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Case Report

Granulomatous hepatitis by *Nocardia* species: An unusual case

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ABSTRACT

A case of granulomatous hepatitis due to *Nocardia* is reported here. The case patient was a 63-year-old immunocompetent man who presented with persistent fever, weight loss, and malaise. Radiology suggested an enlarged liver with dense diffuse to multiple tiny micronodular areas of parenchymal involvement, possibly granulomatous. Liver biopsy showed necrotizing granulomas and anti-tuberculosis therapy was initiated, but the patient showed no improvement. A repeat liver biopsy showed similar histopathology; however PCR for *Mycobacterium tuberculosis* was negative, while MGIT 960 culture grew filamentous Gram-positive bacilli, acid-fast by 1% H_2SO_4, identified biochemically as *Nocardia* spp. 16S rRNA sequencing confirmed *Nocardia* spp. A diagnosis of granulomatous hepatitis due to *Nocardia* spp. was made. Treatment based on drug sensitivity testing was initiated, resulting in a resolution of symptoms. The patient's history revealed that stray dogs adopted by his family had skin lesions, likely canine distemper (two newborn puppies had died recently). *Nocardia* is known to co-infect animals with distemper. This could have been the possible source of a zoonotic infection to the case patient. *Nocardia* spp. are seldom reported from sites other than the lungs, skin, or brain; the current case highlights the involvement of the liver. Due to the granulomatous tissue response, it could represent a differential diagnosis of tuberculosis in such cases.

Introduction

Nocardia is an aerobic actinomycete responsible for localized or disseminated infections in animals and humans (reported from the lungs, brain, and skin). A case of pyrexia of unknown origin (PUO) with granulomatous hepatitis caused by *Nocardia* spp. is reported here. This etiology is not often suspected. With this case report, we wish to highlight the diagnostic dilemma faced during the investigation of this case, and how the diagnosis was reached and linked to a possible source.

Case presentation

The case patient was a 63-year-old man who presented in March 2013 with fever (with evening rise), significant weight loss, and malaise occurring over a period of a few weeks. Physical examination did not reveal any significant finding. Liver function tests showed raised alkaline phosphatase and gamma-glutamyl transferase, low albumin, and a low albumin-to-globulin ratio. Initial evaluation demonstrated sterile blood and urine cultures, normal chest radiography, and an unremarkable abdominal sonography. Investigations including peripheral smear for malaria parasites, a malaria antigen test, enteric fever serology, *Leptospira* serology, retroviral serology, viral hepatitis serology, and *Brucella* serology were within normal limits, and a peripheral blood film demonstrated no evidence of toxic granules or atypical cells. Bone marrow aspiration with cultures was subsequently performed, the results of which were non-contributory.

Further investigations were done, including serum and urine protein electrophoresis, anti-nuclear antibody levels, anti-smooth muscle antibody levels, and anti-mitochondrial antibody levels, which were inconclusive. Advanced imaging was subsequently sought with contrast-enhanced computed tomography scanning of the abdomen. This suggested diffuse liver involvement with multiple tiny micronodular areas, possibly granulomatous. Liver biopsy revealed granulomatous hepatitis with bridging fibrosis (Figure 1), suggestive of tuberculosis (TB), and the patient was started on anti-TB therapy with isoniazid, rifampicin, streptomycin, and ethambutol. This initial biopsy sample could not be cultured due to inadequate material and the patient was subjected to a second liver biopsy after 2 weeks, which corroborated the histopathological findings of the first biopsy. The patient failed to demonstrate a clinical response to the initiated anti-TB treatment.

Retrospective history-taking revealed the presence of stray dogs – a new mother and her puppies – which had been adopted as pets by the patient's family. The death of two puppies and

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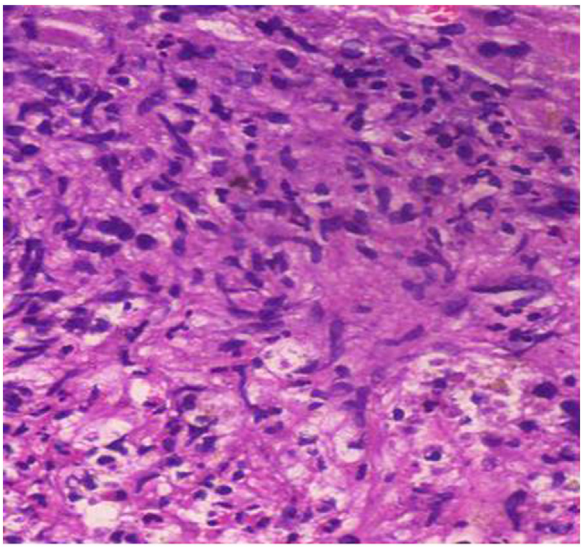

Figure 1. Biopsy shows acinar disarray. There are several large necrotizing epithelioid cell granulomas mainly involving zone 3 and 2. These granulomas show peripheral epithelioidhistiocytes admixed with neutrophils and central acute inflammatory cells, necrosis and bacterial colonies. There is prominent central to central bridging necrosis with edema and hepatocyte loss. Portal tracts show minimal to mild chronic inflammation. Periportal hepatocytes are viable, uninvolved by the granulomatous process and display mild ballooning degeneration and mild macrovesicular steatosis. ZN staining done for AFB is noncontributory. Viral inclusions, fungus or atypical cells are not seen in the submitted biopsy. Impression: Granulomatous Hepatitis with Bridging Necrosis.

cutaneous lesions over the mammary glands of the lactating mother were thought to be due to canine distemper. Of note, *Nocardia* is known to co-infect animals infected with distemper virus (Ribeiro et al., 2008). The patient also reported using the same bed as that used to house the sick puppies.

