CASE REPORT

Successful Treatment of Nasal and Parotid *Mycobacterium avium* Complex Infection in Adult-Onset Immunodeficiency: A Case Report with Literature Review

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Non-tuberculous mycobacteria (NTM) infection has increasingly been reported throughout the world, especially in Asia. Autoantibodies to interferon-γ are implicated in the pathogenesis of adult-onset immunodeficiency resulting in multiple opportunistic infections, in particular NTM infection. There are few reports regarding *Mycobacterium avium* complex infection of the nasal cavity or parotid gland in this condition. The authors reported the first case of nasal and parotid *Mycobacterium avium* complex presenting with recurrent epistaxis, nasal mass, and parotitis successfully treated with combined systemic and topical anti-mycobacterial agents in Thailand.

Keywords: Nasal and parotid *Mycobacterium avium* complex; Nontuberculous mycobacteria; Autoantibody to interferon-γ; Nasal mass; Epistaxis; Parotitis

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Non-tuberculous mycobacteria (NTM) are ubiquitous organisms with low virulence. However, disseminated NTM infection to multiple organs can occur in immunocompromised hosts. Adult-onset immunodeficiency caused by anti-interferon-γ antibody, which binds to either interferon-γ or its receptor, neutralizes the pathway of eradicating intracellular pathogens. In particular, NTM are among the most common opportunistic infections in this setting. Hereby, the authors reported a rare manifestation of this disease presenting as recurrent epistaxis, nasal mass, and parotitis caused by *Mycobacterium avium* complex (MAC) infection.

Case Report

A Thai female, 40 years old, presented to the authors' hospital with recurrent epistaxis for three months. Low-grade fever and enlargement of the left neck area were noted two weeks prior to this visit. A spontaneous sinus tract with draining pus developed, leading the patient to the hospital. The patient was non-diabetic and non-alcoholic. She denied herbal use. Physical examinations revealed a low-grade fever of 38°C. Otherwise, her vital signs were within the normal range. Anterior rhinoscopy showed an irregular necrotic mass at the left inferior turbinate and nasal floor with diffuse mucosal bleeding (Figure 1A). No pus was seen in the left Stensen duct os. The left parotid gland was swollen, warm, and painful on palpation without fluctuation. The surrounding subcutaneous tissue extended to the left temporal area and was also warm and swollen. Palpable, painless, matted left cervical lymph nodes at levels Ib and II, 1.5 cm in size, were noted. No other lymphadenopathy or hepatosplenomegaly was detected.

Laboratory results only showed leukocytosis of 15,120 cells/mm^3 with 72% neutrophils, and coagulation tests, blood chemistry, and urinalysis were unrevealing. High sensitivity C-reactive protein (hs-CRP) was 31 mg/dL. Anti-HIV was negative. There were minimal reticular opacities in both upper lung fields. Sputum polymerase chain reaction (PCR) for the *Mycobacterium tuberculosis* complex and mycobacterial culture were negative. Blood culture for mycobacterium was not done. Computed

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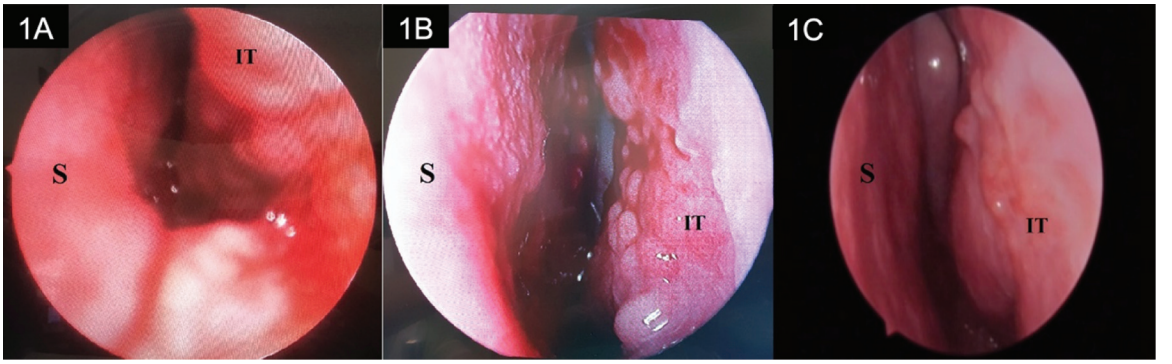

Figure 1. The sequential figure from 1A-1C demonstrates endoscopic findings of the left nasal cavity from initial presentation (1A) to posttreatment with anti-tuberculous agents (1B) and 2 months posttreatment with the appropriate regimen (1C) in which mass-like lesions regressed.

