

## Atypical mycobacterial infection in pediatric age group: Case report and literature review.

Albar Rawia F<sup>1</sup>, Selati Saife A<sup>2</sup>, Alghamdi Abdullah A<sup>2</sup>, Salahi Ahmed S<sup>2</sup>, Ahmed Mohammed Alfaidi<sup>2</sup>, Binmahfoodh Dina S<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of General Pediatrics and Pediatric Pulmonology, King Saud bin Abdulaziz University for Health Sciences, Kingdom of Saudi Arabia.

<sup>2</sup>Department of General Pediatrics, Ministry of National Guard–Health Affairs, King Abdulaziz Medical City, Kingdom of Saudi Arabia.

### Abstract

***Mycobacterium avium* complex organisms mainly affect immunocompromised patients, presenting as lymphadenitis in children. The host's defense against intracellular infections, especially non-tuberculosis mycobacterium, depends mainly on the function and activity of Interferon Gamma (IFN-G) and Interleukin 12 (IL-12). Here we present a case of a seven-month-old boy presented with multiple neck and axillary swellings. The patient was treated medically and then came back with a relapse. Eventually, he was diagnosed with IL-12 deficiency.**

**Keywords:** Lymphadenitis, *Mycobacterium avium* complex, Atypical mycobacterial.

Accepted February 22, 2017

### Introduction

Mycobacteria are classified as tubercular and non-tubercular organisms. Non-tubercular Mycobacteria (NTM), such as *Mycobacterium avium* Complex (MAC), is free living organisms present in the environment. They can be found in food, soil, surface water, tap water, domestic and wild animals. MAC infection can present as a progressive pulmonary disease, disseminated disease in severally immunocompromised patients, skin disease by direct inoculation or benign lymphadenitis. In surveillance studies done on children with NTM in Australia, Germany and Netherlands, lymphadenitis was the most common presentation, especially in children who had MAC positive culture. MAC organisms are mainly composed of two species; *Mycobacterium avium* and mycobacterium intracellulare. Unlike *Mycobacterium tuberculosis* (MTB), these organisms are not usually reported, leading to underestimation of their actual incidence and significance [1,2].

### Case Report

Seven month old Saudi boy presented with fever, multiple neck and axillary swellings with two weeks of fatigability. Two weeks prior to presentation, he had intermittent fever associated with sweating and loss of appetite but no rigors or weight loss. Two days prior to presentation, he had

multiple neck and axillary swellings, with no history of skin rash, joint swellings, cough or hemoptysis. There was no history of raw milk ingestion, recent travel, animal contact or blood transfusion. He was a product of an uncomplicated spontaneous vaginal delivery, and all of his vaccinations were up to date. Regarding his physical examination, he looked pale, but not jaundiced nor cyanosed. His vitals showed a heart rate of 140 beats per second, blood pressure of 99/58 mm Hg, respiratory rate of 46 breaths per minute and a temperature of 38°C. On chest auscultation, normal vesicular breath sounds with equal bilateral air entry was noted. Abdominal examination was unremarkable. There were multiple neck swellings with enlarged, matted, non-tender submandibular and anterior cervical lymph nodes with no overlying skin change. In addition, the patient had a similar enlarged axillary lymph node that measured seven centimeters in diameter. Complete blood count showed hemoglobin of 6.8 g/dL, white blood cells count of  $7.8 \times 10^9/L$ , neutrophils of  $2.2 \times 10^9/L$ , leukocytes of  $2.6 \times 10^9/L$  and platelet count of  $423 \times 10^9/L$ . His Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) were 79 and 310, respectively. Serological tests for brucella, cytomegalovirus, Epstein-Barr virus and herpes simplex virus were all negative. The patient's blood film was negative for malaria and lymphoblasts, with a normal ratio in T cell subset analysis. Early morning gastric aspirate for Acid Fast Bacilli (AFB) was negative,

and Purified Protein Derivative (PPD) was normal. Chest X-ray showed bilateral hilar lymphadenopathy. Histopathological report of lymph node biopsy showed acute granulomatous infiltrations with AFB. Culture after six weeks was positive for mycobacterium tuberculosis. An antibiotic sensitivity test was done and the patient was treated with isoniazid, rifampicin, pyrazinamide and ethambutol.

