Disseminated *Mycobacterium avium* Complex in an Immunocompetent Host

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Abstract

Disseminated *Mycobacterium avium* complex (DMAC) has historically been described in the immunocompromised. The current epidemiologic research suggests that the incidence of nontuberculous mycobacterial infections is increasing. We present a case of DMAC infection manifesting as hepatic granulomas in a 35-year-old immunocompetent female. This case suggests DMAC infection in a patient without traditional epidemiological risk factors.

**Keywords:** Immunocompetent, *Mycobacterium avium* complex, unusual infection

**INTRODUCTION**

*Mycobacterium avium* complex (MAC) is the most common etiology of nontuberculous mycobacterial (NTM) infection in the United States.¹ The MAC is ubiquitously distributed in the environment, and previous studies have isolated specimens in soil, both natural and man-made water sources as well as food stuffs.¹² Historically, disseminated infection due to MAC is described in immunocompromised patients such as those with HIV/AIDS, malignancy, and solid organ transplants. Disseminated M. avium complex (DMAC) in the immunocompetent is rare. We present a case of presumptive DMAC infection presenting as hepatic granulomas in a 35-year-old immunocompetent female.

**CASE REPORT**

A 35-year-old Hispanic female was admitted for a 2-week history of intermittent fevers with 39°C (103°F) and a 1-day history of acute onset abdominal pain after an outpatient liver biopsy was performed to evaluate multifocal hepatic lesions. Initial symptoms of midepigastric pain with radiation to the right upper quadrant started 9 months before admission and at the time were attributed to *Helicobacter pylori* peptic ulcer disease based on a gastric mucosa biopsy. The patient’s symptoms failed to improve with triple combination therapy for *H. pylori* infection, and before initiation of quadruple therapy, she was noted to have elevated liver enzymes (outside facility; results not available), which prompted magnetic resonance imaging (MRI) of the abdomen. This imaging (obtained 9 months before admission; image not able to be obtained) showed multiple hepatic lesions suggestive of hepatic cysts, leading to the decision to treat symptomatically with over the counter pain medications and perform serial imaging. On repeat imaging, 6 months before admission, there appeared to be resolution of the lesions. Despite these results, the patient continued to have intermittent discomfort and, given that the prior esophagogastroduodenoscopy only showed nonspecific gastritis, an MRI was again repeated 3 weeks before admission. This study showed redevelopment of multiple, heterogeneous, enhancing hepatic lesions concerning for an indolent infectious process, with the largest measuring 4.3 cm × 3.2 cm. Concurrent liver function testing revealed elevated liver-associated enzymes (LAEs) consistent with a hepatocellular injury pattern (aspartate aminotransferase [AST] 1104 U/L, alanine transaminase [ALT] 967 IU/L, alkaline phosphatase [ALP] 176 IU/L, and total bilirubin 1.8 mg/dL).

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During the time of this evaluation, the patient had experienced a 10-pound unintentional weight loss over 2 months, followed by the 2 weeks of fevers that prompted the liver biopsy. The patient had no significant prior medical history other than a cholecystectomy (for cholecystitis) and right salpingectomy due to ectopic pregnancy. She denied tobacco or significant alcohol use. She also denied travel outside the United States and had resided in Texas since birth.

Vital signs on presentation revealed rectal temperature of 39°C (102.4°F), heart rate of 134 beats per minute, blood pressure of 119/82 mmHg, respiratory rate of 20 breaths per minute, and oxygen saturation at 98% on room air. Physical examination displayed mild right upper quadrant tenderness on deep palpation without organomegaly. No cardiac murmurs, pulmonary or dermatologic abnormalities were appreciated. Diagnostic evaluation was notable for elevated LAEs (AST 172 U/L, ALT 220 IU/L, ALP 359 IU/L, and total bilirubin of 1.4 mg/dL). White blood cell count was 6.6 × 10^3/µL but otherwise within normal limits and renal function testing was normal. Abdominal computed tomography (CT) with contrast revealed a 1.2 cm hypodensity along the posterolateral margin of the right hepatic lobe but no discrete fluid collections or abscesses. Chest X-ray showed no acute cardiopulmonary disease. Testing for HIV, endemic fungi, and autoimmune diseases were negative [Table 1]. Repeat MRI during admission displayed multiple bilobar intrahepatic lesions, the largest in the right lobe measuring 5.4 cm and largest in the left measuring 4.9 cm [Figure 1]. The patient remained clinically stable and defervesced shortly after initiation of empiric antibiotic therapy with ciprofloxacin and metronidazole. Based on a negative infectious workup, empiric antibiotics were discontinued, and the patient was discharged home to await liver biopsy results to guide further management.