S=nasal septum; IT=inferior turbinate

tomography of the chest showed fibrotic changes consistent with an old granulomatous process.

Computed tomography (CT) of the paranasal sinuses demonstrated chronic sinusitis with hyperdense content consistent with blood in the left maxillary sinus. There were several subcutaneous enhancing soft tissue lesions at the left-sided buccal, left parotid, left temporalis muscle, and left temporofrontal regions measuring approximately 1.5×4.7×5.8 cm (Figure 2A). Increased vascularity and fat reticulation of the left parotid gland were noted, reflecting left parotitis. CT also showed infiltrative contrast-enhancing lesions involved in the left nasal cavity, predominantly at the left inferior turbinate (Figure 2B).

Differential diagnoses from the radiologist included infectious abscess and parotitis with reactive lymph nodes or neoplastic process such as lymphoma or infiltrative tumors. However, specific etiologies of infectious process could not be specified by the imaging findings alone.

The provisional diagnosis was left parotitis with parotid abscess and left nasal mass. The patient underwent nasal endoscopy with a left nasal mass biopsy. Incision and drainage of the left parotid abscess with incisional biopsy were performed. Only necrotic tissue was found at the left parotid gland. Ziehl-Neelsen staining revealed rare acid-fast bacilli from a draining fluid but was 2+ and 1+ from the left inferior turbinate tissue and left parotid tissue, respectively. Histopathology of the parotid gland tissue was consistent with lymph node structure (intra-parotid lymph node), showing small granuloma with acute lymphadenitis. Histopathology from left inferior turbinate tissue revealed intracellular acid-fast bacilli within foamy histiocytes and acute and chronic xanthogranulomatous inflammation.

Subsequent cultures grew the MAC from both tissues. The bacterium was susceptible to clarithromycin with a minimum inhibitory concentration (MIC) of 0.5 µg/mL. The final diagnosis was nasal and parotid MAC infection. Acquired adult-onset immunodeficiency was diagnosed from a strong positivity of anti-interferon-γ antibody detected by indirect enzyme-linked immunosobent assay (ELISA). The titer was 4.00 (cut-off of less than 1 at optic density, OD 405/630 nm).

Clarithromycin of 1,000 milligram per day, ethambutol 15 milligram per kilogram per day, and rifampicin 10 milligram per kilogram per day were administered. Soft tissue, cervical lymphadenopathy, and draining sinus dramatically improved within two weeks.

Nevertheless, recurrent massive epistaxis at the left nasal cavity was still encountered, requiring red cell transfusion. The patient underwent endoscopic sphenopalatine artery ligation. Absorbable packs at both nasal cavities were performed, but the lesion rebled two weeks thereafter. Packs were changed to non-absorbable merocel. Due to uncontrolled infection in the nasal cavity, the team decided to give additional once daily intravenous amikacin 15 milligram per kilogram per day and local amikacin nasal drops. The MIC of amikacin was 2 µg/mL. However, no standard interpretation for MAC was available. To allow the amikacin drop to adequately contact the pathologic area, the merocel packs were adapted to combine with rubber porous finger cod made from a sterile rubber glove.

