CASE REPORT

Disseminated Mycobacterium chelonae infection in a patient with T-cell lymphoma

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Abstract
Infections with rapidly growing mycobacteria are rare and most often seen in immunocompromised patients. We herein present the case of a 69-year-old man with a T-cell lymphoma treated by chemotherapy and mogamulizumab with a 6-month history of febrile episodes and subcutaneous nodules in both arms and arthritis of metacarpophalangeal joints. Blood cultures and DNA sequencing results demonstrated the growth of Mycobacterium chelonae. The patient was successfully treated with clarithromycin, moxifloxacin, and tobramycin, but died shortly after due to lymphoma progression.

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Introduction
Infections with rapidly growing mycobacteria (RGM) are rare and most often seen in patients with a compromised immune system. We herein present the case of a 69-year-old man with a disseminated Mycobacterium chelonae infection after he had undergone treatment for a peripheral T-cell lymphoma (PTCL).

Case report
A 69-year-old man presented with a 6-month history of febrile episodes with signs of lethargy, cough, and shortness of breath, but with moderate recovery after antibiotic treatment. Furthermore, he noticed red-purple nodules on both upper arms (Fig. 1) and a painful swelling of both third
metacarpophalangeal joints (Fig. 2) for a couple of weeks. His medical history was remarkable for a PTCL (PTCL not otherwise specified, with aberrant CD20 expression), Stage III, International Prognostic Index Score 3, for which he was initially treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and rituximab, which had a partial response. Disease progression occurred after 12 months and he received second-line treatment with R-PECC (rituximab with lomustine, etoposide, chlorambucil, and prednisolone). After partial remission, his treatment was interrupted for toxicity reasons. Unfortunately, within several months, his disease progressed with growing cervical lymphadenopathy with biopsy-proven recurrence of T-cell lymphoma. He was included in a Phase II trial with mogamulizumab [anti-CC chemokine receptor 4 (anti-CCR4) antibody]. Although his disease stabilized, treatment had to be stopped after 7 months according to the trial protocol due to Grade III thrombocytopenia. A positron emission tomography—computed tomography (PET—CT) showed uptake of fluorodeoxyglucose (FDG) in the upper and middle lobes of the lung and in multiple subcutaneous nodules in both arms. An enlarged FDG-positive spleen and inguinal and parailiac lymph nodes were observed; however, these lymph nodes were unchanged in size compared with an abdominal CT scan 1 year earlier.

In the synovial fluid aspirated from his left third metacarpophalangeal joint, acid-fast bacilli were found by Ziehl–Neelsen staining. There was not enough material for further cultures. His blood cultures grew *M. chelonae*, which was in vitro sensitive for clarithromycin and moxifloxacin. Two nodules were excised from his left arm, from which *M. chelonae* DNA was identified by LIPA gene sequencing. Pathologic examination of the nodules showed a panniculitis with granulomatosis, in which no T-cell lymphoma could be demonstrated. The patient was initially treated with oral clarithromycin and moxifloxacin, and intravenous tobramycin. After 1 month, the nodules diminished in size and he reported an improved general well-being. Because of renal insufficiency, tobramycin was discontinued after 2 months of treatment, after which the nodules and fever did not reoccur.

Two months after discharge, the patient was readmitted because of shortness of breath. A PET—CT was repeated and a decrease in subcutaneous nodules was seen. However, increases in lymphadenopathy, splenomegaly, and bilateral pulmonary infiltrates were visible. Lymph node biopsy followed in which no mycobacterial DNA was detectable. Pathological examination of the lymph node revealed relapse of the T-cell lymphoma.

By this time, the patient’s clinical condition deteriorated. No further treatment options were available and the patient was discharged home, with palliative care. He died at home within several days.

**Discussion**

Mycobacteria other than *Mycobacterium tuberculosis* and *Mycobacterium leprae* are called “atypical” or “nontuberculous mycobacteria” (NTM) and can be divided into slow-growing mycobacteria and RGM. *Mycobacterium avium* complex, *Mycobacterium kansasi*, and *Mycobacterium xenopi* are the best known slow-growing mycobacteria,
whereas *Mycobacterium fortuitum*, *Mycobacterium abscessus*, and *M. chelonae* are well-known RGM. They are environmental organisms isolated from water, soil, and aerosols. They can be cultured in regular culture media, although they need a lower optimal growth temperature (around 30°C) [1].

