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CLINICAL CASE REPORT

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Disseminated *Mycobacterium marinum* Infection With a Destructive Nasal Lesion Mimicking Extranodal NK/T Cell Lymphoma

A Case Report

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Abstract: *Mycobacterium marinum* is a ubiquitous waterborne organism that mainly causes skin infection in immunocompetent patients, and its disseminated infection is rare. Extranodal NK/T cell lymphoma, nasal type (ENKL) usually localizes at the nasal and/or paranasal area, but occasionally disseminates into the skin/soft tissue and gastrointestinal tract. Compromised immunity is a risk factor for developing nontuberculous mycobacterial (NTM) infection and malignant lymphoma, and the 2 diseases may share similar clinical presentation; however, only a few reports have described NTM infection mimicking malignant lymphoma.

A 43-year-old Japanese man presented to our hospital complaining of multiple progressive skin nodules and purulent nasal discharge for 3 weeks. He was diagnosed with Crohn disease with refractory enteropathic arthritis and has been treated with anti-tumor necrosis factor alpha agents for 25 years. Fiberoptic nasal examination revealed septal perforation with hemorrhagic mucus and purulent rhinorrhea. Histological examination of the nasal septum revealed the infiltration of atypical medium-to-large-sized cells with erosion. The cells were positive for cytoplasmic CD3, granzyme B, and Epstein–Barr virus-encoded small RNA. Histological examination of the skin nodules and auricle also showed infiltration of atypical lymphocytes. The patient was tentatively diagnosed with ENKL, and chemotherapy was considered. However, the skin lesions decreased in size after discontinuation of immunosuppressive agents and minocycline administration. Two weeks later, nasal septum and lavage fluid and left leg skin cultures were positive for *M marinum*, and minocycline was discontinued. The skin and the nasal lesions improved after 2 months.

To the best of our knowledge, this is the first case of disseminated *M marinum* infection with a destructive nasal lesion mimicking ENKL. The differentiation between *M marinum* infection and ENKL is clinically important because misdirected treatment leads to a poor prognosis. NTM infections including *M marinum* should be considered in differential diagnosis of ENKL. Bacterial cultures, pathological analysis, and close monitoring are required for the differentiation of ENKL and disseminated *M marinum* infection; both are serious diseases and early diagnostic distinction between them and immediate appropriate treatment will improve the patient's prognosis.

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Abbreviations: EBER-ISH = Epstein–Bar virus-encoded small RNA in situ hybridization, EBV = Epstein–Bar virus, ENKL = extranodal NK/T cell lymphoma, nasal type, NTM = nontuberculous mycobacterial, TNF-α = tumor necrosis factor alpha.

INTRODUCTION

The prevalence of nontuberculous mycobacterial (NTM) infection is increasing worldwide.[1,2] *Mycobacterium marinum* is a ubiquitous waterborne organism that naturally infects a variety of fish and frog species[3] and uncommonly, humans.[4] In humans, *M marinum* mainly causes skin infection in healthy persons who have jobs or hobbies related to exposure to aquatic environments,[4] while the disseminated infection other than the skin with *M marinum* can occur in immunocompromised patients.[5] The skin lesions include a painful solitary papule or nodule at the inoculation site, some extending proximally with a sporotrichoid distribution.[6] Accurate diagnosis requires tissue cultures and routine histopathological examination[7]; however, histopathological features are sometimes difficult to differentiate other possible causes, especially until positive culture conversion and species identification. Compromised immunity in particular may result in atypical histopathological findings because of inhibiting granuloma formation.

Extranodal NK/T cell lymphoma, nasal type (ENKL), a rare type of non-Hodgkin lymphoma, is highly prevalent in Asia. It predominantly occurs in the nasal/paranasal area including adjacent skin/soft tissue, and early treatment is required due to an aggressive clinical course with poor prognosis.[8] EKNL

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may also cause multiple skin lesions mimicking clinical presentation of *M marinum* infection. However, only a few reports have described NTM infection mimicking malignant lymphoma.[9,10] We herein report a case presenting with skin and destructive nasal lesions and finally diagnosed as disseminated *M marinum* infection mimicking ENKL.

