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Case Report

# Disseminated mycobacterium avium complex spinal osteomyelitis in a patient with interferon gamma receptor deficiency: A case report ☆

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ABSTRACT

Disseminated mycobacterium avium complex (MAC) infection is rare and is classically associated with immunodeficient states. Osteomyelitis is a rare manifestation of disseminated MAC infection. The overwhelming majority of MAC infections occur in patients with human immunodeficiency virus (HIV). Disseminated MAC infection has been described in interferon gamma receptor deficiency, an immunodeficiency mechanistically linked to mycobacterial infection. We present a case of disseminated MAC vertebral osteomyelitis in a patient with interferon gamma receptor deficiency.



## Introduction

Mycobacterium avium complex (MAC) is a mycobacterium that is classically associated with immunodeficient states [1]. Interferon gamma (IFN-$\gamma$) is an intercellular signaling molecule that plays a central role in regulating the immune response to mycobacteria [2]. IFN-$\gamma$ receptor deficiency is a genetically acquired immunodeficiency that is mechanistically linked to mycobacterial infection [2]. Although IFN-gamma receptor deficiency leaves affected patients particularly susceptible to mycobacterial infection, disseminated MAC infection associated with IFN-$\gamma$ receptor deficiency is extremely rare [3]. The majority of disseminated MAC infections occur in the setting of human immunodeficiency virus (HIV) [4]. Vertebral osteomyelitis is an unusual manifestation of a disseminated MAC infection. There are very few case reports describing MAC vertebral osteomyelitis in non-HIV infected individuals [5,6]. We describe the fourth reported case of MAC osteomyelitis in IFN-gamma receptor deficiency [7].

## Case presentation

A 21-year-old male with a history of interferon-gamma receptor deficiency (IFGRD) presented for outpatient neurosurgical consultation for neck pain.

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The reported patient was diagnosed with IFGRD at birth. Both his mother and older brother were previously confirmed to have IFGRD. He had a childhood history notable for MAC infections. He was briefly hospitalized at age 6 for MAC ethmoidal and frontal sinusitis that was successfully treated with azithromycin, rifampin, and ethambutol. At age 10 he was admitted for inpatient care following a 2-week history of fever, abdominal pain, and myalgia in the setting of prophylactic azithromycin noncompliance. Imaging at that time revealed lytic lesions in the left acetabulum, L5 vertebra and right frontal bone, as well as multiple splenic abscesses and bowel wall thickening in the terminal ileum, proximal colon, and appendix (imaging not available). Splenic biopsy findings were consistent with MAC infection. The patient was successfully treated during this admission for disseminated MAC with azithromycin, rifampin, and ethambutol, which he continued for long-term management in the outpatient setting. Interferon-gamma 1b therapy was initiated in the outpatient setting. He continued with regular pediatric immunology and pediatric infectious disease care for the next several years but was eventually lost to follow up.

Following years without medical care, the patient presented for neurosurgical evaluation at the age of 21. He was not taking prophylactic medications to protect against opportunistic infections. Notably, he worked as a janitor at a local hospital and was thus exposed to a range of infectious pathogens. Besides his occupation, he had no notable exposure to mycobacteria.

At his initial neurosurgical consultation, he reported a progressive “soreness and pain” in his neck with occasional “shock-like pain” in his left arm along the deltoid. He denied lower extremities symptoms, imbalance, or genitourinary/gastrointestinal complaints. Physical exam findings were unremarkable, with no neurological deficit observed. Radiographic imaging demonstrated sclerosis and lucency of the C5 vertebra with irregularity involving the superior end-

