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CASE REPORTS

NON-TUBERCULAR MYCOBACTERIAL (NTM) INFECTIONS IN CHILDREN; ONE GAME, MANY PLAYERS CASE SERIES FROM A TERTIARY PEDIATRIC CENTRE

Vandana Bharadwaj, Indumathi Chikkanayakanahalli.

Department of Paediatrics, St John's Medical College & Hospital, Bengaluru, Karnataka, India.

ABSTRACT

Non-Tubercular Mycobacterial (NTM) infection is rare in children. As Interleukin-12 interferon gamma (IL-12/IFN-γ) axis plays an important role in conferring immunity to mycobacterial infections, its disorders have been increasingly reported in association with disseminated NTM and Bacillus Calmette Guerin (BCG) infections, known as Mendelian Susceptibility to Mycobacterial Diseases (MSMD). NTM infection occurs infrequently in patients with hematological malignancies undergoing chemotherapy. They have also been implicated in infections following intramuscular injections, laparoscopic and bronchoscopy procedures. We report a series of NTM infections in children with diverse aetiology, treated at a tertiary paediatric centre.

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Introduction

Non-tubercular mycobacteria (NTM) are ubiquitous organisms, occasionally causing clinically significant infections in children. Clinical spectrum varies from mild infections at the site of intramuscular injections and laproscopic ports to disseminated life threatening disease in immunosuppressed children. Underlying immunodeficiencies that predispose to NTM infection include human retroviral infections, primary immunodeficiencies including Mendelian Susceptibility to Mycobacterial Diseases (MSMD) and chemotherapy drugs.[1,2] In this study, we describe clinical, bacteriological and immunological characteristics of four non-HIV children with NTM infections, at a tertiary care centre, details of which are given in Table 1.

Case 1: A 5 months old male child presented with persistent seropurulent discharge following 3rd dose of pentavac injection at right anterolateral thigh since one month. There was no history of fever or contact with tuberculosis (TB). Examination revealed a well child with a sinus track having purulent discharge. Other systems were normal. Grams stain and bacterial cultures on the discharge were negative. Acid fast bacillus (AFB) stain was positive. Cartridge Based Nucleic Acid Amplification (CB NAAT) test did not detect *mycobacterial tuberculosis* (MTB). Mycobacterial cultures yielded NTM growth after 2 weeks. Chest x ray was normal and mantoux test was negative. Child was treated with 4 weeks of clarithromycin (15 mg/kg/day) and ethambutol (20 mg/KG/day). Sinus track healed completely in 4 weeks.

CONTACT Dr Indumathi Chikkanayakanahalli

Email: ckindumathi@gmail.com

Address for Correspondence: Dr Indumathi Chikkanayakanahalli, Department of Paediatrics, St John's Medical College & Hospital, Sarjapura road, Bengaluru 560034.

Case 2: A 12 year old girl, who had undergone laproscopic cholecystectomy 4 months ago for cholelithiasis, presented with skin nodule followed by persistent seropurulent discharge from the laproscopic site for the past 2 months. There was no history of pain in abdomen, fever or cough. Examination revealed a sinus track over the laproscopy site with seropurulent discharge. There was no organomegaly. Discharge was positive for AFB and CB NAAT failed to detect MTB. Culture revealed NTM growth. She was treated with 6 weeks of clarithromycin (15 mg/KG/day) and ciprofloxacin (20 mg/KG/day) Sinus gradually healed.