Two months later, the patient was readmitted with a febrile seizure. Lumbar puncture was done and the cerebrospinal fluid culture was negative. During the admission, the axillary and supraclavicular lymph nodes got swollen, raising suspicion of a secondary infection. A second excisional biopsy was taken and revealed granulomas with AFB. The patient was discharged on the same medications as before. Three weeks later, histopathology report demonstrated granulomatous infiltration formed from sheets of histiocytes filled with AFB, which was consistent with MAC infection. The patient was kept on rifampicin and

ethambutol as the earlier regimen, with the addition of clarithromycin and streptomycin. One month later, the patient was readmitted with a relapse and the culture of lymph node biopsy grew MTB and MAC. The patient was transferred for further workup and treatment of combined MTB and MAC infection. Two months later, the patient was diagnosed with IL-12 deficiency.

### Discussion

A review of pediatric MAC infections with lymph node enlargement was conducted (Table 1). The search was made using the PubMed engine. Six cases were gathered, with an average age of five years, ranging from one to 10 years. The most common complaint was swelling in three out of six cases. The culture showed *Mycobacterium avium intracellulare* in nearly all cases. IFNG production was discussed in two cases; one showed diminished level, and the other was within normal range. Most of the cases were treated with rifampicin, isoniazid and surgical removal. The outcome was good recovery after the completion of treatment course in most cases.

**Table 1.** Atypical mycobacterial infection cases in pediatric age group

Reference numbers	Case number	Age	Gender	Biopsy	Culture	Immune work up
3	1	6 years	Male	Histology appearance consistent with tuberculosis, no AFB.	MAI	Not done
3	2	4 years	Male	Epithelioid granulomatous with Langhans giant cells, no AFB.	MAI	Not done
3	3	10 years	Female	Marked epithelioid granulomatous with diffuse lymphocytes and Langhans giant cells, no AFB.	Failed to provide a definitive microbiological diagnosis	Not done
4	4	3 years	Female	Necrotizing granuloma.	<i>M. Avium</i>	Normal complement, T cell, natural killer cells and B cells. IL12 production normal, IFNG production diminished
5	5	8 Months	Not mentioned	Histocyte loaded with AFB.	<i>M. Avium</i>	HIV positive with low CD4 count
6	6	7.5 years	Female	No AFB.	<i>M. Avium</i> and <i>M. Tuberculosis</i>	WBC=3.5 × 10 <sup>9</sup> /L, increased IgG, normal IgA and IgM, normal T cell helper/suppressor ratio. Normal IFNG

AFB: Acid Fast Bacilli; CD: Cluster of Differentiation; MAI: *Mycobacterium avium intracellulare*; WBC: White Blood Cells; IL: Interleukin; Ig: Immunoglobulin

Mycobacteria are aerobic, non-motile, non-spore-forming bacilli. These intracellular bacteria contain a cell wall formed by long-chained glycolipids which protect them from lysosomal attack. There are over 140 species of NTM, 13 of them were recognized to cause human infections [2-6]. MAC is opportunistic species and it is the most commonly reported out of those 13 species, usually affecting immunocompromised patients [7]. The primary portals of entry for these organisms are thought to be the respiratory and gastrointestinal tracts, causing pulmonary infection, lymphadenitis or even disseminated infection in immunocompromised patients [8]. Following entry to the body, MAC organisms start colonization, adhere to and penetrate the mucosal walls. Then phagocytosis by macrophages occurs, triggering a complex immune response that leads to the activation of other macrophages and the release of cytokines such as, IFN-G, IL-12 and tumor necrosis factor-alpha. With intact immunity, this response results in intracellular elimination of the organism. However, patients with compromised immunity are unable to achieve this, resulting in further multiplication of the organism and subsequent dissemination [9,10].

MAC infections are broadly classified into four clinical syndromes: pulmonary disease, disseminated disease, skin disease and lymphadenitis. Pulmonary infection with MAC organism is acquired by inhalation. Patients usually present with non-specific symptoms and may be indistinguishable from TB or other lung diseases. These symptoms include fever, fatigue, weight loss, cough, dyspnea and chest discomfort. Symptoms are also influenced by the presence or absence of underlying lung disease [11]. MAC-lung diseases are thus further classified into fibrocavitary type, nodular bronchiectatic type, and hypersensitivity pneumonitis [12-15].