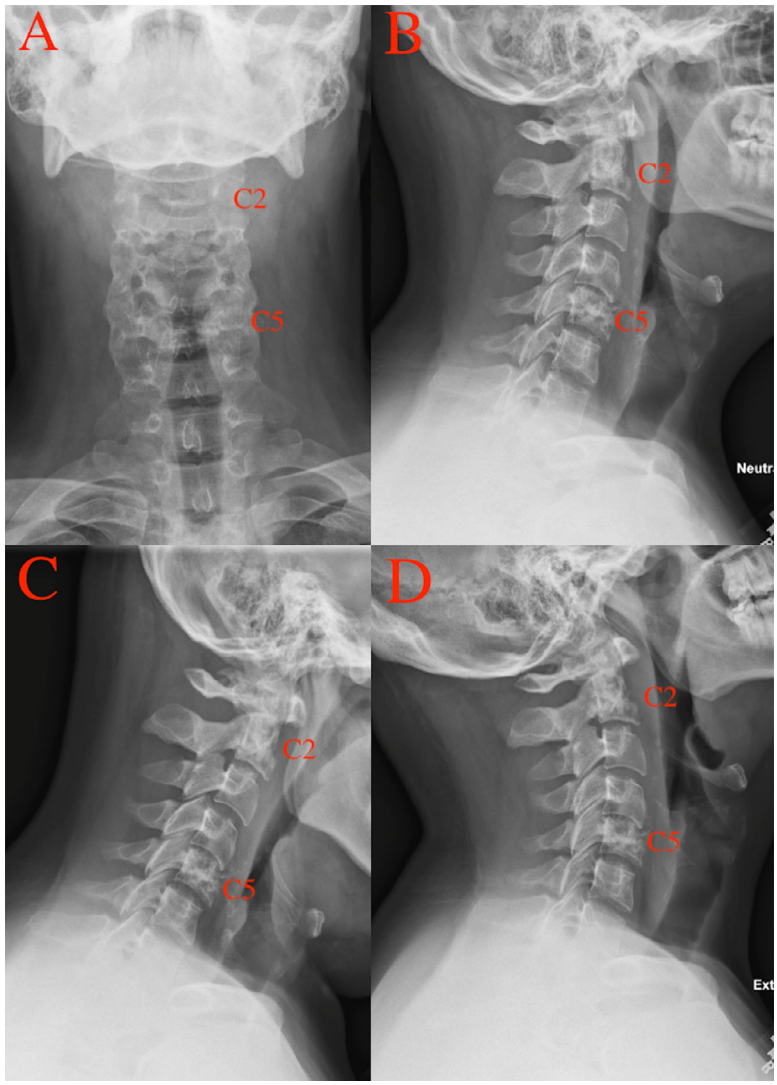


**Fig. 1 – Cervical spine radiographs in the anterior-posterior (A) and sagittal views (B-D). Although partially obscured, the C2 body demonstrates lucent and sclerotic irregularities (C2 labeled in red). There is a mixed lucent and sclerotic appearance of the C5 body (C5 body labeled in red), with moderate-to-severe loss of height in the C4-5 intervertebral disc space (disc space labeled in red, denoted by arrow). Dynamic instability is not demonstrated with flexion (C)-extension (D).**