The preparation of topical amikacin was 25 mg/

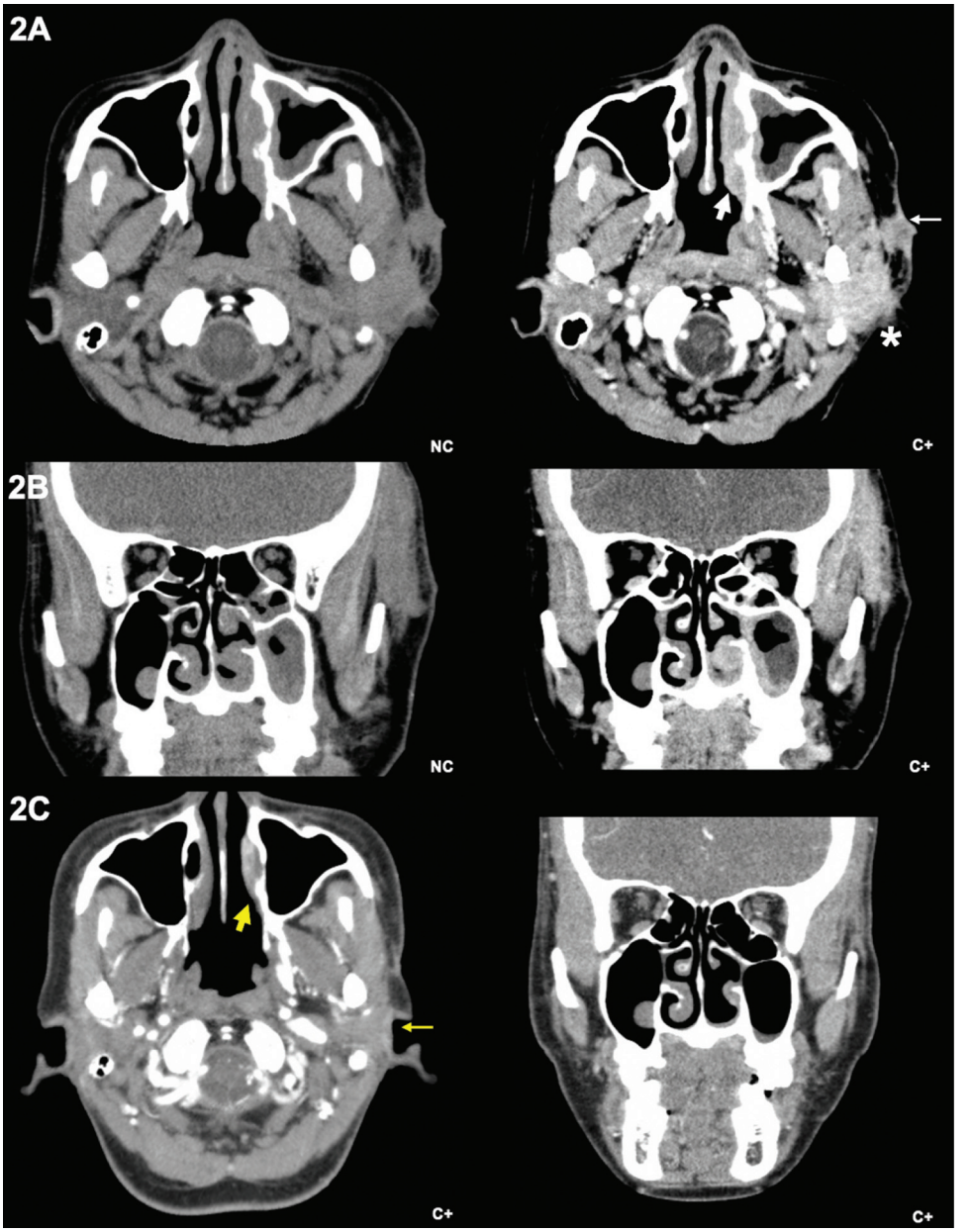

Figure 2. Computed tomography (CT) of paranasal sinuses and adjacent soft tissues comparing between pre- and post-treatment. (2A) Axial view of pre- and post-contrast phases revealed heterogenous enhancing subcutaneous soft tissue (asterisk; axial view C+) at left-sided buccal and temporalis muscle area along with sinus tract (thin white arrow; axial view C+) and enhancing infiltrative lesion at left inferior turbinate (bold white arrow; axial view C+). (2B) Coronal view of pre- and post-contrast phases. (2C) Axial and coronal view of post-contrast phase after 2 months of treatment revealed near-complete resolution of soft tissue swelling (thin yellow arrow; axial view C+), infiltrative left nasal mass (bold yellow arrow; axial view C+), and left parotitis.

NC=non-contrast; C+=post-contrast

mL using 1 mL of amikacin vial (500 mg/2 mL), diluted in 9 mL of sterile water. During nasal packing, the packing cotton was soaked with amikacin drop, and additional drops were performed on a once daily basis. The epistaxis ceased, and the patient was discharged two weeks thereafter with an alternate day of intravenous amikacin 25 milligram per kilogram per dose as outpatient parenteral antimicrobial therapy (OPAT) in combination with three oral drugs. Sterile cotton soaked with amikacin drop packed

anteriorly at both nasal cavities once daily was carried out at home by the patient.

Significant improvement was seen at the left inferior turbinate and floor of the left nasal cavity (Figure 2C) after two months of treatment. Normalization of leukocytosis and hs-CRP was achieved. Complete regression of lymphadenopathy, parotitis, and soft tissue swelling was achieved (Figure 2C). Clarithromycin was later switched to azithromycin of 500 milligram per day and continued to complete at least a one-year course of azithromycin, ethambutol, and rifampicin. The patient was doing well without recurrent epistaxis, nasal cavity mass, nor lymphadenopathy at 6-month of follow-up.

