

[CASE REPORT]

Device-related *Mycobacterium mageritense* Infection in a Patient Treated with Nivolumab for Metastatic Breast Cancer

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Abstract:

Treatment with anti-programmed cell death-1 (PD-1) antibodies improves the anti-cancer immune response and can provide a meaningful clinical benefit to cancer patients. However, this treatment can result in specific autoimmune toxicities, termed immune-related adverse events (irAEs). Although irAEs are well recognized, the development of infectious diseases due to this treatment is not often observed. Some recent reports have indicated that patients who receive anti-PD-1 antibodies are at a higher risk for tuberculosis than others. However, reports on nontuberculous mycobacterial infection during anti-PD-1 antibody treatment are still rare. We herein report the first case of *Mycobacterium mageritense* infection during anti-PD-1 antibody treatment.

Key words: anti-PD-1 antibody, *Mycobacterium mageritense*, nontuberculous mycobacteria, breast cancer, nivolumab

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Introduction

The emergence of immune checkpoint inhibitors (ICIs) that target programmed cell death-1 (PD-1) signaling has ushered in a new era of cancer treatment (1, 2). Inhibition of the interaction between PD-1 and PD-ligand 1 (PD-L1) reverses immunosuppressive conditions and improves the ability of the patient's immune cells to recognize and eliminate cancer cells (2). Although treatment with ICIs may result in activation of the patient's immune cells, ICIs can cause unique toxicity profiles, known as immune-related adverse events (irAEs), which include autoimmune phenomena, such as dermatitis, colitis, hepatitis, thyroid dysfunction, and adrenal insufficiency (3, 4). Although these side effects have been well characterized, the influence of ICIs on infectious disease development is still unclear.

Some recent studies have reported that the use of anti-PD-1 antibodies (nivolumab and pembrolizumab) is associated with mycobacterial infection, specifically *Mycobacterium tuberculosis* (TB) (5-7). Therefore, in its approval summary, the US Food and Drug Administration cautioned that the use of anti-PD-1 antibody treatment can increase the risk of TB reactivation (8, 9). However, few reports have been published concerning the relationship between infection with nontuberculous mycobacterium (NTM) and anti-PD-1 antibody treatment.

We herein report the first case of a patient who developed an NTM infection (*M. mageritense*) during nivolumab treatment.

Case Report

We encountered a 44-year-old Japanese woman who was

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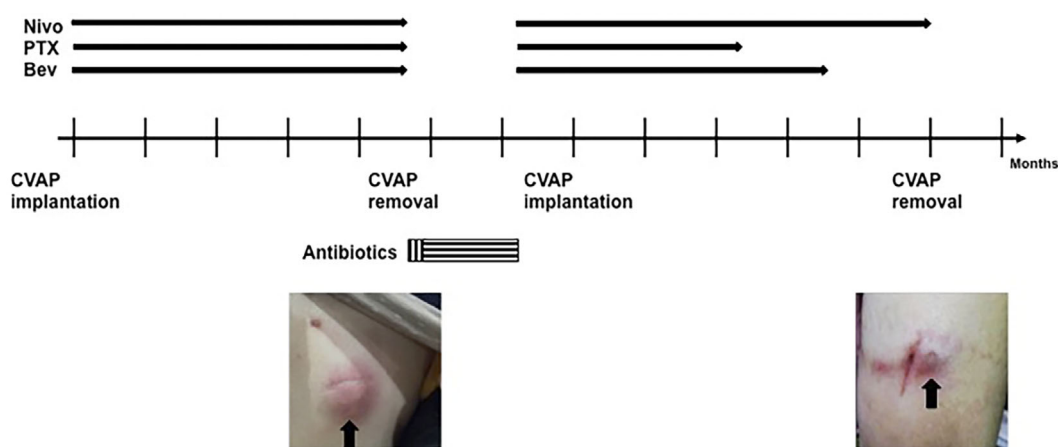


