Mycobacterium simiae: a rare cause of cervical lymphadenitis—case report

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Abstract: There are over 140 species of non-tuberculosis bacteria that cause a wide range of infections in the human host, with cervical lymphadenitis being the most common in immunocompetent children. Due to the slow growing nature of the species, this usually presents as a slowly-enlarging, non-tender unilateral swelling in the neck. We present the case of previously healthy 7-year-old indigenous female, who presented with a 3-month history of right sided, non-tender neck swelling, without systemic symptoms. Ultrasound demonstrated an enlarged right submandibular node and subsequent fine needle aspirate did not yield a microbiological diagnosis, thus she progressed to incision and drainage. Histology revealed necrotising granulomas, consistent with mycobacterial infection. Further stains and extended cultures did not yield a specific diagnosis. She was commenced on empiric therapy for *Mycobacterium avium* complex (MAC), however was lost to follow-up, before re-presenting with progressive neck swelling. The patient then underwent surgical excision of the node, and histology revealed chronic inflammation with non-necrotic granulomas, while polymerase chain reaction identified *Mycobacterium simiae* (*M. simiae*). The child recovered well, and at a follow-up review 5 months post operatively, the wound had healed well, with no palpable adenopathy present, and repeat ultrasound revealed only non-pathological small lymphadenopathy. This case demonstrates a rare cause of cervical lymphadenitis which was ultimately successfully treated with surgical resection; highlighting the challenges of both diagnosis and treatment of the pathogen given its multi-drug-resistant tendency.

Keywords: Infectious disease; paediatrics; cervical lymphadenitis; *Mycobacterium simiae* (*M. simiae*); case report

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Introduction

Nontuberculous mycobacteria (NTM) are acid-fast organisms that can be classified as either rapid-growing or slow-growing pathogens. There exist over 140 species that cause a range of infections in both immunocompetent and immunosuppressed hosts (1-4). Of these, NTM cervical lymphadenitis is the most common manifestation in immunocompetent children and slowly-growing *Mycobacterium avium* complex (MAC) is the most common causative pathogen, though other rarer causes have been reported (1,2,4,5). *Mycobacterium simiae* (*M. simiae*) is a slow-growing, multidrug-resistant obligate aerobe that generally causes pulmonary, intra-

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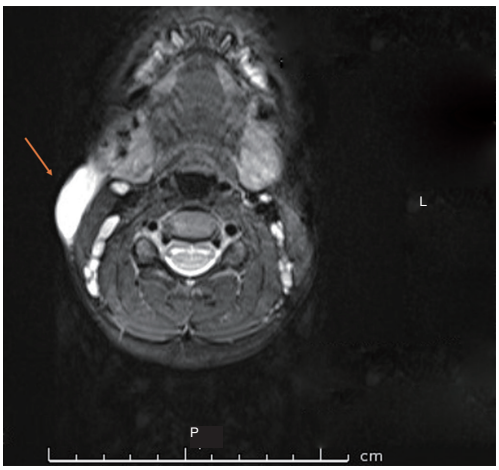

Figure 1 Diagnostic T2 axial MRI image of neck showing a hyperintense signal from the lesion and the superficial fluid collection (arrow). L, left; P, posterior; MRI, magnetic resonance imaging.

abdominal and occasionally disseminated infections in immunocompromised hosts, within a restricted geographic distribution. This organism is generally difficult to identify, and is also difficult to treat as it is one of the most highly multidrug resistant organisms in the mycobacterium species. Complete surgical resection remains the gold standard of therapy for all NTM cervical lymphadenitis infections, while choice of antibiotic regime remains a difficult decision due to a lack of clinical trials as a result of the low incidence of infection with *M. simiae* (6-10). We present the following case in accordance with the CARE reporting checklist (available at https://www.theajo.com/article/view/10.21037/ajo-21-50/rc).