Initial biopsy results were negative, but due to concern for sampling error, a repeat CT-guided hepatic biopsy of one of the lesions was obtained 1 month later. Histopathologic examination of this specimen displayed necrotizing granulomas with rare acid-fast bacilli (AFB). Mycobacterial cultures showed no growth after 6 weeks. *Mycobacterium* genus polymerase chain reaction (PCR) assays targeting the 16s rRNA gene were negative. However, PCR assay targeting the groEL gene detected the presence of MAC species DNA in the specimen. Based on the patient’s clinical course, imaging, and histopathology results, antymycobacterial therapy with clarithromycin, rifampin, and ethambutol was initiated, with an expected duration of 6–9 months. Repeat MRI 6 months after initiation of therapy showed overall improvement with a decrease in size of the largest right lobe lesion from 5.5 cm to 3.9 cm in diameter, stability of the left lobe lesion, and no

| Table 1: Summary of laboratory investigation performed; including trend of liver function testing |
|----------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| **Total protein (g/dL)**         | October 20, 2015  | November 10, 2015 | November 11, 2015 | November 12, 2015 | November 13, 2015 | December 18, 2015 | January 11, 2016   |
|                                  | 8.3               | 8.4               | 6.1               | 6.1               | 7.3               | 7.7               | 7.8               | 7.2               |
| **Albumin (g/dL)**               | 4.6               | 3.9               | 2.8               | 2.8               | 3.3               | 4.4               | 4.5               | 4                 |
| **ALT (U/L)**                    | 960               | 220               | 134               | 134               | 76                | 24                | 22                | 16                |
| **AST (U/L)**                    | 1091              | 172               | 88                | 88                | 26                | 22                | 15                | 14                |
| **Total bilirubin (mg/dL)**      | 1.9               | 1.4               | 0.8               | 0.8               | 0.4               | 0.4               | 0.4               | 0.3               |
| **ALP (U/L)**                    | 176               | 359               | 238               | 238               | 196               | 114               | 101               | 84                |
| **ANA**                          | Negative          | Negative          | Negative          | Negative          |                   |                   |                   |                   |
| **H. pylori**                    | Negative          | Negative          | Negative          | Negative          |                   |                   |                   |                   |
| **Cocci IgG/IgM**                |                   |                   |                   |                   |                   |                   |                   |                   |
| **Histoplasma Ag**               |                   |                   |                   |                   |                   |                   |                   |                   |
| **RPR**                          |                   |                   |                   |                   |                   |                   |                   |                   |
| **HCV Ab**                       | Negative          |                   |                   |                   |                   |                   |                   |                   |
| **HBsAg**                        | Negative          |                   |                   |                   |                   |                   |                   |                   |
| **CMV IgG**                      |                   |                   |                   |                   |                   |                   |                   |                   |
| **CMV IgM**                      |                   |                   |                   |                   |                   |                   |                   |                   |
| **IgG**                          |                   |                   |                   |                   |                   |                   |                   | 1605              |
| **IgA**                          |                   |                   |                   |                   |                   |                   |                   | 324               |
| **IgM**                          |                   |                   |                   |                   |                   |                   |                   | 86                |
| **HIV Ag/Ab**                    |                   |                   |                   |                   |                   |                   |                   | Negative          |
| **CD3/CD4 absolute**             |                   |                   |                   |                   |                   |                   |                   | 660               |
| **CD3/CD8 absolute**             |                   |                   |                   |                   |                   |                   |                   | 586               |
| **PT (s)**                       |                   |                   |                   |                   |                   |                   |                   | 16.4              |
| **APTT (s)**                     |                   |                   |                   |                   |                   |                   |                   | 36.9              |
| **INR**                          |                   |                   |                   |                   |                   |                   |                   | 1.3               |