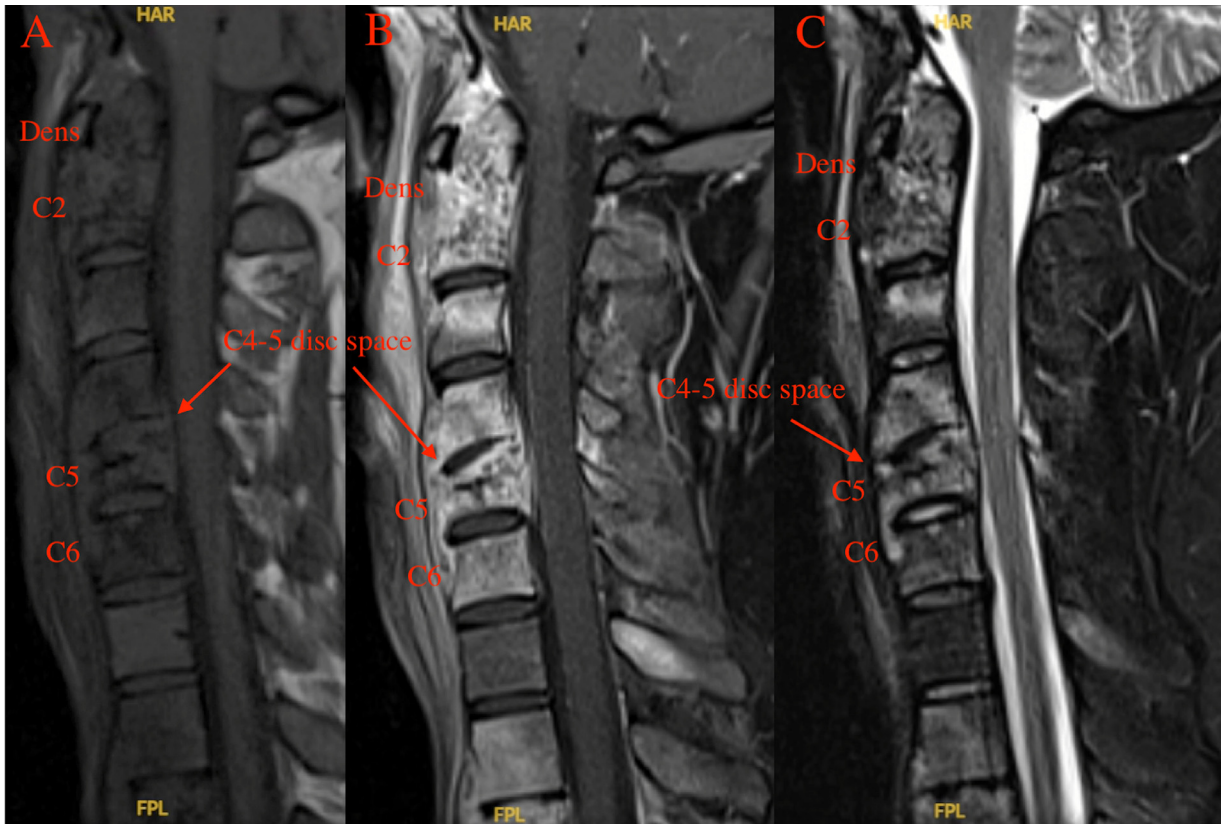


**Fig. 2 – T1-weighted pre-contrast (A), T1-weighted post-contrast (B), and STIR MR images in the sagittal view. Enhancing destructive signal abnormalities are demonstrated throughout the cervical spine, including the odontoid process and the C2, C5, and C6 vertebral bodies (red arrows, vertebral levels labeled). The C5 vertebral body demonstrates a moderate anterior compression deformity with associated moderate canal stenosis (C5 body labeled in red). There is a loss of height at the C4-5 space (disc space labeled in red, denoted by arrow). The cervical spinal cord does not demonstrate abnormal caliber, signal intensity, or enhancement.**

plate, accompanied by decreased width of the C4-5 disc space. There was also irregularity of the C2 body, although it was partially obstructed. There was no instability demonstrated with flexion-extension (Fig. 1). Significant findings on magnetic resonance imaging (MRI) included enhancing destructive signal abnormality at several cervical levels, including C2 vertebral body and dens, C5 vertebral body, C6 vertebral body, and the partially visualized T2 vertebral body. There was loss of disc height in the C4-5 and T1-2 disc heights, and the C5 body demonstrated moderate anterior compression deformity (Fig. 2). At this visit, the patient was deemed neurologically intact. Conservative measures, including cervical collar and muscle relaxers, were prescribed. The patient was also referred to an infectious disease physician for medical management. He was instructed to return for re-evaluation after establishing care with infectious disease. Following neurosurgical referral, the patient established care with an infectious disease physician. The iliac crest was biopsied, which confirmed the diagnosis of mycobacterial infection. The patient was subsequently started on rifampin, azithromycin, and ethambutol to treat his active infection.

At his scheduled 1 month follow-up appointment with neurosurgery, the patient reported a moderate improvement in neck pain after initiating medical therapy. Interval thoracic and lumbar spine computed tomographic (CT) imaging revealed bony destruction of several vertebral bodies and disc spaces throughout the thoracic spine. There were also pathological fractures involving the T2 and T5 vertebral bodies with no significant retropulsion (Fig. 3).

Currently, the patient is continuing medical management by infectious disease with an anti-mycobacterial regimen consisting of rifampin, azithromycin, and ethambutol indefinitely. He will continue routine outpatient care with neurosurgery with no immediate plans for surgical intervention.