Severely immunocompromised patients were associated with disseminated disease. It is believed that a previously localized lung or gut infection multiply locally and eventually enter the bloodstream, thus affecting other organs and systems. Disseminated-MAC infection manifests clinically with fever, night sweats, weight loss as well as organ-specific symptoms. Major sites of involvement include bone marrow, liver and spleen [9,16].

Skin and soft tissue infection were seen in both healthy and immunocompromised children [17]. They can be transmitted by direct inoculation through skin abrasions or penetrating trauma from water [18]. Lesions may appear as ulcerations, plaques, folliculitis, erythematous papules or nodules. This variation contributes to the usual delay in diagnosis [19,20]. In contrast to other pyogenic infections, these skin lesions are mostly painless, rarely associated with regional lymphadenopathy and systemic manifestations are absent.

Finally, the most common manifestation of MAC infection in childhood is lymphadenitis. It usually follows ingestion of the organism, resulting in cervical lymphadenitis.

However, lymphadenitis in other sites suggests direct tissue penetration. MAC-Lymphadenitis generally presents with a unilateral, non-tender, slowly enlarging lymph node. With lack of experience and exposure, it might be diagnosed initially as staphylococcus or streptococcus infections, leading to delay in diagnosis and treatment [21]. Management of MAC-Lymphadenitis in children may require surgery and/or antimicrobial therapy. The treatment of choice still remains a debate [22,23]. Many studies have proven that surgical excision has higher rates of cure, lower chances of recurrence, more rapid healing and fewer adverse effects compared to antimicrobial therapy or observation [24,25]. Children who are not candidates for surgery may benefit from antimicrobial therapy. According to a retrospective study that was done in Australia, a combination of clarithromycin and rifampicin, which were both used in our case, had lower recurrence rate than clarithromycin alone or no antimicrobial treatment [2].

In conclusion, in an infant or a child who is presenting with chronic multiple unilateral lymphadenitis with weak reaction to tuberculin skin test and unresponsiveness to anti-mycobacterium antibiotics, the clinician should suspect NTM. The most prevalent NTM is MAC. Patients with IL12 deficiency have a significant susceptibility to NTM, which is why the clinician should consider IL12 immunodeficiency in a patient with no risk factors for NTM who presents with resistance to treatment. Early recognition with medical and surgical treatment is a crucial part in treating this infection.

## References

1. Field SK, Fisher D, Cowie RL. *Mycobacterium avium* complex pulmonary disease in patients without HIV infection. Chest Journal 2004; 126: 566-581.
2. Tebruegge M, Pantazidou A, MacGregor D, et al. Nontuberculous mycobacterial disease in children—epidemiology, diagnosis and management at a tertiary center. PloS ONE 2016 26; 11: e0147513.
3. Falworth MS, Simpson MT. Cervical lymphadenitis in children: The role of *Mycobacterium avium* intracellulare. Br J Oral and Maxillofac Surg 1996; 34: 511-514.
4. Gollob JA, Veenstra KG, Jyonouchi H, et al. Impairment of STAT activation by IL-12 in a patient with atypical mycobacterial and staphylococcal infections. J Immunol 2000; 165: 4120-4126.
5. Mahapatra S, Mahapatra A, Tripathy S, Rath G, Dash AK. *Mycobacterium avium* intracellulare complex associated extrapulmonary axillary lymphadenitis in a HIV-seropositive infant-A rare case report. Indian J Med Microbiol 2005; 23: 192.
6. Tuerlinckx D, Bodart E, Beckers D, et al. Intrathoracic lymphadenitis caused by *Mycobacterium avium* and *Mycobacterium tuberculosis* in an immunocompetent child. Pediatr Infect Dis J 2008; 27: 759-760.