Case 3: A 11 months old male child, born to second degree consanguineously married couple, presented with fever, recurrent diarrhoea, left axillary swelling and oral thrush since 3 months of age. He was vaccinated with BCG at birth. His elder sibling died of similar complaints at 10 months of life. On examination, he had axillary lymphadenitis and hepatosplenomegaly. Needle aspiration showed AFB and CB NAAT detected MTB that was rifampicin sensitive. Chest X-ray revealed consolidation of right middle lobe. Gastric AFB was positive and culture for mycobacteria was negative. A diagnosis of BCGiosis was made and he was treated with isoniazid (INH), rifampicin, pyrazinamide, ethambutol and levofloxacin. He continued to develop multiple discharging sinuses over next 6-9 months and culture from the inguinal nodes grew NTM which was identified as *Mycobacterium chelonae*. Pyrazinamide and INH were stopped and clarithromycin, linezolid and aminoglycoside were given along with levofloxacin for the next one year. Immunological workup for classic primary and secondary immunodeficiencies were carried out. Serum immunoglobulins and lymphocyte subsets were normal. Di Hydro Rhodamine (DHR) test for Chronic Granulomatous Disease (CGD) was negative. Retro viral infection was also ruled out. Whole exome sequencing revealed a novel Autosomal Recessive partial Interferon gamma R2 (AR IFNGR2) deficiency (homozygous nucleotide deletion, c.4delC.

Interferon γ injection could not be procured and parents were unwilling for Hematopoietic Stem Cell Transplantation (HSCT). He succumbed to persistent disseminated NTM infection at the age of 4 years.

Case 4: A 4 year old boy on intensive treatment for acute lymphoblastic leukemia (ALL), in remission, presented with fever for 48 hours.

He was the first child of a non consanguineous marriage, with appropriate development for age, immunized upto date without any complications. He had a younger sibling 1 year of age who was well. He had tender erythematous papular rashes predominantly over the lower limbs , suggestive of erythema nodosum (EN). (Fig 1) There was no lymphadenopathy or hepatosplenomegaly. Subsequently, he developed infection at central venous access device site, requiring removal. Blood culture and pus from the line exit site showed AFB and growth of *Mycobacterium Chelonae*. Skin biopsy showed pannculitis and AFB. Gastric aspirate was negative for CBNAAT and AFB. Chest x ray and echocardiography were normal. CT thorax showed patchy consolidation. Genetic analysis for MSMD mutations was negative. He was initially treated with amikacin 15 mg/kg/d, clarithromycin 125 mg twice daily rifabutin 10 mg/kg/day and ethambutol 20 mg/kg, for 7 months. Fever settled with waxing waning course of EN. Due to recurrence of EN, ethambutol was stopped, and linezolid 10 mg/kg twice daily, and levofloxacin 15 mg/kg were added to rifabutin and clarithromycin. Linezolid was stopped after 6 months. Chemotherapy for ALL was continued. Currently the child remains well on NTM treatment with Rifabutin, Clarithromycin and Levofloxacin, and ALL maintenance therapy.

Figure 1. Skin manifestation of disseminated M.Chelonae infection (patient 4)