## Discussion

Mycobacterium avium complex (MAC) is a rare cause of infection that is classically associated with immunodeficient states [4]. MAC is commonly found in nature and has been isolated from a wide variety of sources, including soil, water, and animal samples [8,9]. The route of transmission of MAC is through inhalation or ingestion [10]. MAC organisms are gram positive bacilli that are acid resistant, hydrophobic, and capable of surviving in host phagolysosomes [11]. They are resistant to many types of disinfectants and antibiotics due to their lipid-

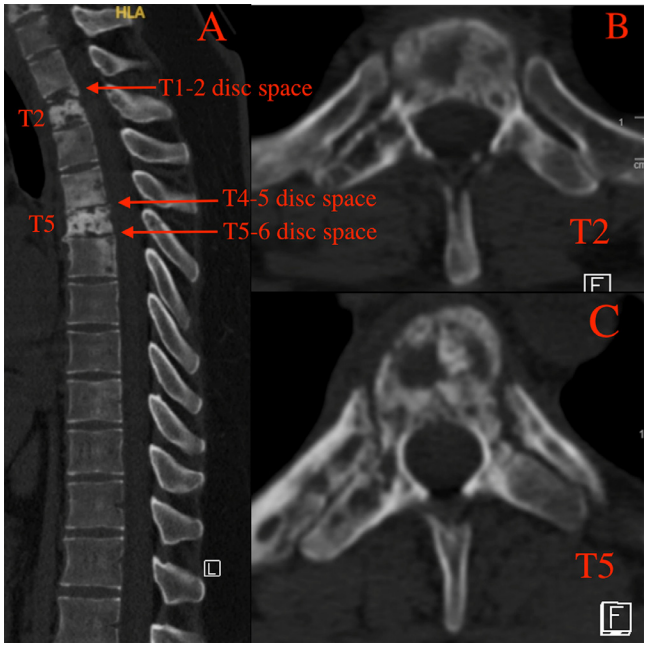


**Fig. 3 – CT images of the thoracic spine. Panel A is a sagittal view that demonstrates bony destruction in multiple vertebral bodies and posterior ribs throughout the thoracic spine. Pathological fractures in the T2 and T5 vertebral bodies are demonstrated (T2 and T5 bodies labeled). Pathological involvement of the T1-2, T4-5 and T5-6 disc spaces can be seen (disc spaces labeled in red, denoted by arrows). Panels A and B are CT images in the axial view that represent pathological destruction of the T2 (B) and T5 (C) vertebral bodies and associated ribs.**

rich outer membrane containing long chain mycolic acids [11]. This outer membrane also makes it easier for them to survive in water sources and in the human gastrointestinal tract [12]. As one of the most hydrophobic types of bacteria, MAC organisms easily form biofilm, which provides them with even more protection [12].

The lipids in MAC cell membranes also subdue the host immune response by increasing the secretion of immunosuppressive molecules, a major one being prostaglandin E2 (Barrow). These molecules suppress IFN-$\gamma$ and TNF-$\alpha$, which are important cytokines in controlling MAC infections [13]. MAC organisms also have the ability to invade human epithelial cells, likely due to their surface adhesion proteins [11]. These proteins also give them the ability to adhere to extracellular matrix proteins including fibronectin (Bermudez, Ratliff).

In the body, MAC cells are recognized by toll-like receptor 2 (TLR2) on mononuclear macrophages which phagocytose them and release reactive metabolites [11]. These metabolites initiate intracellular signaling to release pro-inflammatory cytokines, like interleukins, tumor necrosis factor $\alpha$ (TNF$\alpha$), as well as the chemokines C-X-C motif and chemokine 10 (CXCL-10) [11,14]. These cytokines and chemokines activate the host immune response by recruiting inflammatory cells such as lymphocytes, dendritic cells, and more macrophages to the inflammation site [11]. Inside the macrophages, MAC cells produce substances that inhibit oxidative burst and phagolysosome fusion [14]. The macrophages containing the MAC cells migrate to lymph nodes where they present MAC antigens to T helper cells through the major histocompatibility complex class II (MHC II) [11].

Macrophages can trap and kill mycobacteria with the help of Th1 lymphocytes, which aggregate around the macrophages and secrete IFN-$\gamma$ and IL-2. INF-$\gamma$ activates the macrophages and binds to IFN$\gamma$R1/IFN-$\gamma$R2 receptor complexes, enabling them to kill intracellular bacteria and to present more antigens to the Th1 helper cells which causes further release of IFN-$\gamma$. Over a period of a few weeks, the macrophages become fibroblast-like cells and surround the Th1 helper cells to wall off the infection. At this point, the granuloma is formed and the MAC cells are trapped and can no longer multiply. However, many MAC cells can survive in these granulomas for a long time by subduing the host immune response with the immunosuppressive molecules released from the lipids in their outer membrane. The MAC cells that do not survive aggregate in the center of the granuloma, creating the characteristic area of caseous necrosis.