The exact incidence and prevalence of NTM-related disease are unclear, because reporting cases is not mandatory. Second, due to their environmental existence, isolates from humans cannot be used to determine the incidence of NTM, because an isolation of an NTM does not necessarily indicate clinical disease [2].

Infection with RGM can lead to several clinical syndromes. First of all, pulmonary disease due to RGM has been reported. Pulmonary disease due to RGM is predominantly due to *M. abscessus* (80% of cases). Although pulmonary disease is associated with underlying lung disease, this is not the case in all patients. Most patients have a prolonged time from onset of symptoms to diagnosis [3]. Moreover, infection with RGM can present, although rare, with disseminated disease. It is most often seen in patients with severe immunosuppression and hematological malignancies. The disseminated form of the disease presents with multiple subcutaneous nodules or abscesses [4]. Finally, RGM infections can be caused by inoculation, surgery, or prosthetic implantation, resulting in multiple, recurrent abscesses and wound infections [5,6].

One of the risk factors for developing a disseminated infection with RGM is immunosuppression. Although immunocompetent patients have also been reported with disseminated disease, the majority of patients have an obvious underlying condition that compromises immunity. Patients with renal transplant, collagen vascular disease, or hematological malignancies are more likely to develop a disseminated RGM infection, especially when cell-mediated immunity is impaired by corticosteroids or cytotoxic agents [7,8].

Our patient was treated with several immunosuppressing medicines such as prednisolone, rituximab, and mogamulizumab (anti-CCR4). CCR4 is highly expressed by regulatory T cells (Tregs) and T-helper cells, inducing homing. CCR4 is expressed in tumor cells in approximately 30–65% of the patients with PTCL. Mogamulizumab is a defucosylated, humanized, IgG1 monoclonal antibody that binds to CCR4, with enhanced antibody-dependent cellular cytotoxicity. The mechanism of action of mogamulizumab is twofold: it enhances antibody-dependent cellular cytotoxicity and depletes CCR4+ Tregs, potentially evoking antitumor immune responses by autologous effector cells. A Phase II trial in PTCL and cutaneous T-cell lymphoma patients reported an overall response rate of 35% in those who relapsed after their last systemic therapy [9], leading to its approval in Japan.

The exact mechanism of the increased risk of developing an infection with RGM in immunocompromised hosts is unknown. Most research has been conducted in the host defense against *M. tuberculosis*, which shows a prominent role for interleukin-12 (IL-12), interferon-γ (IFN-γ), and tumor necrosis factor-α. These cytokines are responsible for promoting a Type 1 T helper cell (Th-1) response, activating antigen presentation, and phagocytosis [10]. CCR4 is normally associated with a Th-2 immune response, although recent research showed a comparable Th-1 and Th-2 granulomatous response after the introduction of *Mycobacterium bovis* antigen-coated agarose beads in the lungs of mice. CD4+ T cells secreting IL-4 and IFN-γ also expressed transcripts for CCR4 and responded to CCR4 ligands [11].

In our patient, the total CD4 count during mogamulizumab therapy dropped from 390 × 1000/mL to 220 × 1000/mL (normal count: 404–1612 × 1000/mL). Furthermore, it could be hypothesized that the blockage of CCR4 by mogamulizumab can ultimately lead to a blockage of the Th-11 immune response needed to form granulomas and overcome an infection with mycobacteria, thus increasing the risk of developing a disseminated infection with RGM, such as *M. chelonae*.

After the patient stopped treatment with mogamulizumab, he presented with recurrent cervical lymphadenopathy, which was considered at that moment to be a progression of his T-cell lymphoma. However, no biopsy was done to confirm the diagnosis. Possibly, at that time, there was no disease progression after all, but rather a first presentation of an *M. chelonae* infection with cervical lymphadenitis and fever, which temporarily responded to prednisolone and antibiotic treatment but disseminated due to inadequate treatment.

**Conclusion**

In this case report, we presented a patient with a history of febrile episodes with lung involvement and subcutaneous nodules and arthritis, caused by a disseminated *M. chelonae* infection. To the best of our knowledge, this is the first case to describe an infection with a rapid-growing mycobacterium in a patient with a T-cell lymphoma after treatment with a CCR4 antibody. In patients with a comprised cell-mediated immunity and infectious episodes with negative blood culture, one should consider an infection with RGM.

**Conflicts of interest**

All contributing authors declare no conflicts of interest.

**References**


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