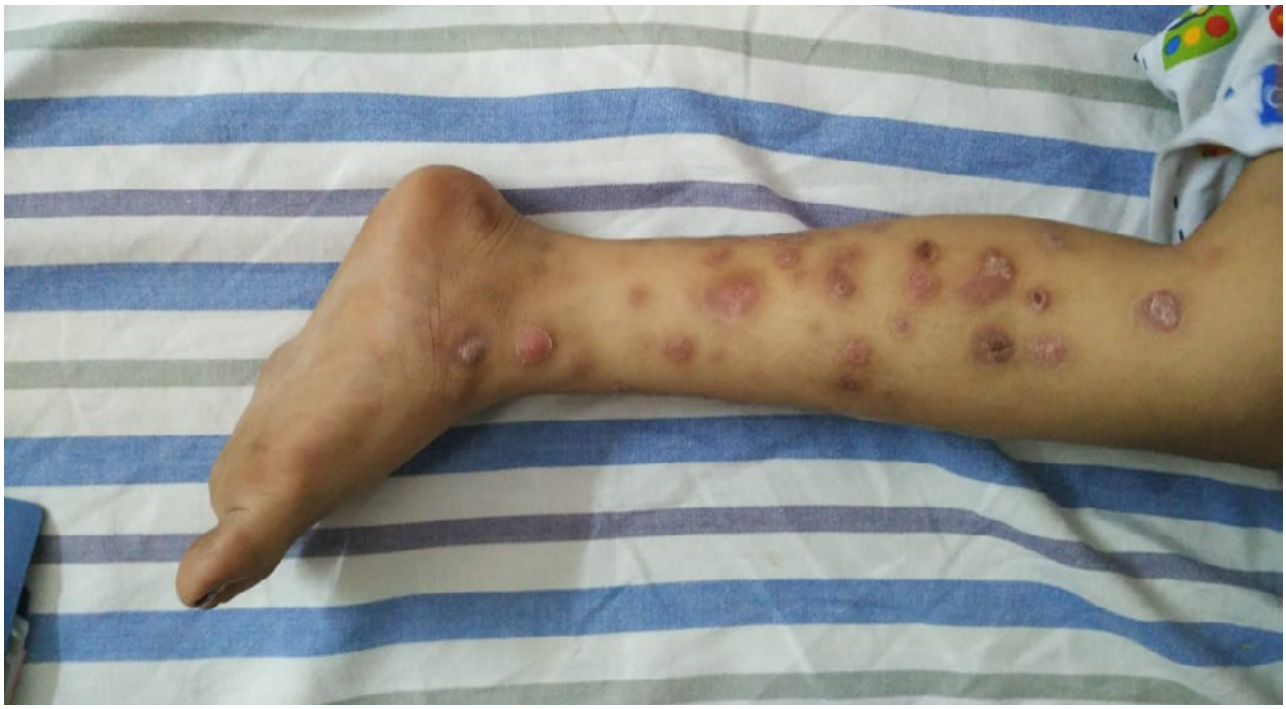

Table 1. Clinical characteristics of NTM infection in children

	Case 1	**Case 2**	**Case 3**	**Case 4**
Age at presentation/sex	5 months Male	12 years Female	11 months Male	
Organism	Species not identified	Species not identified	*M. Chelonae*	*M. Chelonae*
Site of infection	Sinus antero-lateral thigh	Port site (cholecystectomy)	Disseminated - inguinal nodes, multiple sinuses	Disseminated - Skin, blood, central venous catheter site, lung
Other infections	No	No	BCG disease Candida	Pseudomonas UTI
Trigger for NTM	Immunisation 2 months prior	Laparoscopic surgery	IFN-γ R2 (AR IFNGR2) deficiency (homozygous nucleotide deletion, c.4delC)	Acute lymphoblastic leukemia (ALL)

Drugs/ Duration of treatment	Clarithromycin/ Ethambutol for 4 weeks	Clarithromycin /Ciprofloxacin for 6 weeks	INH, Rifampicin, pyrazinamide, Ethambutol, levofloxacin, linezolid - multiple courses in various combination	Amikacin, Clarithromycin, Rifabutin/Ethambutol/Linezolid/Levofloxacin 24 months
Status	Well	Well	Unremitting NTM disease Succumbed at 4 years	Well. Continues NTM & ALL therapy

Discussion

The spectrum of NTM infections varies from infections limited to skin and lymph nodes in immunocompetent children to disseminated life threatening disease in immunocompromised children.[1,2,3] In our series, children 1 & 2 presented with skin and port site infections respectively with no evidence of immunodeficiency, where as IFNGR2 deficiency was responsible for disseminated M. chelonae infection in case 3, chemotherapy induced immunosupression predisposed to same in case 4.

Cluster outbreaks and isolated abscesses due to contamination of injectables with NTM species have been reported in literature. A study from Korea described an outbreak of intramuscular abscesses with *M. massiliense* infection in 77 patients, youngest being 4 year old[4] like our child (case 1). Devi et al reported a 3 year child with M fortuitum abscess following IM injection in isolation.[5] Abscesses require short courses of antitubercular drugs which act specifically on NTM. Clarithromycin alone was used in Korean series; Devi et al used 3 drug combination therapy; we found good response with clarithromycin and ethambutol for 4 weeks.