MAC infection is classically associated with acquired immunodeficiency syndrome (AIDS) and other immunodeficiencies, such as interferon gamma receptor deficiency [15,16,17]. The link between immunodeficiency and disseminated MAC infection is due largely to the disruption of IFN-$\gamma$ signaling pathways, which disrupts granuloma formation and prevents macrophages from receiving the signaling necessary to enable them to kill MAC cells [3,10,18]. As such, IFN-$\gamma$ receptor deficiencies typically cause severe and/or disseminated nontuberculous mycobacterial infections and are associated with a poor prognosis [2].

Genetic abnormalities in the IFN-$\gamma$ receptor, IL-12 receptor and IL12 p40 subunit have all been reported to cause disseminated MAC infections by disrupting intercellular signaling, although the incidence of these disorders causing MAC infections is extremely rare [3]. Two broader categories of IFN-$\gamma$ deficiencies include IFN-$\gamma$R1 and IFN-$\gamma$R2 deficiencies, which together contain 10 specific types of deficiencies. These deficiencies include autosomal recessive and autosomal dominant disorders, complete, and partial functional defects, forms in which the surface receptors are dysfunctional, forms in which the surface receptors are absent, and other mechanisms disrupting the function of the IFN-$\gamma$ receptors. STAT1, JAK1, and gp91$^{phox}$ deficiencies also impair cellular responses to IFN-$\gamma$ [19].

Vertebral osteomyelitis is an unusual manifestation of MAC infection. Most cases of MAC vertebral osteomyelitis occur in hosts infected with Human Immunodeficiency Virus (HIV) [15]. There are rare case reports describing MAC vertebral osteomyelitis in non-HIV infected individuals [5,6,20,21]. Prior trauma [22,23] and pulmonary MAC infection [24] have been previously theorized as risk factors for developing MAC osteomyelitis in susceptible populations. Because most cases of MAC osteomyelitis lack constitutional symptoms and exposure history, and because most mycobacterial blood cultures acquired near the time of MAC osteomyelitis diagnosis are negative, MAC can prove difficult to diagnose [5,25]. As such, it is not possible to estimate the prevalence of MAC osteomyelitis. In our presented case, considering that his immunodeficiency rendered him susceptible specifically to

mycobacterium, and given his prior history of known MAC osteomyelitis, we did not proceed with bone biopsy and instead elected to treat with empiric antibiotics. He improved clinically with treatment. Although not biopsy-proven, we consider it extremely probable that our patient suffered MAC vertebral osteomyelitis. According to our literature review, this case comprises the fourth reported case of MAC osteomyelitis in IFN-gamma receptor deficiency.

The diagnosis of a MAC infection is usually established by isolating the organism from blood or culturing samples of biopsy material [18]. Blood cultures are generally negative and require a bone or soft tissue biopsy for microbiological diagnosis. These, however, may also be unrevealing or require a long time to grow the mycobacterium. Consequently, repeat biopsies are often recommended, but are not always performed due to the risks associated with these invasive procedures [26]. An early diagnosis of a MAC infection is a challenge to obtain due to the slow growing nature of mycobacteria. Cultures often require up to 6 weeks of incubation time to show evidence of growth. Histopathologic appearance of MAC infection is variable and is not typically useful for diagnostic purposes [4].

Radiographic imaging can sometimes help confirm a diagnosis of MAC osteomyelitis. Plain radiographs can be used to reveal the degree of disc degeneration [25]. But, as the course progresses, radiography can show lytic and sclerotic destructive changes on the affected disk spaces as well as a paravertebral abscess [24]. Common CT observations also include lesions of varying sizes that may or may not have enhancement, and vague shadowed areas (Yu). MRI will often show enhancement of the affected areas of the vertebral bodies [27]. As the osteomyelitis progresses, MRI may also show an increase in the size of the paravertebral abscess if one was present before [27].