Discussion

To the authors' knowledge, this is the first case of combined nasal and parotid MAC infection in adult-onset immunodeficiency caused by anti-interferon-γ antibody presenting as epistaxis, nasal mass, and parotitis in Thailand. Previous case reports of MAC infection in adult-onset immunodeficiency mostly affected the lung, lymph nodes, skin, or bone marrow[1-6].

According to the clinical course of preceding epistaxis prior to the onset of parotitis, the infectious foci were suspected to originate in the nasal cavity, drained to the intraparotid and cervical lymph nodes, and subsequently infected the parotid gland. Thorough examinations of the imaging revealed no fistula or tract that connected the intranasal cavity to the parotid gland or adjacent soft tissues. However, a previous case report regarding NTM parotitis proposed that the pathogen ascends via the stenotic Stensen duct or via the duct with reduced saliva production, which subsequently causes parotid infection[7]. Moreover, no concomitant nasal lesions were noted in the previous reports regarding NTM parotitis[7-11]. These observations suggest that the route of acquiring infection may be different.

NTM infection of the nasal cavity has been reported in mostly presumed immunocompetent hosts. Most of these cases presented with a mass at the nasal septum, some causing perforation. Mycobacterial spindle-cell pseudotumors in the nasal cavity mimicking extranodal nasal NK/T cells or Kaposi's sarcoma were another rare manifestation. Complete resection without antimycobacterial agents yielded a favorable outcome in most cases (Table 1). A brief review of the clinical presentations, treatment, and outcomes of the previous case reports regarding mycobacterial infection of the nasal cavity and parotid gland in adults are shown in Table 1[7-17].

It is noteworthy that only one case from the previously published literature investigated the anti-interferon-γ antibody, which was negative. Adult-onset immunodeficiency caused by anti-interferon-γ antibody is more prevalent in Asia[18]. Atypical manifestations of severe local or disseminated NTM infection in previously healthy young adults should prompt clinicians to look for this condition. Unfortunately, the underlying mechanism of autoantibody production remains unknown.

Clarithromycin, rifampicin, and ethambutol are the core systemic agents used in the treatment of MAC. However, most reported cases required additional fluoroquinolones such as moxifloxacin or levofloxacin, or intravenous aminoglycosides (amikacin or streptomycin), to achieve adequate response, particularly cases with positive anti-interferon-γ antibody[1-6]. The present case is the first to introduce topical therapy with an amikacin nasal drop to successfully control the local infection in addition with the local vascular ligation. Possible immune modulation with topical aminoglycoside may aid in the clearance of infection by recruiting and promoting CD8+ T-cell response[19].

In conclusion, NTM infection of the nasal cavity and parotid gland is a rare condition but can be fatal if massive epistaxis was encountered. Underlying immunodeficiency, especially autoantibodies to interferon-γ, should be investigated. The combination of susceptible systemic and topical antimycobacterial agents can lead to a favorable outcome in MAC infection of the nasal cavity and parotid gland.

What is already known on this topic?

Severe NTM infection is a common opportunistic infection among adults with interferon-γ autoantibody. Common clinical presentations of NTM infection are lymphadenitis or disseminated infection involving lung and bone marrow. Systemic anti-mycobacterial therapy is the core therapy. Occasionally, an adjunctive immunosuppressive therapy including cyclophosphamide, rituximab, or daratumumab have been shown to achieve NTM control in case series among refractory NTM infection unresponsive to a systemic anti-mycobacterial therapy.

What this study adds?

NTM infection of the nasal cavity and parotid gland as the first presentation of autoantibody to interferon-γ, is rare. However, this clinical presentation

Table 1. Published case reports regarding NTM infection of the nasal cavity and parotid gland

