary involvement being the most common infection (9-13). NTM infections are typically related to immunocompromised conditions, such as AIDS/HIV infection, cancers, hematologic and solid organ transplantation, immunosuppressive therapy (14-16). However, there is a paucity of reports regarding hepatic NTM infection to date. It was reported that an old Japanese woman was suspicious of the liver tumor with a solitary, low-density lesion (17 mm in diameter) in S7 of the liver (17). The liver biopsy was performed, and histopathological examination revealed a caseating granuloma caused by *Mycobacterium avium* complex.

In our series of cases, the primary diagnoses were generally hepatic metastases. In the first and second patients, they were found with multiple variable-sized nodules, and the third patient manifested as a solitary nodule in the liver. The successful FNA was performed on one of the nodules in the first and second patient, and the isolated

nodule in segment S5 in the third patient. Moreover, the definite diagnoses of three patients were obtained as hepatic nontuberculous granulomas. As the nontuberculous granulomas demonstrate overlapped imaging features with hepatic metastases, it is very hard to differentiate if only depending on CT or MRI imaging when they occurred in patients with malignancy. Because of the history of primary malignant tumors, the metastatic nodules could be the initial diagnosis or could not be excluded from for these three cases. Other differential diagnoses may include pyogenic abscess, cholangiocarcinoma, inflammatory pseudotumor and atypical hemangioma (18,19).

Since there is a scarcity of literature on imaging findings of hepatic nontuberculous granulomas, we summarized the radiological manifestations of hepatic NTM infections from three cases and the review of the literature on hepatic tuberculosis (20-22). In the first patient, there were two comparatively large hypoattenuating nodules (>2 cm in size) with slightly rim enhancement in the right lobe of the liver in portal venous phase on contrast-enhanced CT. The lesions that measure >2 cm in size are considered as the macronodular type (20). CT imaging features of hepatic macronodular granulomas depend on the compositions and stages of nontuberculous infections (23). Granulomas without caseation appear hypodense and generally display no enhancement or merely peripheral enhancement on enhanced CT. However, the imaging appearance of caseous granuloma can be variable and different. They may demonstrate multiple enhancing septations within necrosis, similar to pyogenic abscesses (20). In the second patient of our series, the lesions were multiple, generally less than 2 cm in size and tended to be randomly distributed or scattered across the liver parenchyma. The lesions appeared as hypodensity nodules in the form of small foci on CT and exhibited peripheral enhancement or without obvious enhancement on contrast-enhanced CT. The lesions showed hypointensity on T1WI images and slight hyperintensity on T2WI images. After administration of contrast agents (Gd-EOB-DTPA), the lesions demonstrated rim enhancement in the arterial and portal venous phase, and low signal intensity without Gd-EOB-DTPA uptake in the hepatobiliary phase (24). Regardless of the macronodular or miliary pattern, it can make it difficult to distinguish them from metastases, tuberculosis, or other forms of granulomatous diseases. The isolated lesion of the third patient was discovered before the operation. It presented as a solitary hypovascular nodule for 1 year and became larger after the operation. It appeared as a hypoattenuating or hypointensity nodule with minimal

peripheral enhancement on contrast-enhanced CT or MRI. Based on the history of malignant tumors, it is extremely difficult to differentiate it from a single metastatic nodule.

Due to the similarity in imaging manifestations with hepatic tuberculosis or metastasis, hepatic NTM infection is often either misdiagnosed or labeled as indeterminate lesions. Misdiagnosis or delayed diagnosis of NTM infections can result in improper treatment or intervention, even serious morbidity and mortality (25,26). Liver biopsy should be the most specific diagnostic modality, which is indicated in anyone with a radiographic suspicion or exclusion of hepatic lesions (27).

Conclusions

We have described three rare cases of hepatic granulomas caused by NTM infection mimicking metastases in patients with cancer. The diagnosis could be difficult to make since the symptoms and imaging findings are nonspecific. Therefore, hepatic nontuberculous granuloma should be considered when imaging findings were controversial to clinical presentations, especially in patients with a history of malignant tumors. However, the final definite diagnosis is obtained through histopathologic and microbiological examinations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Ethics Committee of all the hospitals and written informed consent was obtained from all patients.

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