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, ANA: Antinuclear antibody, *H. pylori: Helicobacter pylori*, RPR: Rapid plasma regain, HCV: Hepatitis C virus, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, CMV: Cytomegalovirus, HBsAg: Hepatitis B surface antigen, *Date of admission
new lesions [Figure 2]. No further elevations of the hepatic enzymes were observed during therapy.

**DISCUSSION**

Although no formal definition for DMAC infection exists, this case of DMAC infection is consistent with previous definitions documented in the literature.\(^1,^3\) MAC infection in immunocompetent patients typically occurs as a localized pulmonary infection in patients with underlying pulmonary disease. Case series of disseminated NTM infections of immunocompetent patients frequently cite cervical lymphadenopathy as a common presenting clinical feature, but isolated hepatic granulomas are extremely rare.\(^4\) Lymphadenopathy, fevers, weight loss, and night sweats are typical manifestations in the immunocompromised where DMAC has been widely documented, particularly in HIV-infected patients.\(^2-5\) In 1992, Nightingale et al. found that up to 50% of AIDS patients (median CD4 counts of 13/mm\(^3\)) developed MAC mycobacteremia by 827 days whereas in the current era of antiretroviral therapy, DMAC is comparatively rare.\(^5\) Given that this patient was immunocompetent with repeatedly negative HIV tests, the pathogenesis of hepatic MAC infection was unclear.

In an attempt to elucidate the etiology of DMAC infection, several theories were considered. The possibility of iatrogenic infection was considered, given that chronic infections following surgical and endoscopic interventions have been reported.\(^6\) However, our patient’s prior abdominal surgeries preceded her presentation by more than 5 years, making this etiology unlikely. New rheumatic therapies directed at suppressing tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) have been cited as increasing the risk of NTM infection but did not play a role in our patient. Given the concern for disseminated infection, a defect in the cellular immune pathways that protect against mycobacterial infections was also investigated and found to be negative.

Disseminated mycobacterial infections have previously been described as part of a primary immunodeficiency with congenital defects in production of interferon gamma (IFN-\(\gamma\)).\(^7\) Autoantibodies to components of the interleukin-12 (IL-12)/IFN-\(\gamma\) and TNF-\(\alpha\) pathways have also been reported to be causative factors in NTM infections with the vast majority of cases occurring in patients of Asian heritage.\(^3\) Recent reports have also documented DMAC infections occurring outside of these genetic and geographic clusters with acquired autoantibodies discovered in Caucasian Americans.\(^8\) To date, defects in the pathway attributed to mutations in *IL12B*, *IL12RB1*, *ISG15*, *IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*, *IKBKG*, and *CYBB* have been suggested to confer an increased susceptibility to disseminated NTM infection. The aforementioned mutations are more likely to clinically present in childhood whereas other associated factors such as deficiency of *GATA2* and anti-IFN autoantibodies typically present in late childhood and adulthood.\(^9\) Additional genetic research of affected individuals has led to the discovery of an increased risk in specific polymorphisms of HLA-DRB1 and DQB1 alleles.\(^10\) Testing for acquired autoantibodies performed at the National Institutes for Health was negative and HLA typing not pursued.