Vertebral osteomyelitis, regardless of the causative pathogen, is a challenge to diagnose and only 28% of pyogenic osteomyelitis cases are diagnosed within the first month of symptom onset [28]. Because there is frequently a delay in diagnosing MAC osteomyelitis, it often leads to advanced disease, including abscess formation, fistulous tracts, progressive destruction of vertebral bodies, and neurologic compromise [28]. MAC species are difficult to treat because they are resistant to anti-tuberculous drugs at higher rates than tuberculous mycobacteria. The treatment regimen for MAC consists of clarithromycin, rifampin, and ethambutol. Because antibiotics penetrate poorly into the bone, a longer duration of treatment than that for respiratory infections is frequently necessary [27]. There have also been a few cases of disseminated MAC infection secondary to IFN-y deficiency that have been treated with IFN-y in addition to the standard triple antibiotic regimen [1,25,27]. This treatment method was successful in all cases, but still remains uncommon [1,6,29]. Surgical intervention is often employed in pyogenic osteomyelitis and could theoretically likewise be useful in MAC osteomyelitis. Indications for surgery for pyogenic osteomyelitis include destruction of vertebral bodies, neurological compression, and abscess formation [28]. In our presented case, we treated empirically with rifampin, azithromycin, and ethambutol, which provided sufficient results; we did not have to resort to surgical intervention.

## Patient consent

Consent was obtained from the patient.

## REFERENCES


[1] Alangari AA, Al-Zamil F, Al-Mazrou A, Al-Muhsen S, Boisson-Dupuis S, Awadallah S, et al. Treatment of disseminated mycobacterial infection with high-dose IFN-$\gamma$ in a patient with IL-12R$\beta$1 deficiency. Clin Dev Immunol 2011;2011:691956.

[2] Döffinger R, Helbert MR, Barcenas-Morales G, et al. Autoantibodies to interferon-$\gamma$ in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis 2004;38: e10–e14.

[3] Muszlak M, Chapgier A, Barry Harivelo R, Castella C, Crémades F, Goulois E, et al. Infection multifocale à Mycobacterium intracellulare: premier cas de déficit partiel dominant du récepteur de l'interféron gamma en milieu tropical français [Multifocal infection due to Mycobacterium intracellulare: first case of interferon gamma receptor partial dominant deficiency in tropical French territory]. Arch Pediatr 2007;14(3):270–2. doi:10.1016/j.arcped.2006.11.023.

[4] Rubin DS, Rahal JJ. Mycobacterium-avium complex. Inf Dis Clin North Am 1994;8:413–26.

[5] Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, et al. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 2006;18:347–61.

[6] Sharma V, Pai G, Deswarte C, Lodha R, Singh S, Kang LW, et al. Disseminated mycobacterium avium complex infection in a child with partial dominant interferon gamma receptor 1 deficiency in India. J Clin Immunol 2015;35(5):459–62. doi:10.1007/s10875-0150173-1.

[7] Inderlied CB, Kemper CA, Bermudez LE. The mycobacterium avium complex. Clin Microbiol Rev 1993;6:266–310. doi:10.1128/CMR.6.3.266358286.

[8] Cosma C, Sherman D, Ramakrishnan L. The secret lives of the pathogenic mycobacteria. Annu Rev Microbiol 2003;57:641–76.

[9] Gray ME, Liu PW, Wispelwey B. Mycobacterium Avium complex vertebral osteomyelitis in the absence of HIV infection: a case report and review. BMC Infect Dis 2018;18(1):1–7 N.PAG. doi:10.1186/s12879-018-3143-4.

[10] Rotstein AH, Stuckey SL. Mycobacterium avium complex spinal epidural abscess in an HIV patient. Australas Radiol 1999;43(4):554–7. doi:10.1046/j.14401673.1999.00732.x.

[11] Kaczmarkowska A, Didkowska A, Kwiecień E, Stefańska I, Rzewuska M, Anusz K. The Mycobacterium avium complex - an underestimated threat to humans and animals. Ann Agric Environ Med 2022;29(1):22–7. doi:10.26444/aaem/136398.

[12] Falkinham JO. Mycobacterium avium complex: Adherence as a way of life. AIMS Microbiol 2018;4(3):428–38. doi:10.3934/microbiol.2018.3.428.

[13] Pourshafie MR, Sonnenfeld G, Barrow WW. Immunological and ultrastructural disruptions of T lymphocytes following exposure to the glycopeptidolipid isolated from the Mycobacterium avium complex. Scand J Immunol 1999;49:405–10.

[14] Hulinova Stromerova N, Faldyna M. Mycobacterium avium complex infection in pigs: a review. Comp Immunol Microbiol Infect Dis 2018;57:62–8. doi:10.1016/j.cimid.2018.06.005.