Figure. Clinical course of treatment of breast cancer and *Mycobacterium mageritense* infection. The vertical striped bar indicates treatment with antibiotics amikacin, meropenem, and ciprofloxacin. The horizontal striped bar indicates antibiotic treatment with amikacin and ciprofloxacin. The dotted bar indicates topical treatment with ointment. Left picture: appearance of the patient's left chest after central venous port (CVP) infection. Right picture: Appearance of the patient's upper arms after CVP infection. Arrows indicate implanted ports.

initially diagnosed with estrogen receptor- and progesterone receptor-positive, human epidermal growth factor receptor 2-negative, right-sided breast cancer in 2000. She underwent right radical mastectomy and axillary lymph node dissection and then received doxorubicin-based adjuvant chemotherapy; she also subsequently received hormone therapy with tamoxifen. During the hormone therapy treatment period, the cancer recurred in the axillary lymph node and was detected in 2004. Lymph node dissection was conducted, and adjuvant chemotherapy was administered. From 2012 to 2018, she experienced repeated recurrence of subcutaneous axillary lesions and underwent multiple resection procedures, radiotherapy, and hormone therapy with leuprolerin acetate.

In June 2018, systemic metastases were detected in her right chest wall, and dissemination to the pleura and multiple bones was diagnosed. She was scheduled to receive nivolumab (3 mg/kg on days 1 and 15 of a 4-week cycle), bevacizumab (10 mg/kg on days 1 and 15 of a 4-week cycle), and paclitaxel (90 mg/m² on days 1, 8, and 15 of a 4-week cycle) as a clinical trial (UMIN000030242) participant. A central venous access port (CVAP) was inserted in the left subclavicular site for chemotherapy administration. Three months after the first dose was administered, follow-up computed tomography revealed partial remission. Five months after the first dose, the patient complained of a fever, general fatigue, and skin redness surrounding the CVAP insertion site (Figure, left image). Chemotherapy was postponed because a catheter-related bloodstream infection was suspected. Blood culture was conducted, and acid-fast Gram-positive rod bacteria were found, determined to be *M. mageritense* by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry with an identification score of 2.24 (MALDI Biotyper; Bruker, MA, USA). In addition, partial sequencing of the 16S rRNA gene confirmed this identification as well. Computed tomography

(CT) showed no evidence of disseminated infection, and the only detectable lesion was the CVAP insertion site.

To treat the catheter-related bloodstream infection caused by *M. mageritense*, we conducted surgical debridement, removed the CVAP, and initiated the administration of amikacin, meropenem, and ciprofloxacin. Based on the susceptibility testing findings (Table), we stopped meropenem treatment and continued the other two drugs for four weeks after clearance of *M. mageritense* from the bloodstream was documented and after the resolution of symptoms. After antibiotic therapy was completed, a new CVAP was re-implanted in her left upper arm, and treatment with three anti-cancer drugs was resumed. Three months later, paclitaxel was stopped because of drug-induced neuropathy, whereas nivolumab and bevacizumab were continued.

Four months after re-implantation of the CVAP, she again complained of skin redness on her left upper arm. Blood cultures were sterile, and ultrasound revealed central venous port (CVP)-related thrombosis. Anticoagulation treatment with rivaroxaban was initiated, bevacizumab was stopped because of thrombosis, and only nivolumab was continued. Despite the anticoagulation therapy, the area of redness became more prominent and was complicated by the presence of a fistula (Figure, right image). Pustule culture again revealed *M. mageritense*. We then removed the CVP and debrided the infected tissue. Based on her clinical history, we determined that refractory *M. mageritense* infection was associated with anti-PD-1 antibody treatment, and nivolumab was discontinued. Topical iodine ointment was given, and repeated debridement was conducted as a treatment for *M. mageritense* skin and soft tissue infection. Her condition consequently gradually improved.