Case presentation

A previously healthy 7-year-old Indigenous Australian female was seen by a general practitioner (GP) for a 3-month history of increasing swelling and skin changes over the right side of her neck. The patient denied having fevers, night sweats or weight loss. There was no history of preceding upper respiratory or dental infection. The patient took no regular medications and had no known allergies. The patient had recently moved into foster care and the previous history of exposure to unclean water, or animals was unclear.

Two months prior to seeing this GP, the patient had an ultrasound (US) study of her neck to investigate a swollen right submandibular region. This study showed right submandibular lymphadenopathy with 2 enlarged soft lymph nodes, measuring 2.4 cm × 2.2 cm. A fine needle aspirate (FNA) of the enlarged lymph nodes could not be performed at the time of the US study due to lack of patient cooperation.

She was referred by the GP to the ear, nose and throat (ENT) specialists at the local regional tertiary care centre. Physical examination of the child revealed a well-looking child in no apparent distress. Vital signs were within normal limits and her growth was appropriate for age. On examination of the neck, a discrete 3 cm fluctuant mass was palpable over levels Ib and II. The overlying skin was intact but thinned, and erythematous with violaceous discolouration. Examination of the ears and nose were normal as was the remainder of her physical examination.

Laboratory evaluation revealed a full blood count with normal white blood cell, neutrophil, lymphocyte, monocyte, eosinophil and basophil counts. The haemoglobin and haematocrit were normal, and the platelet count was unremarkable. The C-reactive protein was less than 2.9 mg/dL. Liver function tests and biochemistry were unremarkable. Serology for toxoplasmosis was negative. Serology for both Epstein Barr virus and cytomegalovirus IgG were reactive, and IgM was not detected, suggesting past infection.

FNA of the lymph node was performed under sedation. 4 mL of cloudy haemoserous fluid was drained from the neck mass and sent for microscopy, culture, and sensitivity (MCS). Analysis of the aspirate did not yield any results and a pre-operative work-up was undertaken including a repeat US scan and magnetic resonance imaging (MRI) scan of the neck. The US revealed progression of lymph node enlargement while the MRI showed a thin walled peripherally enhancing lesion within the superficial soft tissues over the right sternocleidomastoid muscle, extending from just below the level of the right parotid gland to the level of C5 vertebral body (*Figure 1*). Multiple mildly prominent lymph nodes were seen throughout the neck, but none were pathologically enlarged or necrotic.

The patient underwent incision and drainage of the right neck mass. Necrotic debris was curetted and collected for pathology. The skin easily tore and was unable to be closed primarily and was therefore left to heal by secondary intention. Histology showed fragmented inflammatory tissue with heavy lymphohistiocytic infiltrate and broad zones of fine eosinophilic necrosis with neutrophil debris and dystrophic calcification, features consistent with necrotising granulomatous and mycobacterial infection.

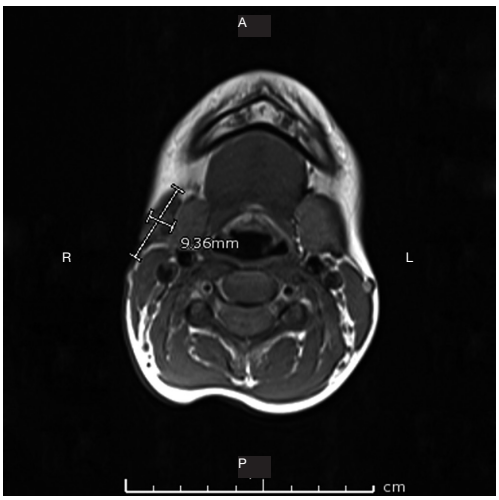

Figure 2 T1 axial MRI image showing nodal mass on the lateral aspect of the submandibular gland prior to surgical excision. L, left; R, right; A, anterior; P, posterior; MRI, magnetic resonance imaging.