CASE PRESENTATION

The patient is a 43-year-old Japanese man who presented to our hospital with multiple progressive skin lesions and purulent nasal discharge for 3 weeks. He had a 25-year history of Crohn disease with refractory enteropathic arthritis treated with immunosuppressive agents: infliximab 10 mg/kg every 3 weeks, tacrolimus 1.5 mg/d, prednisolone 25 mg/d, and methotrexate 6 mg/wk. On physical examination, all vital signs were within normal limits. His fingers, wrists, ankles, and knees were symmetrically swollen and tender. His left auricle had a reddish-black color, swelling, and a painful lesion exposing the cartilage (Figure 1A). His nose showed saddle deformity and a painful erythematous lesion (Figure 1B). His left lower leg also showed reddish and painful nodules (Figure 1C). Multiple subcutaneous nodules were tangible on both the arms and buttocks. Fiberoptic nasal examination revealed nasal septal perforation with hemorrhagic mucus and purulent rhinorrhea (Figure 2). Laboratory examination showed leukocytosis (10,100 per μL; normal range, 3500–8500 per μL), slightly elevated C-reactive protein level (0.63 mg/dL; normal, <0.35 mg/dL), elevated matrix metalloproteinase-3 level (601 ng/mL; normal range, 36.6–121.0 ng/mL), normal soluble interleukin-2 receptor level (350 U/mL; normal range, 145–519 U/mL), normal urinalysis and kidney function, and negative anti-neutrophil cytoplasmic antibody. The results of blood culture were negative. Anti-HIV and anti-HTLV-1 antibodies were negative. Epstein–Bar virus (EBV) antibodies to viral capsid antigens IgG and IgM were negative, but anti-EBV nuclear antigen antibody was positive. EBV viral DNA in the peripheral blood was undetectable by real-time quantitative polymerase chain reaction.[11]

After admission, immunosuppressive agents except prednisolone were discontinued. Minocycline was administered for possible skin infection, and further investigations were performed. Positron emission tomography–computed tomography showed intense ^{18}F-fluorodeoxyglucose (FDG) uptake in the mucus around the perforated lesion in the nasal septum, with a maximum standard uptake value of 9.63 (Figure 3A and B). The multiple subcutaneous lesions on both the arms and buttocks also were FDG-avid. There were no other remarkable findings, including those in the lung field. Histological examination of the nasal septum revealed atypical medium-to-large-sized cells with erosion (Figure 4A and B). Immunohistochemical staining revealed cytoplasmic CD3 (Figure 4C), CD8 (Figure 4D), and granzyme B (Figure 4E) expression, and in situ hybridization (Epstein–Bar virus-encoded small RNA in situ hybridization, EBER-ISH) revealed EBV-encoded small RNA (Figure 4F). However, CD56 was not expressed in the atypical cells. Histological examination of skin biopsy specimens from the left leg and auricle also showed infiltrative atypical lymphocytes (Figure 4G and H) and shared the same immunohistochemical pattern. T-cell receptor gene rearrangement of the nasal septum was not detected. Grocott and Ziehl–Neelsen staining for all biopsy specimens was negative. Cerebrospinal fluid and bone marrow examination revealed no remarkable findings.

Although the histopathological findings were atypical, chemotherapy for ENKL or re-biopsy was considered. However, the skin lesions started improving by the discontinuation of immunosuppressive agents and administration of minocycline after admission. Two weeks later, nasal septum, lavage fluid, and left leg skin culture were positive for mycobacteria, and *M marinum* [GenBank accession no. AF456240] was identified on sequence analysis targeting the 16S ribosomal RNA genes. Random amplified polymorphic DNA polymerase chain reaction analysis revealed identical *M marinum* strains in the nasal septum, lavage fluid, and left leg skin (Figure 5). The patient had a history of rearing aquarium fish. Anti-interferon-γ autoantibodies were not detected. Skin and the nasal lesions improved with discontinuation of minocycline after 2 months without any further treatments.