7. Bentham R, Whiley H. *Mycobacterium avium* complex—making the worst of an opportunity. Microbiology Society 2014.
8. Gray JR, Rabeneck L. Atypical mycobacterial infection of the gastrointestinal tract in AIDS patients. Am J Gastroenterol 1989; 84: 1521-1524.
9. Horsburgh CR. The pathophysiology of disseminated *Mycobacterium avium* complex disease in AIDS. J Infect Dis. 1999; 179: S461-465.
10. Vankayalapati R, Wizek B, Samten B, et al. Cytokine profiles in immunocompetent persons infected with *Mycobacterium avium* complex. J Infect Dis 2001; 183: 478-484.
11. Prince DS, Peterson DD, Steiner RM, et al. Infection with *Mycobacterium avium* complex in patients without predisposing conditions. N Engl J Med 1989; 321: 863-868.
12. Wassilew N, Hoffmann H, Andrejak C, Lange C. Pulmonary disease caused by non-tuberculous mycobacteria. Respiration 2016; 91: 386-402.
13. Ahn CH, McLarty JW, Ahn SS, et al. Diagnostic criteria for pulmonary disease caused by *Mycobacterium kansasii* and *Mycobacterium intracellulare* 1, 2. American Review of Respiratory Disease 1982; 125: 388-391.
14. Teirstein AS, Damsker B, Kirschner PA, et al. Pulmonary infection with *Mycobacterium avium* intracellulare: Diagnosis, clinical patterns, treatment. Mt Sinai J Med 1990; 57: 209-215.
15. Embil J, Warren P, Yakrus M, et al. Pulmonary illness associated with exposure to *Mycobacterium avium* complex in hot tub water: Hypersensitivity pneumonitis or infection? Chest 1997; 111: 813-816.
16. Nightingale SD, Byrd LT, Southern PM, et al. Incidence of *Mycobacterium avium* intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992; 165: 1082-1085.
17. Parent LJ, Salam MM, Appelbaum PC, et al. Disseminated *Mycobacterium marinum* infection and bacteremia in a child with severe combined immunodeficiency. Clin Infect Dis 1995; 21: 1325-1327.
18. Koh SJ, Song T, Kang YA, et al. An outbreak of skin and soft tissue infection caused by *Mycobacterium abscessus* following acupuncture. Clin Microbiol Infect 2010; 16: 895-901.
19. Dodiuk-Gad R, Dyachenko P, Ziv M, et al. Non-tuberculous mycobacterial infections of the skin: A retrospective study of 25 cases. J Am Acad Dermatol 2007; 57: 413-420.
20. Haimi-Cohen Y, Amir J, Eidlitz-Markus T, et al. Chronic cheek lesions: An unusual manifestation of non-tuberculous mycobacterial cervicofacial infection. J Pediatr 2009; 155: 746-748.
21. Thavagnanam S, McLoughlin LM, Hill C, et al. Atypical mycobacterial infections in children: The case for early diagnosis. Ulster Med J 2006; 75: 192-194.
22. Pilkington EF, MacArthur CJ, Beekmann SE, et al. Treatment patterns of pediatric non-tuberculous mycobacterial (NTM) cervical lymphadenitis as reported by nationwide surveys of pediatric otolaryngology and infectious disease societies. Int J Pediatr Otorhinolaryngol 2010; 74: 343-346.
23. Zimmermann P, Tebruegge M, Curtis N, et al. The management of non-tuberculous cervicofacial lymphadenitis in children: a systematic review and meta-analysis. J Infect 2015; 71: 9-18.
24. Fraser L, Moore P, Kubba H. Atypical mycobacterial infection of the head and neck in children: A 5 year retrospective review. Otolaryngology- Head and Neck Surgery 2008; 138: 311-314.
25. Lindeboom JA, Kuijper EJ, van Copenraet ES, et al. Surgical excision versus antibiotic treatment for non-tuberculous mycobacterial cervicofacial lymphadenitis in children: A multicenter, randomized, controlled trial. Clin Infect Dis 2007; 44: 1057-1064.

### Correspondence to:

Ahmed Mohammed Alfaidi,  
Department of General Pediatrics,  
Ministry of National Guard–Health Affairs,  
King Abdulaziz Medical City,  
Kingdom of Saudi Arabia.  
Tel: +966506028863  
E-mail: Ahmed.al.faidi@gmail.com