Special stains did not however yield any mycobacterial or fungal organisms. Following surgery, the child was commenced on a 5-day course of oral amoxicillin-clavulanate 540 mg twice daily to cover for possible bacterial infection. She was reviewed by the Infectious Diseases service and commenced on a planned 6-month course of clarithromycin 180 mg twice daily and rifampicin 180 mg twice daily for presumed MAC cervical lymphadenitis. For reasons unknown, rifampicin and clarithromycin were only continued for 2 weeks and the patient was lost to follow-up.

Five months post procedure, the patient returned for review by ENT and infectious diseases. The right neck mass was still prominent with overlying erythema and the surgical wound from the incision and drainage had healed with extensive scarring and keloid features. Extended cultures had not yielded any pathogens. The child was again commenced on empirical treatment for MAC infection with clarithromycin 380 mg daily divided into twice daily doses, and rifampicin 190 mg twice daily. She was reviewed regularly by both Paediatric and Infectious Diseases services to ensure medication compliance and tolerance. She reported no side effects and completed a 6-month course of antimicrobial therapy. A repeat US was performed which revealed a 1.9 cm heterogenous hyperaemic structure deep to platysma and posterolateral to her submandibular saliva gland. The surgical team favoured avoiding a nodal dissection due to the significant risk to the marginal branch of her facial nerve. Medical management was therefore continued with Ethambutol 400 mg daily added to the antibiotic regimen due to suboptimal response to dual-agent therapy. A chest radiograph was clear with no evidence of pulmonary infiltrates. Baseline ophthalmology assessment was performed and repeated at 3 and 6 months to monitor for signs of optic neuropathy secondary to ethambutol. Triple-antibiotic therapy was continued for an additional 6 months. At the 11th month of medical management, she presented with minor skin breakdown overlying the cervical node with associated intermittent wound discharge.

Discharge from the wound was swabbed and sent for MCS, acid-fast bacilli (AFB) smear and panmycobacterial PCR which were negative, and from a multidisciplinary team opinion, definitive surgical management was now required. Surgical work-up included a repeat MRI which revealed persistent lobulated and heterogenous tissues at the site of the previous collection superficial to the right submandibular gland abutting the inferior aspect of the body of mandible, measuring 2.2 cm × 0.7 cm × 2.7 cm (transverse, anterior-posterior, superior-inferior), with smaller rounded regions of T2 and T1 hypointensity and little peripheral enhancement (*Figure 2*). Reactive lymph nodes persisted within the deep cervical lymph chain and posterior triangle of the neck.

Surgical excision of the right submandibular lymph nodes and revision of scar was undertaken. Intraoperatively both the marginal mandibular and cervical branch of her facial nerve were located and seen to be running directly over an enlarged and fluctuant right perifacial node (*Figure 3*). The nodal mass was dissected off the submandibular gland once the facial nerve branches had been mobilised and preserved. The resected tissue was bisected and sent fresh and in formalin to pathology for histology, MCS, AFB, panmycobacterial PCR and pan fungal PCR. Histopathology revealed granulomatous inflammation with a large central area of necrosis, degenerate material and a thin rim of fibrous stroma surrounding the area of necrosis and residual rim of lymphoid tissue (*Figure 4*). Scattered chronic inflammatory cells and some giant cells with few non-necrotising granulomas were seen in the adjacent fibroadipose tissue. Special stains did not yield any mycobacterial organisms and there was no evidence of atypical cells, malignancy or fungal organisms. Culture from nodal tissue grew *Staphylococcus epidermidis* and PCR identified *M. simiae*.

The child recovered well post-operatively with no palpable adenopathy. Some mild right-sided mandibular

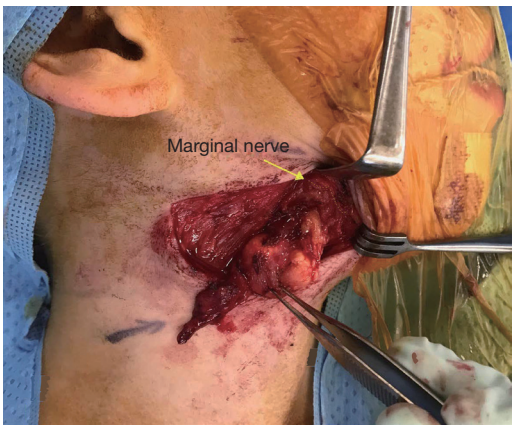

Figure 3 Intra-operative image of nodal dissection demonstrating close proximity of the mass to the marginal nerve.