DISCUSSION

ENKL generally occurs in the upper airway regions, including the nasal cavity, nasopharynx, paranasal sinuses,

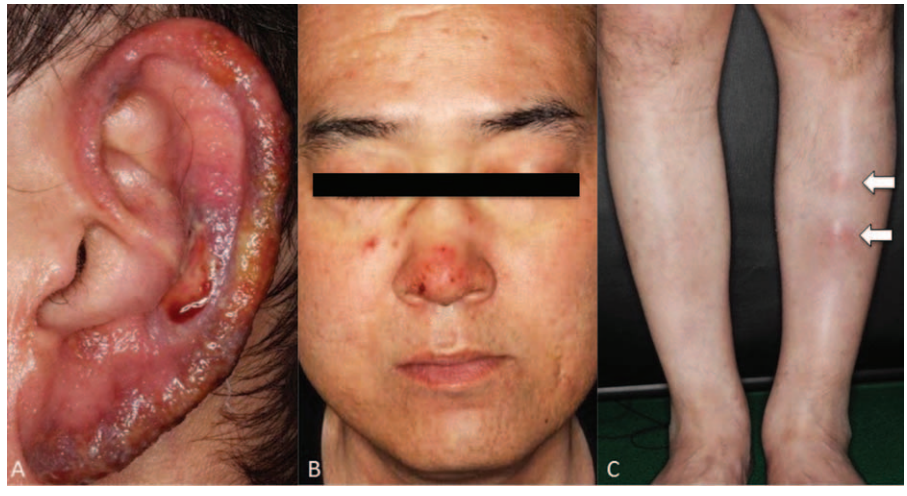

FIGURE 1. Left auricle showed reddish-black appearance, swelling, and a painful lesion with exposed cartilage (A). The nose showing saddle deformity with a painful erythematous lesion (B). The left lower leg showing reddish and painful nodules (C, arrows).

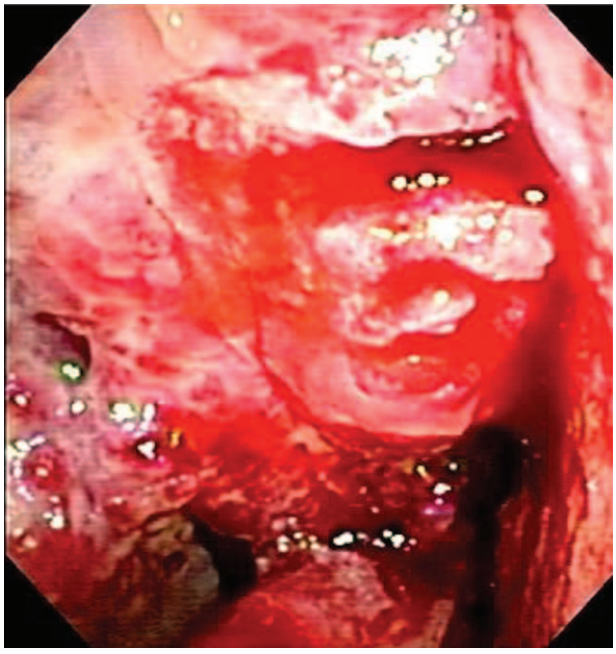

FIGURE 2. Fiberoptic nasal examination revealed nasal septal perforation with hemorrhagic mucus and purulent rhinorrhea.

tonsils, hypopharynx, and larynx, accounting for 60% to 90% of all ENKLs.[13] The second most frequent region is the skin, accounting for approximately 10% of cases.[14] ENKL initially causes nasal symptoms such as obstruction, discharge, and nasal bleeding. Destruction of the nasal area develops in progressive disease. Some cases show localized lesions for a long term, while some show rapidly disseminated disease once the tumor develops in the extranasal area.[8] In this case, the presence of multiple skin and destructive intranasal lesions suggested possible progressive ENKL, for which an early diagnosis and treatment are recommended.

To the best of our knowledge, this is the first case of disseminated *M marinum* infection with a destructive intranasal lesion mimicking ENKL. A diagnostic distinction between *M marinum* infection and ENKL is clinically important, as misdirected treatment will lead to poor prognosis. In this case, *M marinum* infection was a diagnostic challenge because of the following reasons: first, the diagnosis of ENKL itself is sometimes difficult because of inadequate tissue sampling; second, immunosuppressive therapies suppress inflammatory process and modified histopathology; and finally, the initial clinical presentation of *M marinum* infection was a destructive intranasal lesion.