Table. Susceptibility Pattern of This Isolate of *Mycobacterium mageritense*.

| Antibiotics | MIC (µg/mL) | Susceptibility |
|-------------------------------|-------------|----------------|
| Amikacin | <8 | S |
| Clarithromycin | >8 | R |
| Ciprofloxacin | 1 | S |
| Trimethoprim-Sulfamethoxazole | >4 | R |
| Imipenem | <2 | S |
| Meropenem | 8 | I |
| Linezolid | <4 | S |
| Doxycycline | >8 | R |
| Moxifloxacin | <1 | S |

MIC: minimum inhibitory concentration, S: susceptible, I: intermediate, R: resistant

Discussion

Findings from an increasing number of cases suggest that the use of anti-PD-1 antibody treatment is associated with the development of mycobacterial infection (6). Among these reports, almost all cases have described TB infection, whereas only one has described an infection with *Mycobacterium avium* complex (MAC), which accounts for approximately 80% of all NTM infections (7). To our knowledge, this is the first report of a patient who developed an NTM infection other than a MAC infection. The case presented here had multiple recurrence of *M. mageritense* infection during nivolumab treatment.

M. mageritense is an NTM that is classified as a Runyon group IV organism (rapidly growing mycobacteria [RGM]) and was first described as a new species in 1997 by Domenech (10). It is found in environments such as soil, natural products, and processed water sources (11). The present patient had had no exposure to such environments and was not involved in activities like gardening, so the route of infection was unknown. Although human infections due to *M. mageritense* are rare, some case reports involving skin and soft tissue infections, especially surgical site infection and catheter-related bloodstream infection, have been published (12-15). In our case, the patient also developed *M. mageritense* infection after the CVAP was inserted. The present case may thus have been caused by not only CVAP but also a combination of factors, such as cancer-related immune deficiency, dexamethasone as a pre-treatment of paclitaxel, and thrombosis due to bevacizumab. In addition, because repeated infections with *M. mageritense* are very rare, we considered nivolumab treatment to be one of the reasons for the refractory *M. mageritense* infection.

Most strains of *M. mageritense* exhibit resistance to anti-tuberculosis drugs or macrolides owing to the *erm* (40) gene. Therefore, accurate identification (e.g., using MALDI-TOF and 16S rRNA gene sequencing) is required for appropriate treatment (15, 16). *M. mageritense* is susceptible to amikacin, fluoroquinolone, trimethoprim-sulfamethoxazole,

imipenem, and linezolid (15). Although no standard treatment has been established, previous reports have shown susceptibility of *M. mageritense* to a combination of the above-mentioned drugs (12-15).

Active mycobacterial infection often develops when the immune system is suppressed (17, 18). Since anti-PD-1 antibodies block the PD-1/PD-L1 axis, which negatively regulates T cell activation and improves the immune system, anti-PD-1 antibodies theoretically do not cause immunosuppression. However, active mycobacterial infection associated with anti-PD-1 antibody treatment has been reported increasingly frequently worldwide (6). Several hypotheses concerning the mechanism underlying this phenomenon have been proposed. The most probable hypothesis is that immune system activation by anti-PD-1 antibodies leads to an excessive immune response to pathogens, and an activated immune system can manifest as symptoms of mycobacterial infection. The manifestation of excessive activation during anti-PD-1 antibody treatment has been reported in cases of aspergillosis (19) and progressive multifocal leukoencephalopathy (20).

At the onset of the first *M. mageritense* infection, the patient was administered a weekly dose of steroids to prevent an allergic reaction induced by paclitaxel treatment. At the onset of the second infection, steroids were not administered, as paclitaxel treatment had been stopped. Since steroids are known to suppress an excessive response, the discontinuation of steroid administration might have caused worsening of the symptoms at the onset of the second infection compared with the first infection and repeated infections with *M. mageritense*.

In conclusion, we encountered a patient infected with *M. mageritense* during nivolumab treatment. Based on our findings, we recommend that physicians be cautious and consider the possibility of the development of NTM infections as well as TB infections.

Author's disclosure of potential Conflicts of Interest (COI).

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