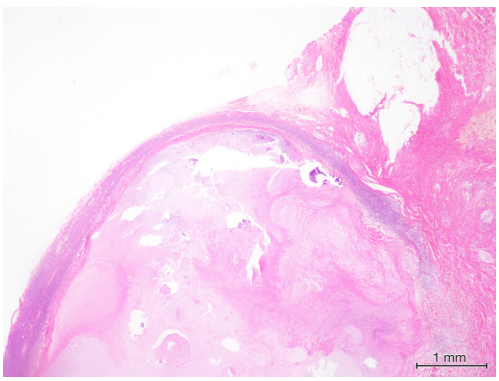

Figure 4 H&E stain of resected lymph node demonstrating extensive necrosis with a thin rim of residual lymphoid tissue only. H&E, hematoxylin and eosin.

facial nerve palsy was evident but improved on outpatient review eight weeks post-operatively. Five months post-operatively the child was clinically well with a healed wound and no palpable cervical adenopathy. An US of the neck revealed non-pathological small lymphadenopathy without central necrosis.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent or legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal on request.

Discussion

NTM are acid-fast organisms that reside in water and soil. There are currently more than 140 recognised species of NTM, classified as rapid-growing or slow-growing pathogens. They can cause a broad range of infections including skin and soft tissue infections (SSTIs), lymphadenitis, pulmonary disease, otitis media and osteomyelitis (1-4,11). In a prospective national study of NTM infection in children in Australia, Blyth *et al.* [2009] found that disseminated disease and mediastinal lymphadenitis are atypical presentations, and are more likely to be associated with underlying immunodeficiency (12). Additionally, pulmonary infection, though not atypical, is more likely to occur in association with underlying lung disease. Cervical lymphadenitis is the most common manifestation in immunocompetent children and slow-growing MAC is the most common causative pathogen followed by *M. scrofulaceum*, *M. kansasii*, *M. fortuitum* and *M. haemophilum* (1,2,4,5). *Table 1* outlines the available case reports of NTM presentations in the paediatric population since 1989 in Australia and New Zealand. Notably, the species isolated in each report is variable with some cases identifying multiple NTM species, and there appears to be no consistent mode of treatment amongst reports (1,13-28). None of these case reports identified a case of *M. simiae*. Due to their slowly-growing nature, NTM cervical lymphadenitis typically presents as a non-tender slowly enlarging unilateral neck mass in the submandibular, parotid and pre-auricular regions with violaceous skin discolouration secondary to inflammatory reactions (6,7). Over several months, the enlarging mass can undergo central necrosis, liquefaction, fluctuation, eruption and sinus formation and at this stage most children are already referred to or seen by an ENT or paediatric infectious disease specialist (1,4,6).

In our case, *M. simiae* was detected on PCR. *M. simiae* is a slow-growing, multidrug-resistant obligate aerobe, and gram-positive AFB, first isolated from Macacus rhesus monkeys in 1965 (3,8). The primary mode of transmission and the natural habitat of this organism still remains unclear although *M. simiae* isolates have been recovered from sporadic pseudo-outbreaks from contaminated water supplies (9). Initially, *M. simiae* was geographically restricted to Southwestern United States, Cuba, Israel and the island of Guadeloupe however rare clinical cases of *M. simiae* infections including pulmonary, intra-abdominal

Table 1 Comparison of paediatric nontuberculous mycobacterium infections in Australia and New Zealand from 1989 to 2022

