Abstract:
A 63-year-old woman presented with a fever, eruption, and sterile pyuria. A cystoscopic examination revealed submucosal nodular lesions in the trigone of the bladder, and a biopsy specimen showed epithelioid cell granulomas in the lamina propria of the bladder. Mycobacterium avium grew in the urine culture. Other organ involvement, such as the lungs, spleen, bones, muscles, and pelvic lymph nodes, was observed on radiological examinations, and M. avium was isolated from some organ lesions. Interferon-γ-neutralizing autoantibodies were detected in the patient’s serum. Therefore, the patient was diagnosed with disseminated M. avium infection, which was resolved with antimycobacterial treatment.

Key words: disseminated nontuberculous mycobacterial infections, interferon-γ neutralizing autoantibodies, bladder lesion, sterile pyuria

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Introduction
The presence of serum interferon-γ-neutralizing autoantibodies (nIFNγ-autoAbs) has been reported to be associated with disseminated nontuberculous mycobacterial (NTM) infections (1-3). Previously reported cases of disseminated NTM infections were found to be complicated by pulmonary, liver, skin, bone, and lymph node involvement (4-6). However, to our knowledge, cases of urinary tract involvement in disseminated NTM infections have rarely been reported (7).

In this report, we describe a case of disseminated Mycobacterium avium infection presenting with bladder lesions in a patient with nIFNγ-autoAbs.

Case Report
A 63-year-old woman presented with erythema on her lower legs, anorexia, and a fever and was referred to our hospital for detailed examinations. Her medical history was unremarkable. No family history of adult-onset immunodeficiency was evident.

Physical examinations showed a blood pressure of 128/84 mmHg, pulse rate of 113 beats per min, and body temperature of 38.2°C. Laboratory data showed an elevated white blood cell count (17,000 cells/μL) and C-reactive protein level (9.4 mg/dL). Computed tomography of the chest showed nodular opacities and bronchiectasis in the right middle lobe and nodular opacities in the left lower lobe (Fig. 1A). A urinalysis showed pyuria, and antimicrobial treatment with oral levofloxacin (500 mg/day) was initiated...
because she was diagnosed with a urinary tract infection. Subsequently, the patient became afebrile, and the C-reactive protein level normalized; the erythema of the lower legs also resolved.

However, two months later, she experienced general fatigue, a fever, and urinary incontinence. Around the same time, erythema with induration reappeared on her lower legs. A skin biopsy specimen revealed septal panniculitis with predominant lymphocytic infiltration, which indicated erythema nodosum. The white blood cell count and C-reactive protein level were 12,600 cells/μL and 11.5 mg/dL, respectively. The results of an enzyme-linked immunospot assay for the IFN-γ response to *Mycobacterium tuberculosis* antigens (T-SPOT.TB; Oxford Immunotec, Marlborough, USA) yielded negative results. However, serum antibodies to the glycopeptidolipid core antigen specific to *Mycobacterium avium* complex were detected (10.0 U/mL, normal range: ≤0.70 U/mL), indicating the presence of a *Mycobacterium avium* complex infection.

A urinalysis revealed pyuria again, but the cultures did not show any bacterial growth; however, staining and culture for acid-fast bacilli was not performed at this time. Computed tomography of the abdomen showed multiple low-density areas in the spleen (Fig. 1B). Ultrasonography also revealed splenic lesions as well as enlargement of the pelvic lymph nodes and a mass lesion between the bladder and cervix. Magnetic resonance imaging showed multiple cystic lesions and swelling of the posterior wall of the bladder (Fig. 2A). In addition, the patient reported a painful subcutaneous nodule in the right shoulder, and ultrasonography showed a low-echoic mass around the clavicle measuring 41 ×37×28 mm. First, we presumed the mass to be metastasis from cervical or bladder cancer. Transvaginal ultrasonography showed a cervicovaginal mass measuring 22×22 mm, but the biopsy specimen showed only nonspecific inflammation. A cystoscopic examination showed submucosal nodular lesions in the trigone of the bladder (Fig. 2B). A biopsy specimen from a bladder lesion showed epithelioid cell granulomas in the lamina propria that were surrounded by several infiltrating lymphocytes, plasma cells, and neutrophils (Fig. 2C); these findings were compatible with those of a mycobacterial infection. Compared to the lamina propria, the mucosa was relatively intact (Fig. 2B). Additional urine cultures for mycobacteria were performed, and *M. avium* was isolated three weeks later. We therefore diagnosed the bladder lesions as *M. avium* infection.

It took seven months from the patient’s first visit to isolate *M. avium*, and the clavicular lesion displayed ulceration over the skin at the time of the diagnosis (Fig. 3A). Fluorine-18-labeled fluorodeoxyglucose positron emission tomography with computed tomography was performed to evaluate the extent of the infection and showed increased accumulations in multiple bones, lymph nodes, muscles, and the spleen (Fig. 1C). *M. avium* was also isolated from the
right clavicle bone, iliopsoas muscle abscess, and a cervicovaginal lesion. Based on the clinical features and isolation of M. avium from various organs, the patient was diagnosed with disseminated NTM infection due to M. avium. The patient did not have serum anti-human immunodeficiency virus antibodies and also did not receive immunosuppressive agents. The results of a whole blood IFN-γ release assay for M. tuberculosis antigens using the QuantiFERON TB Gold In-Tube test (QFT-GIT) (ARUP Laboratories, Salt Lake City, USA) were indeterminable, suggesting that IFN-γ was inhibited by some factors in the patient’s serum. A high titer of neutralizing autoantibodies to IFN-γ (concentration of anti-IFN-γ: 427 E.U., control: 22 E.U.; STAT1 phosphorylation index: 113, control: 1042) was identified in the serum using an enzyme-linked immunosorbent assay and a flow cytometry-based method conducted at Niigata University Medical and Dental Hospital (8).