M. fortuitum and M. chelonae has emerged as common aetiology of port site infections (PSI) following laparoscopic surgeries due to breach in sterilisation protocols. Similar to our child, Chaudhuri et al described 19 patients with PSI due to *M. chelonae-fortuitum* infections following laproscopic cholecystectomy.[5] Treatment of NTM PSI lacks consensus; in general there is an agreement on using clarithromycin and quinolones for 4-6 weeks.[6,7] We found good response with 6 weeks of clarithromycin and ciprofloxacin. Sterilisation of laproscopes with orthophthaldehyde and per acetic acid largely prevent NTM infections.[7] Positive AFB and negative CB NAAT results on sterile pus alerted us to a possibility of NTM infections in the above mentioned patients.

Genetic disorders of IL-12/IFN-γ axis have been increasingly reported in association with disseminated NTM/BCG infections.[3] Our child (case 3) with novel IFNGR2 mutation presented with disseminated *M. chelonae* infection similar to recurrent, disseminated disease by *M. simiae* in children with IFNGR2 mutations described by Martinez Barricarte et al.[8] Dual/sequential mycobacterial infections should arouse a suspicion of MSMD. Whereas Glanzmann et al reported a child with IFNGR1 having simultaneous *Mycobacterium tuberculosis* and NTM, index child presented with sequential BCG and NTM strains.[9] Interferon gamma injections have been tried as an adjunctive therapy to ATT in partial IFNGR2 deficiencies with varied success.[3] It was considered in our child, but could not be procured. A transplant centre in India has reported successful HSCT on 2 siblings with IFNGR2 deficiency.[10] Unfortunately, limited availability and high cost of HSCT was a limiting factor in our child.

NTM infection in children on treatment for malignancy is rare. A recent case series showed an incidence of 0.4 infections/100,000 patient days, and half the patients had a haematological malignancy.[11] Our patient (case 4) with ALL had a catheter related infection similar to most patients in the above series, although pulmonary and skin involvement seen in the index case was less common. The presence of AFB and panniculitis in the skin biopsy was akin to that of case report of patient with AML and disseminated M.Chelonae infection.[12] Similar to our patient, central venous line was removed and combination antimicrobial therapy was given to most patients with disseminated infection.[11] As with our patient, clinical response was used by other groups to determine duration of treatment.[12] It was deemed prudent to continue lympholytic therapy (oral 6-Mercaptopurine and Methotrexate) as per standard guidelines whilst on NTM treatment (expert opinion, personal correspondence).

Whilst *Mycobacterium avium* complex (MAC) is a common NTM causing infections in HIV infected individuals, *M. chelonae* and *M. abscessus* are most commonly implicated in non HIV immunosuppressed patients.[2] Similarly case 3 and case 4 with IFNGR2 defect and leukemia respectively presented with disseminated *M.chelonae* infections. Optimal regimen and duration of treatment of disseminated *M. chelonae* infections is not well established in non-HIV immunosuppressed patients. Clarithromycin being the back bone, is supplemented with other drugs including amikacin in initial phase. Our therapy was guided by sensitivity pattern suggested in a review article, wherein *M. chelonae* exhibited 100% sensitivity to clarithromycin, 90% to linezolid and 60% to amikacin.[13] Duration of treatment is for at least 6 months.[2,13] Both our patients required longer duration of therapy for persistent/recurrent disease. There is no consensus on the role of prophylaxis in this group of patients. Though amikacin had greater toxicity when co-administered with cancer chemotherapy in other series, our child tolerated it well.[11]

This study is subject to the limitations of a retrospective series, including reporting bias. Lack of antibiotic sensitivity patterns led to use of empirical treatment regimes for NTM.

In summary, we report a single center experience of children without HIV infection, who developed different forms of NTM infection. Our study contributes

significantly to limited literature of pediatric NTM in non-HIV patients, particularly in the Indian subcontinent.

Compliance with Ethical Standards

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Conflict of Interest None

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