Author	Year of publication	Patient demographics	Pathogens isolated	Management
Joshi *et al.* (13)	1989	Review of 86 children	Unspecified isolates	All children were treated surgically and recurrence occurred in five patients
Pang (14)	1992	Review of 118 children	*M. tuberculosis*, *avium* complex and *scrofulaceum*	Total excision with 10% of patients requiring second excision due to relapse or residual disease
Goutzamanis and Gilbert (15)	1995	Review of 8 children	*M. ulcerans*	Surgical excision for all patients with one patient requiring limb saving heat treatment after both anti-mycobacterial drug and surgery failed to stop progression of necrotizing ulceration
Wright (16)	1996	Review of 89 children ages 1 to 10 years old	Unspecified NTM isolates	55 surgical excisions with one recurrence and eight excision and curettage with two recurrences
Wark *et al.* (17)	1998	Review of 10 children ages 1 to 5 years old	*M. avium*, *intracellulare*, *gordanae*	Nine surgical excisions as initial management with one developing a discharging sinus requiring 2 weeks of Trimethoprim/Sulfamethoxazole and Rifampicin
				1 incision and drainage with recurrence of disease requiring complete excision
Fergusson and Simpson (18)	1999	Review of 10 children	Unspecified NTM isolates	Ten successful curettages with two experiencing delayed wound healing and one requiring a repeat curettage 7 months post-primary excision due to recurrence
O'Brien *et al.* (19)	2000	Review of 4 children ages 0 to 9 years old	*M. avium* complex, *fortuitum*, *gordanae*	All 4 underwent surgical excision for lymphadenitis with no adjunctive chemotherapy and no relapse of disease detected
Flint *et al.* (20)	2000	Review of 57 children	*M. avium intracellulare*, *kansasaii*	Eleven received surgical excisions, 30 patients received incision and drainage, 13 received incision and curettage and three had aspirations
Daley (11)	2001	3-year-old patient	*M. avium* complex	Spontaneous resolution of lymphadenopathy, no medical or surgical intervention
Blyth *et al.* (12)	2009	Review of 102 children ages 1 to 14 years old	*M. avium* complex, *intracellulare*	78 surgical procedures and 42 received anti-mycobacterial therapy, 25 received both therapies
Sparks and Khatami (21)	2014	14-year-old patient	*M. fortuitum*	10-week course of oral Trimethoprim/ Sulfamethoxazole and Moxifloxacin
Chong *et al.* (22)	2015	12-year-old patient	*M. avium* complex, *intracellulare*	12-month course of Ethambutol and Clarithromycin
Tebruegge M *et al.* (1)	2016	Review of 140 children with NTM disease	*M. avium* complex, *ulcerans*, *marinum*	97.2% of lymphadenitis cases underwent surgical excision with reduced disease recurrence in groups treated with Clarithromycin and Rifampicin compared with groups with Clarithromycin alone or no anti-mycobacterial drugs
Mahadevan (23)	2016	Review of 97 children ages 8 to 15 years old	Unspecified NTM isolates	Higher cure rates with excision compared to incision and drainage

Table 1 (*continued*)

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Author	Year of publication	Patient demographics	Pathogens isolated	Management
Freyne and Curtis (24)	2017	3-year-old patient	*M. gordonae*	Excision biopsy followed by treatment of Clarithromycin, Rifampicin and Ethambutol for 3 months. Clarithromycin changed to Azithromycin for improved compliance and oral regimen continued for 6 months total
Berkhout A *et al.* (25)	2020	13-year-old patient	*M. abscessus*	Initial treatment with two surgical debridements and insertion of Vancomycin beads followed by 8-week oral course of Azithromycin and Linezolid followed by 6-month course of same while awaiting definitive procedure
Aliano and Thomson (26)	2020	Review of 99 children ages 0 and 12 years old	*M. avium* complex, *intracellulare*, *haemophilum*	Not discussed in article
Foley *et al.* (27)	2021	12-year-old patient	*M. fortuitum*	Initial treatment with surgical debridement, oral Rifampicin and Doxycycline. Changed to intravenous Meropenem and oral Azithromycin, Doxycycline, Ciprofloxacin and Fluconazole on day 6. Antimicrobials rationalised to Doxycycline, Ciprofloxacin and Fluconazole on day 30
Weng *et al.* (28)	2022	20-month-old patient	*M. avium* complex	Unspecified in abstract