The diagnosis of ENKL was highly suspected based on the evaluation of biopsy specimens from the involved lesions. However, repeated biopsies were required because of the existence of wide necrotic regions. Histologically, the tumor cells are most commonly but not universally medium-sized or have a mixture of small and large cells, showing an angiocentric and angiodestructive growth pattern and coagulative necrosis.[15] Immunohistochemical staining and EBER-ISH are the key diagnostic methods. Almost all tumor cells were positive for EBER-ISH[8] and commonly expressed cytoplasmic CD3, CD56, and cytotoxic granule-associated proteins such as granzyme B or TIA-1.[16] Although CD8 is not usually expressed, its expression may occur.[16,17] The tumor cells that did not express CD56 in the present case were classified as ENKL if both cytotoxic molecules and EBER-ISH were positive.[18]

In the present case, the following features made diagnosis more difficult. First, the infiltrated atypical lymphocytes expressed immunohistochemical markers, a feature typical of ENKL. Second, anti-TNF-α therapy might have inhibited granulomatous formation because TNF-α has been correlated with the formation of granuloma.[19] Although histopathological examination is useful, patterns differ between immunocompromised and immunocompetent hosts: in immunocompetent hosts, prominent epidermal changes such as acanthosis, pseudoepitheliomatous hyperplasia, and exocytosis are observed. Granulomatous inflammation, involving lymphocytes, macrophages, giant cells, and polymorphonuclear leukocytes, is also observed.[7,20] On the contrary, less specific findings are encountered, especially in immunocompromised hosts,[20] as in the present case. Only 4 reports describe NTM mimicking T cell or B cell lymphoma (2 cases of *M fortuitum* and 2 of *M kansasii*).[9,10] In a previous report, a case of ENKL with small bowel perforation was initially misdiagnosed as *M marinum*

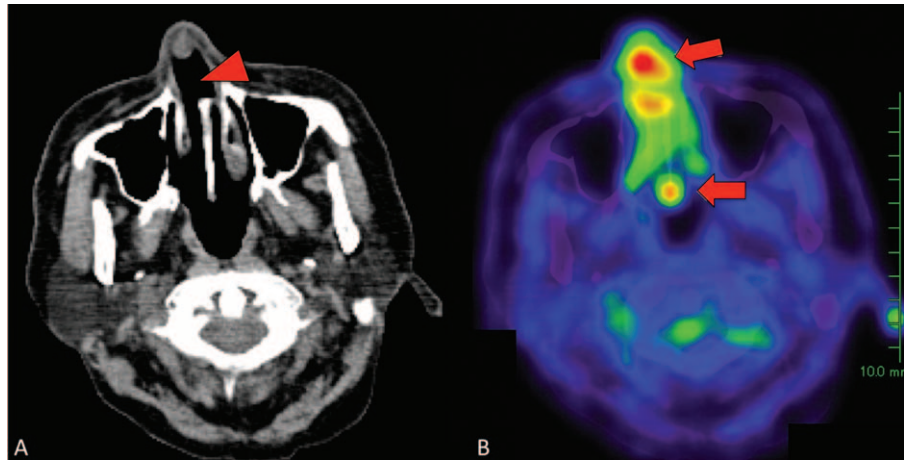

FIGURE 3. Computed tomography image showing a perforated lesion in the nasal septum (A, arrowhead). Positron emission tomography–computed tomography image showing intense ^{18}F-fluorodeoxyglucose uptake in the mucus around the perforated lesion and backward of nasal septum with a maximum standard uptake value of 9.63 (B, arrows).