Further avenues of investigation in identifying cellular immune defects for DMAC infection have evaluated circulating levels of complement. Koitilainen et al. theorized that defects in complement genes would in turn produce decreased levels of complement protein.\(^11\) The overall decrease in circulating proteins may hinder the opsonization and positive feedback of IL-12/IFN of macrophages allowing mycobacteria to evade the immune system and propagate within the host. Two hundred and fifty-seven patients with culture-positive NTM infection were studied, and those with NTM infections were found to have a deficiency in C4 levels compared to healthy controls. The majority of these patients were female, which suggests
gender may be an additional risk factor for the development of mycobacterial disease. However, C4 deficiency overall is relatively common, suggesting that it may serve as a risk factor for disease rather than the sole etiology.\textsuperscript{[11]}

Review of the literature of presumed immunocompetent patients with DMAC showed the majority of affected patients having other opportunistic infections, further suggesting an undiagnosed cell-mediated immunity defect.\textsuperscript{[4]} In the case patient, no coinfections were identified. The lack of coinfections, along with the finding of MAC in this immunocompetent patient, also raised concern for the possibility of sample contamination or a false positive MAC test. The current methods used to test for the presence of MAC rely on differences in genomic sequences, making false positive results unlikely.\textsuperscript{[12]} Real-time PCR was utilized, which provides the added benefit of not needing additional processing steps (such as agarose gel electrophoresis) that might increase the likelihood of contamination.\textsuperscript{[13]} Case series have documented NTM detection in formalin-fixed paraffin embedded specimens to have sensitivities ranging between 30% and 60%, and a study by Kim et al. found specificity of PCR for NTM as high as 97%–100%.\textsuperscript{[13-15]} FITE stain visualization of mycobacteria in conjunction with a positive PCR in this patient provides additional support for a true NTM infection. Finally, DMAC diagnosis was further supported by the patient’s clinical improvement and normalization of liver enzymes following initiation of therapy.

MAC cases with an initial hepatic presentation have been described, with the overwhelming majority occurring in patients with immunocompromising conditions, or case patients were not evaluated for an acquired immunologic defect.\textsuperscript{[16]} Cases similar to ours were found but had differing methods of confirmation for MAC disease. One case involved an 89-year-old immunocompetent female with an isolated hepatic granuloma. Ziehl–Neelsen staining and PCR for mycobacteria were performed on liver biopsy and found to be negative. Microscopy likewise did not reveal AFB but histologic appearance of the liver biopsies was consistent with mycobacterial infection and gastric acid sampling was positive for MAC, which led the authors to assume this was the etiology of the hepatic granuloma.\textsuperscript{[17]} Unfortunately, in addition to the lack of culture data supporting the diagnosis, investigation into defects in the IL12/IFN-\(\gamma\) pathway was not performed. A second case involved a 70-year-old immunocompetent female who was evaluated for a suspected hepatic malignancy and found to have multiple pulmonary nodules. MAC was cultured from bronchoalveolar lavage, and the liver lesion was assumed to have been secondary to DMAC.\textsuperscript{[18]} No direct testing of the liver lesion was ever performed.

In general, proposed mechanisms for hepatic involvement include dissemination through bloodstream infection and ingestion with direct extension to the hepatic parenchyma. MAC has been shown to be capable of penetrating intestinal epithelial cells and colonizing Peyer’s patches and interestingly, one of the risk factors for infection present in our patient was decreased gastric acidity due to proton pump inhibitor therapy.\textsuperscript{[17]} This factor could have created an environment amenable to MAC evasion of host defense systems.

NTM incidence has increased at an annual percentage of 5%–10% over the past 20 years.\textsuperscript{[19]} Diagnosis requires a high level of suspicion and a patient found to have disseminated disease, but not having traditional risk factors, should prompt evaluation for acquired autoantibodies. Research into otherwise healthy individuals with DMAC has only recently recognized acquisition of autoantibodies to key aspects of the IL12/IFN-\(\gamma\) pathway as one possible etiology. Although these tests were negative in our patient, it is still possible that she may have had an additional pathway defect that was not tested. Our case suggests DMAC infection of a patient without traditional epidemiological risk factors. With the aging population and expanding demographics of infected patients, further investigation is needed to identify patients at risk, aid in prompt diagnosis and treatment, and improve prevention of disease.

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Conflicts of interest

There are no conflicts of interest.

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