NTM, nontuberculous mycobacteria.

and disseminated disease in immunocompromised hosts, particularly patients infected with human immunodeficiency virus have now been reported worldwide (3,8,29). It is also a rare cause of cervical lymphadenitis in immunocompetent children and to the best of our knowledge, there have only been two case reports of *M. simiae* cervical lymphadenitis in children and our case is the first reported case in Australia (3,8,30).

Our case report highlights the diagnostic and therapeutic challenges posed by *M. simiae* cervical lymphadenitis. Firstly, identification of *M. simiae* proved difficult. Despite FNA, swabs, and tissue examined by AFB smear, culture and other special stains, standard laboratory techniques including pigmentation, growth rate and biochemical testing were unable to isolate and identify the NTM species (31). It was presumed that the child had MAC infection, based on clinical features, and was thus treated accordingly. Definitive surgical management was initially not favoured because of the concern that an excision would endanger the marginal mandibular branch of her facial nerve.

Choice of antibiotic therapy for *M. simiae* is difficult as it is the most drug-resistant organism of all the NTM (3,8). *In vitro* and *in vivo*, *M. simiae* has demonstrated resistance to all conventional antituberculous drugs including rifampin and ethambutol and to date, there are no published clinical trials of treatment for *M. simiae* complex disease due to its rarity (10). In the absence of robust clinical trials, the American Thoracic Society has suggested a clarithromycin-based multiple drug regimen based on several cases that have reported favourable clinical outcomes (8,30). Duration of antimycobacterial therapy is also reportedly variable from 6 months to more than 1 year, based upon clinical response (8,30). Combinations of clarithromycin, ethambutol and ciprofloxacin have been reported to have varying success in adults with disseminated *M. simiae* infection in the setting of acquired immunodeficiency syndrome (32). In our case, the child received 6 months of clarithromycin-based dual antibiotic therapy followed by 6 months of triple antibiotic-therapy without a significant clinical response. There was no palpable reduction in mass size which was corroborated on repeat imaging, and the child developed intermittent skin breakdown with discharge which necessitated complete excision of the involved nodal mass.

Surgical treatment with complete excision is considered the gold standard treatment of NTM cervical lymphadenitis (4), with incision and curettage an alternative. To date, there

is only one randomised controlled trial that compared the cure rates of surgical treatment and conservative antimycobacterial therapy. This study concluded that surgical treatment was the superior of the two with cure rates of 96% compared to 66% (5). Nevertheless, surgical treatments are not without their risks and complications such as wound infection, infection recurrence, formation of sinus tract or haematoma, scarring and poor cosmesis and most importantly, facial palsy from facial nerve damage (1,3,5,8). Arguably, in the absence of clinical trials for conservative antimycobacterial therapy, surgical excision may be the prudent choice of therapy in confirmed cases of *M. simiae* due to its limited susceptibility to antimicrobial agents (3).

Our reported case, the first of its kind in Australia, was a diagnostic and therapeutic dilemma from onset of symptoms until definitive surgical treatment. While *M. simiae* is usually associated with immunocompromised individuals and while our patient is immunocompetent, she is of indigenous background, living in foster care and was living rurally at the time of onset of symptoms. There are multiple factors that could explain infection such as contact with contaminated soil or water sources. This case serves to remind treating physicians that atypical and rare mycobacterial infections such as *M. simiae* should be included in the differential diagnosis of an immunocompetent child with cervical lymphadenitis. If *M. simiae* is suspected, early surgical intervention should be considered given *M. simiae* is a multidrug resistant organism that is difficult to cure with antimycobacterial therapy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://www.theajo.com/article/view/10.21037/ajo-21-50/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent or legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal on request.

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