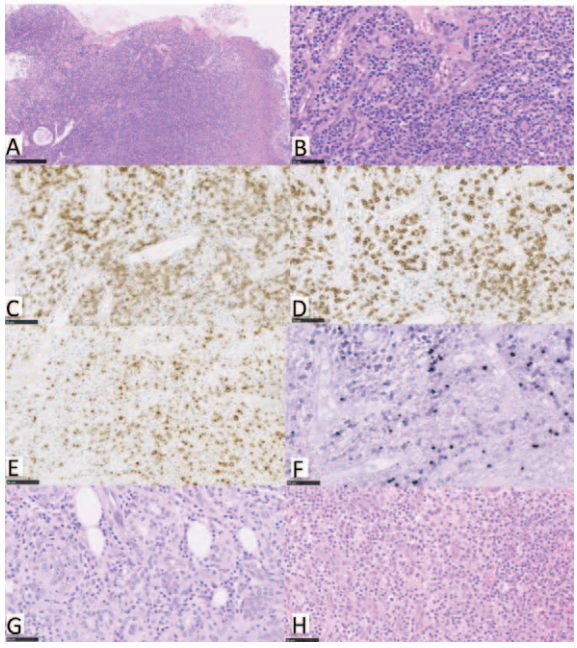

FIGURE 4. Histological examination of biopsy specimens in the nasal septum showing atypical medium-to-large-sized cells with erosion (A and B, hematoxylin–eosin staining). Lymphocytes cells expressed CD3 (C), CD8 (D), and granzyme B (E), as assessed on immunohistochemistry, and Epstein–Barr virus-encoded small RNA, as assessed on in situ hybridization (F). The skin biopsies of left leg (G) and auricle (H) also show infiltrative atypical lymphocytes.

infection. Hence, close monitoring is necessary to avoid misdiagnosis.[21]

To our knowledge, this is the first report of destructive intranasal lesions due to *M marinum* infection in adults. Disseminated *M marinum* infection is rare but occurs particularly in immunocompromised patients. The disseminated infection usually involves the skin, the lung, and the viscera.[22] A rare case of laryngeal lesions due to *M marinum* infection has been reported.[23] We found only 1 case of NTM infection resulting in an intranasal mass obstructing the right nasal fossae, displacing the septum, in a 3-year-old girl.[24] Although she was initially suspected of having sarcoma based on frozen-section biopsy, she was finally diagnosed with *M fortuitum* infection upon molecular histochemical analysis.

In conclusion, we suggest that NTM infections with *M marinum* should be considered in the differential diagnosis of ENKL. Bacterial cultures, pathological analysis, and close monitoring are required for the differentiation of this disease. Both ENKL and disseminated *M marinum* infection are serious diseases, and early diagnostic distinction between them and initiating the appropriate treatment will improve the patient's prognosis.

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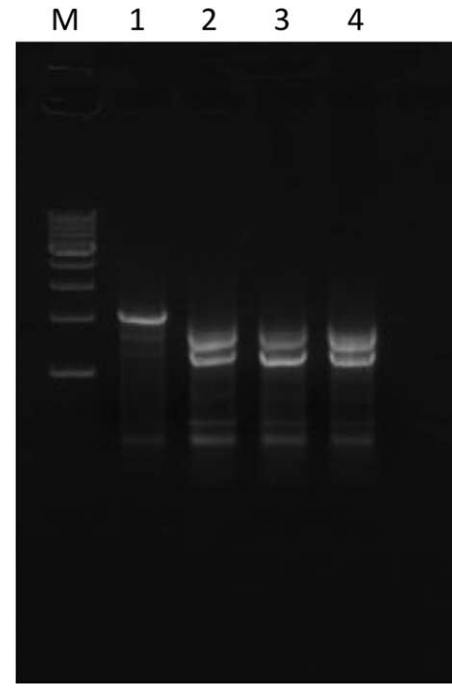

FIGURE 5. Randomly amplified polymorphic DNA polymerase chain reaction analysis with mycobacteria-specific primers.[12] In brief, a 50-μL mixture of 60 mM Tris–HCl (pH 9.0), 2.5 mM $MgCl_2$, 15 mM $(NH_4)_2SO_4$, 250 μM each of deoxynucleoside triphosphate (dNTP), 50 pmol of the primer, and 1 U of AmpliTaq 360 DNA Polymerase (Thermo Fisher Scientific, MA) with 360 GC enhancer. The primer used was 5′-GCGTAGTGCGTCGGTGA-CAAA-3′. Amplification condition was 40 cycles at 94°C for 1 min, 36°C for 1 min, and 72°C for 2 min. The PCR products were separated by 2% agarose gel electrophoresis and ethidium bromide staining. Lane M, 100-bp DNA ladder size markers; lane 1, type strain of *M marinum* (ATCC 927 strain); lanes 2, 3, and 4, *M marinum* clinical isolates from the culture of the nasal septum and lavage fluid, and the left leg skin, respectively. The gel loading patterns among the lanes 2, 3, and 4 were same but were different from that in lane 1 (type strain).

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