[15] Gordin F, Horsburgh CR. Mycobacterium avium complex. In: mandell, douglas, and bennett's principles and practice of

infectious diseases, 3. Philadelphia, PA: Elsevier; 2015. p. 2833–4. 8 ed.2832.
[16] Rossi M, Flepp M, Telenti A, Schiffer V, Egloff N, Bucher H, et al. Disseminated M. avium complex infection in the Swiss HIV cohort study: declining incidence, improved prognosis and discontinuation of maintenance therapy. Swiss Med Wkly 2001;131:471–8.
[17] Wagner D, Young LS. Nontuberculous mycobacterial infections: a clinical review. Infection 2004;32:257–70. doi:10.1007/s15010-004-4001-4.
[18] Pombo D, Woods IML, Burgert SJ, Shumsky IB, Reimer LG. Disseminated mycobacterium avium complex infection presenting as osteomyelitis in a normal host. Scand J Infect Dis 1998;30(6):622–3. doi:10.1080/00365549850161269.
[19] Jia J, Zhu Y, Guo Q, Wan C. Case report: disseminated *Mycobacterium intracellulare* infection with more than 1-year follow-up in a young boy with *IFNGR1* deficiency. Front Pediatr 2022;10:761265. doi:10.3389/fped.2022.761265.
[20] Arend SM, Janssen R, Gosen JJ, Waanders H, de Boer T, Ottenhoff TH, et al. Multifocal osteomyelitis caused by nontuberculous mycobacteria in patients with a genetic defect of the interferon-gamma receptor. Neth J Med 2001;59(3):140–51. doi:10.1016/s0300-2977(01)00152-8.
[21] Kerner G, Rosain J, Guérin A, Al-Khabaz A, Al-Khabaz A, Oleaga-Quintas C, Rapaport F, et al. Inherited human IFN-$\gamma$ deficiency underlies mycobacterial disease. J Clin Invest 2020;130(6):3158–71. doi:10.1172/JCI135460.
[22] Chan ED, Kong PM, Fennelly K, Dwyer AP, Iseman MD. Vertebral osteomyelitis due to infection with nontuberculous mycobacterium species after blunt trauma to the back: 3 examples of the principle of locus minoris resistentiae. Clin Infect Dis 2001;32:15061510. doi:10.1086/320155.
[23] Zvetina JR, Demos TC, Rubinstein H. Mycobacterium intracellulare infection of the shoulder and spine in a patient with steroid-treated systemic lupus erythematosus. Skelet Radiol 1982;8:111–13. doi:10.1007/BF00349575.
[24] Takakuwa O, Oguri T, Kasai D, Nakamura A, Sato S, Ueda R. A case of spinal osteomyelitis due to mycobacterium intracellulare with pulmonary mycobacterium avium complex. Nihon Kokyuki Gakkai Zasshi 2010;48:759–64.
[25] Wood BR, Buitrago MO, Patel S, Hachey DH, Haneuse S, Harrington RD. Mycobacterium avium complex osteomyelitis in persons with human immunodeficiency virus: case series and literature review. Open Forum Infect Dis 2015;2(3):1–7. doi:10.1093/ofid/ofv090.
[26] Berbari EF, Kanj SS, Kowalski TJ. Executive summary: 2015 infectious diseases society of america (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015;61:859–63. doi:10.1093/cid/civ633.
[27] Shimizu H, Mizuno Y, Nakamura I, Fukushima S, Endo K, Matsumoto T. Vertebral osteomyelitis caused by non-tuberculous mycobacteria: case reports and review. J Infect Chemother (Springer Science & Business Media BV) 2013;19(5):972977. doi:10.1007/s10156-013-0550-8.
[28] Petitjean G, Fluckiger U, Scharen S, Laifer G. Vertebral osteomyelitis caused by nontuberculous mycobacteria. Clin Microbiol Infect 2004;10:951–3. doi:10.1111/j.14690691.2004.00949.x.
[29] Takeda K, Kawai T, Nakazawa Y, Komuro H, Shoji K, Morita K, et al. Augmentation of antitubercular therapy with IFN$\gamma$ in a patient with dominant partial IFN$\gamma$ receptor 1 deficiency. Clin Immunol 2014;151(1):25–8.