The patient was treated for the disseminated M. avium infection with a combination chemotherapy consisting of clarithromycin (800 mg/day), rifampicin (450 mg/day), ethambutol (750 mg/day), and streptomycin (600 mg/day, 3 times a week). One month after the initiation of antimycobacterial treatment, she became afebrile and did not note any urinary incontinence, and a cystoscopic examination revealed the resolution of the submucosal lesions (Fig. 2D). The erythema of the lower legs also resolved. Streptomycin was administered for two months. Three months later, the clavicle skin ulcer improved and epithelialized (Fig. 3B), and the white blood cell count and C-reactive protein level normalized. A year later, regression of multiple organ involvement was seen on radiological examinations, but the splenic lesions did not disappear completely. Upon submission of this manuscript (20 months after the initiation of treatment), the patient was still asymptomatic and was receiving antimycobacterial therapy.

**Discussion**

We described a case of disseminated M. avium infection presenting with submucosal nodular lesions in the trigone of the bladder in a patient with nIFNγ-autoAbs. Recently, cases of anti-human immunodeficiency virus antibody-negative disseminated NTM with detectable nIFNγ-autoAbs have been reported in Asian countries (3). The primary manifestations of patients with disseminated NTM with nIFNγ-autoAbs are nonspecific, which makes the diagnosis diffi-
cult, although disseminated NTM patients with nIFN-γ-autoAbs have a more favorable prognosis than those without nIFN-γ-autoAbs (7). The reported mean period from the disease onset to the diagnosis is 4 months (interquartile range, 2-8 months) in disseminated NTM patients with nIFN-γ-autoAbs (7). Therefore, the period from the disease onset to the diagnosis in our case was comparable to that in previously reported cases. An indeterminate QFT-GIT result because of undetectable or extremely low IFNγ levels in the mitogen tube reportedly suggests the presence of nIFN-γ-autoAbs in previously healthy patients with disseminated NTM infection (9). Methods of measuring the titers of nIFNγ-autoAbs are currently unestablished and commercially unavailable. Physicians should suspect the presence of nIFNγ-autoAbs when the results of QFT-GIT are indeterminate.

Our patient presented with sterile pyuria, and we did not detect *M. tuberculosis* or any other bacteria other than *M. avium* in the urine. Furthermore, we identified submucosal nodular lesions in the bladder via a cystoscopic examination, and the lesions resolved after the initiation of antimycobacterial treatment. In addition, the histopathological findings showed no malignancy and only a few epithelioid cell granulomas. Therefore, this patient was diagnosed with bladder lesions caused by a disseminated *M. avium* infection.

Urinary NTM infections are rare, and little is known about bladder lesions that develop during an NTM infection (10). To our knowledge, this is the first case report of a disseminated *M. avium* infection presenting with submucosal nodular lesions in the trigone of the bladder in a patient with nIFNγ-autoAbs, and the cystoscopic and pathological findings are described herein. In the present case, the bladder lesions due to the *M. avium* infection presented as submucosal nodular lesions in the trigone of the bladder. The histopathological findings showed that the mucosa of the bladder was relatively spared, with some epithelioid cell granulomas accompanied by inflammatory cell infiltration in the lamina propria of the bladder. The pathological findings of *M. tuberculosis* infection of the bladder are usually granulomas and inflammation in the mucosa and submucosa, findings that are particularly observed in the trigone with an intact epithelial layer in the early stages (11, 12). Intestinal tuberculosis also presents as granulomas in the submucosa (13) and usually occurs in the ileocecum, which has an abundance of lymphoid tissue (14). Similarly, NTM can invade the intestinal mucosa (15); indeed, cases involving macrophages containing acid-fast bacilli presenting in the lamina propria of the duodenum have been reported (16). Furthermore, lymphoid tissue is abundant in the lamina propria of the trigone (17). Based on these observations, we believe that NTM can invade the bladder mucosa, leading to granuloma formation in the submucosa of the trigone.

In the present case, *M. avium* infection of the bladder manifested as sterile pyuria. Sterile pyuria is the persistent presence of white blood cells in the urine in the absence of bacteria, as determined by aerobic laboratory techniques (18). Genitourinary tuberculosis is a major cause of sterile pyuria. In the present case, the symptoms improved with a round of levofloxacin treatment but recurred after the cessation of levofloxacin. Fluoroquinolone (FQ) treatment for bacterial infection sometimes delays the diagnosis of tuberculosis and worsens the patient’s outcome (19). However, FQ treatment can resolve the symptoms in genitourinary tuberculosis (20) and is known to be effective against NTM infections; furthermore, FQ is occasionally used for urinary tract infections. Therefore, physicians should consider the possibility of urinary tuberculosis and NTM infections in patients with recurrent urinary tract infections that have been treated with FQ.

In conclusion, we reported the first case of disseminated *M. avium* infection presenting with bladder lesions in a patient with nIFNγ-autoAbs. Physicians should be aware that bladder infections caused by NTM can present as sterile pyuria and submucosal nodular lesions in the bladder as well as *M. tuberculosis* infection.

The authors state that they have no Conflict of Interest (COI).

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