Differential diagnosis

Radiological examination was suggestive of granulomatous hepatitis, and liver biopsy revealed granulomatous hepatitis with bridging fibrosis, suggestive of TB. The first biopsy sample was not sent for culture. The patient did not respond to the anti-TB therapy and was irregular with the treatment. His personal history revealed many pet dogs within the family. Two puppies had died a few months back and cutaneous lesions over the mammary glands of the lactating mother led to the suspicion of a possible zoonotic source of infection. To increase the sensitivity of the diagnosis, a second liver biopsy was done after 2 months and showed similar histopathology findings; this was also sent for culture and PCR.

Microbiological investigations

PCR for *Mycobacterium tuberculosis* was negative (in-house PCR for the *Mpt64* gene) (Singh et al., 2006). MGIT 960 culture tubes turned positive, and subculture on blood agar showed a chalky white, dry adherent growth by the third day. Growth on MacConkey agar was positive. Lowenstein–Jensen medium showed an orange–tan growth by the third day. On Gram staining, Gram-positive, thin, filamentous, branching bacilli were seen. They were acid-fast to 1% H_2SO_4, suggesting *Nocardia* species.

A nitrate reduction test and paraffin bait tests were positive and the isolate did not hydrolyze 12% gelatin or grow in 0.4% gelatin. The isolate was sensitive to co-trimoxazole, gentamicin, amikacin, amoxicillin–clavulanate, imipenem, and levofloxacin and was resistant to cefotaxime, cefixime, ceftriaxone, erythromycin, and tetracycline by disk diffusion, suggesting the organism to be *Nocardia farcinica*.

16S rRNA PCR sequencing (Sanger sequencing using an ABI 3130 analyzer) confirmed results consistent with the isolate being *Nocardia* spp. (Philip and Böttger, 1998). The sequence was submitted to GenBank and assigned accession number **MH712511**.

Treatment

There was a resolution of clinical symptoms following treatment with intravenous amikacin and co-trimoxazole. The patient's condition subsequently improved and he was discharged from the hospital. After about 2 weeks of treatment the patient developed ascites probably following hepatic cirrhosis secondary to diffuse granulomatous hepatitis. By 4 weeks of treatment, the fever and ascites had subsided, but subsequently, the clinical course continued to worsen and the patient died due to worsening cirrhosis.

Discussion

This patient presented with PUO without any immune suppression. The lack of response to anti-TB therapy in a patient with PUO and granulomatous hepatitis should prompt suspicion and investigations for further differential diagnoses. In this case, the treating gastroenterologists were not convinced of *Nocardia* as the causative pathogen due to the lack of similar published evidence. However, the history of companionship of pet dogs with skin lesions due to distemper, known to become co-infected with *Nocardia* (Ribeiro et al., 2008), explained the possible source of the infection in this case.

Infections due to *Nocardia* are acquired by contact with soil or inhalation. In nearly 70% of cases, disseminated nocardiosis occurs in immunocompromised patients with conditions like post-organ transplant, cancer/cancer chemotherapy, lymphoproliferative syndromes, HIV (CD4 counts <100 cells/μl), systemic lupus erythematosus (SLE), or prolonged corticosteroid therapy (Saubolle and Sussland, 2003).

Disseminated nocardiosis presents most commonly as a lesion in the lungs (40%), followed by central nervous system (CNS) (20–40%). It can present as a deep-seated abscess in virtually any organ. Case reports reveal a spectrum of presentations, ranging from retroperitoneal abscess, testicular abscess, thyroid abscess, and salivary gland abscess to cardiac tamponade (Vandĵme et al., 2001; de Montmollin et al., 2012; Shetty et al., 2011; Salazar et al., 2013).

Disseminated nocardiosis, solitary pulmonary and CNS lesions, and single deep-seated abscesses in other organs (salivary gland abscess, breast abscess, and thyroid abscess) have been reported in immunocompetent hosts (Matulionyte et al., 2004).

Nocardia spp. are seldom seen in sites other than the lungs, skin, and brain. This report shows that the liver too is another possible site of infection. Clinicians could confuse this with TB and it is therefore important to keep an open mind when approaching such cases. In addition, this case highlights the possible zoonotic transmission from infected skin lesions in pet dogs.

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Ethical approval

The authors declare that ethical approval was not required for this study.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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