Reference	Site	Age (years)	Sex	Host	Autoantibody to IFN-γ	Isolate of mycobacteria	Duration	Presentation	Characteristics of lesions/endoscopic findings	Imaging	Treatment	Outcome
14	Nasal cavity	60	Male	Immunocompetent	Not done	*Mycobacterium chelonae*	5 years	Crusting, irritation, and recurrent sinus infections	Destruction of the septal cartilage and turbinates	CT: Thinning of the posterior wall of the frontal sinuses, erosion of the bone near the right lacrimal system, and a substantial septal deformity	Clofazimine, amikacin, and azithromycin	Continued to show signs of active infection
15	Nasal cavity	43	Male	On immunosuppresive agents for presumed lymphoma	Negative	*Mycobacterium marinum*	3 weeks	Multiple progressive skin nodules and purulent nasal discharge	Septal perforation	CT: Perforated lesion in the nasal septum	Discontinuation of immunosuppressive agents and administration of minocycline	Improved
16	Nasal cavity	69	Male	Immunocompetent (T2DM)	Not done	*Mycobacterium avium*	2 months	Left lateral and frontal headache	Sessile polypoid lesion (1.5 cm in diameter) on the right anterior nasal septum	CT: A large mucus retention cyst along the floor of the left maxillary sinus	Excisional nasal biopsy	Improved
17	Nasal cavity	83	Male	Immunocompetent	Not done	*Mycobacterium intracellulare*	NA	Right nasal obstruction and bloody nasal discharge	Soft hemorrhagic mass in the right inferior nasal meatus	CT: Well-circumscribed mass measuring 2 cm in diameter with contrast enhancement in the right nasal cavity	Resection of the mass	Improved
12	Nasal cavity	63	Male	Diffuse large B-cell lymphoma post chemotherapy	Not done	*Mycobacterium avium* complex	Several months	Right nasal obstruction and blood tinged discharge from the right nostril	Irregular, polypoid mass	CT: a 1 cm soft, tissue density in the anterior right nasal cavity	Mass removal	Improved
13	Nasal cavity	76	Male	NA	NA	Mycobacteria, species not determined (PCR)	NA	NA	NA	NA	NA	NA
8	Parotid gland	79	Male	Immunocompetent	Not done	Cannot be identified	NA	Swelling and tenderness in the left parotid gland region	A tumorous mass in the left parotid gland, size 7.5×5.5 cm, and exhibited violaceous discolouration, fistula formation, and skin breakdown in the swollen region	CT: Low density region that displayed rim enhancement indicating that parts of the parotid gland were necrotic	RIM, INH, EB, CAM, and LVFX for 6 weeks then RIM, CAM, and LVFX for 5 months	Improved
9	Parotid gland	35	Female	Immunocompromised (post-splenectomy)	Not done	*Mycobacterium chelonae*	1 month	Painful swelling and redness of the angle of her left jaw	Mobile and tender mass measuring approximately 3 cm and occupying the superficial lobe of the left parotid gland	CT: diffuse enhancement of the left parotid gland with an enlarged soft tissue mass lesion, measuring 3×4 cm in size, with a cystic component	RIM, INH, EB, CAM (plan 6 months)	In treatment process
10	Parotid gland	66	Male	AIDS	Not done	*Mycobacterium scrofulaceum*	8 weeks	Swelling posterior to the angles of the jaw bilaterally	Firm smooth masses, more marked on the right than the left, arising from the behind the angles of the jaw and extending inferiorly into the neck	Ultrasonography: parotid glands were diffusely enlarged and showed increased vascularity	Rifabutin and CAM	Improved
11	Parotid gland	40	Male	Immunocompetent	Not done	*Mycobacterium mageritense*	NA	Swelling in the left parotid gland	Erythema with desquamation in a preauricular lesion	MRI: heterogeneously enhancing mass in the left parotid gland	LVFX and trimethoprim-sulfamethoxazole	Improved
7	Parotid gland	76	Female	immunocompromised	Not done	*Mycobacterium avium*	6 weeks	Large lump of the left preauricular parotid region	2×2 cm preauricular lump of the left parotid without fluctuation	MRI: 2.0×1.9×1.8 cm large tumor located at the upper part of the left parotid gland	Complete parotidectomy plus rifabutin and CAM 6 months	Improved

NTM=non-tuberculous mycobacteria; CT=computerized tomography; MRI=magnetic resonance imaging; RIM=rifampicin; INH=isoniazid; EB=ethambutol; CAM=clarithromycin; LVFX=levofloxacin; T2DM=type II diabetes mellitus; PCR=polymerase chain reaction; NA=not available

of NTM infection should alert clinicians to investigate for underlying acquired immunodeficiency, particularly interferon-γ autoantibody. Favorable outcome can be achieved using combined topical and systemic anti-mycobacterial therapy, and surgery when epistaxis is refractory to medical therapy.

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Conflicts of interest

The authors declare no conflict of interest.

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