Disseminated Cutaneous Mycobacterium chelonae Infection in a Patient With Acute Myeloid Leukemia

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We report a case of disseminated cutaneous Mycobacterium chelonae infection in a patient who was treated with chemotherapy for acute myeloid leukemia. We discuss the clinical manifestations, diagnosis, and treatment of this unusual infection in neutropenic patients.

Keywords. acute myeloid leukemia; Mycobacterium chelonae; nontuberculous mycobacterium; skin.

The group of nontuberculous mycobacteria (NTM) consists of all mycobacteria species other than Mycobacterium tuberculosis complex and Mycobacterium leprae. NTM are ubiquitous in the environment and reside in soil and water. Of the over 150 NTM species, only ∼25 are known to cause disease in humans [1]. Skin and soft tissue infections are most commonly caused by Mycobacterium marinum and Mycobacterium ulcerans, which are both slowly growing mycobacteria. Other mycobacteria from this subgroup of NTM, such as Mycobacterium fortuitum, Mycobacterium abscessus, and Mycobacterium chelonae, are less frequently identified as the cause of disease in humans. Nevertheless, the epidemiology is very divergent depending on geography. Focal cutaneous mycobacterial infections usually develop after contamination of wounds with water or other contaminated products. In previous studies, numerous reports on localized M. chelonae skin infection in immunocompetent persons after tattooing have been published [2]. In contrast, in immunocompromised hosts the portal of entry is less clear. In this population, cutaneous M. chelonae infection is most probably the result of hematogenic dissemination, resulting in multiple skin lesions. This clinical entity has been described in patients with immunosuppressive therapy for solid organ transplantation [3], but it occurs infrequently in patients with hematological malignancies, either with or without neutropenia [4–6]. Although it is generally believed to be a very rare complication that mainly occurs in patients with deprived T-cell immune responses, granulocytopenia or impaired granulocyte function has been suggested to be a pivotal element of the underlying immunodeficiency that predisposes to disseminated infection [6]. This hypothesis concurs with the observation that disseminated M. chelonae is not found in patients diagnosed with advanced human immunodeficiency virus infection. We describe a case with disseminated M. chelonae infection in which absolute granulocytopenia possibly constituted the most important immunodeficiency, with a contribution of the patient’s relative lymphopenia.

CASE REPORT

A 53-year-old Dutch woman was admitted to the Hematology ward of the Leiden University Medical Center for chemotherapy as treatment of her acute myeloid leukemia. Because her disease was classified as “good prognosis” acute leukemia (normal cytogenetics, NPM1 positive, FLT3-ITD negative), hematopoietic stem cell transplantation was not pursued. After enrollment in a prospective randomized phase III clinical trial (HOVON 102, study group B, www.trialregister.nl NTR2187), chemotherapy consisted of 1 cycle of cytarabine (200 mg/m², days 1–7), idarubicin (12 mg/m², days 1–3), and clofarabine (10 mg/m², days 1–5); 1 cycle of amsacrine (120 mg/m², days 4–6), cytarabine (1000 mg/m², days 1–6), and clofarabine (10 mg/m², days 1–5); and 1 cycle of mitoxantrone (10 mg/m², days 1–5) and etoposide (100 mg/m², days 1–5). This treatment was the experimental arm of the study. The complications that occurred during the neutropenic phases after chemotherapy were fewer of unknown origin, oral mucositis with herpes simplex (reactivation), superficial thrombosis of the arm due to a peripherally inserted central catheter, and a generalized macular rash due to clofarabine toxicity. The last neutropenic period lasted evidently longer than the other neutropenic episodes (60 days of neutrophil counts <0.1 cells/10⁹ with neutrophilic granulocyte...
counts performed at least twice weekly). Lymphocyte counts during this period were between 0.15 and 0.30 × 10^9/L. After 3 weeks, the patient developed multiple dusky red to purple, tender, subcutaneous nodules on the face, arms, and legs, resulting in firm purple ulcerating nodules. Within weeks, the nodules developed to larger (2–3 cm), livid plaques, several of which spontaneously ulcerated (Figure 1A). The lesions became more infiltrated when the neutropenic phase ended. At the moment of recovery of her lymphocytes and granulocytes, her CD4 cell count was 300 × 10^6/L.

Histological examination of the skin biopsies revealed a septal panniculitis (inflammation of the subcutaneous fat), with similarities to erythema nodosum. Such histopathological findings have been reported sporadically in association with *M. chelonae* [7, 8]. There was no sign of cutaneous manifestation of the leukemia.

The first confirmatory test result of the suspected disseminated mycobacterial infection was the pathologists observation of intracellular acid-fast bacilli in dermal histiocytes in a Ziehl-Neelsen staining. The absence of frank granulomas led to the suspicion of atypical mycobacterial infection. NTM have a wide spectrum of histological features. A study of cutaneous NTM infections showed a granulomatous response in only 33% of immunosuppressed patients in the first 3 months of infection, compared with 80% of the normal hosts [9]. Mycobacterial culture from the second skin biopsy became positive within 1 week (the first biopsy culture remained negative), and treatment of atypical mycobacterial infection was initiated by multiplex probe assay, showing an *M. chelonae*. There was no sign of cutaneous manifestation of the leukemia. NTM have a wide spectrum of histological features. A study of cutaneous NTM infections showed a granulomatous response in only 33% of immunosuppressed patients in the first 3 months of infection, compared with 80% of the normal hosts [9]. Mycobacterial culture from the second skin biopsy became positive within 1 week (the first biopsy culture remained negative), and treatment of atypical mycobacterial infection was initiated by multiplex probe assay, showing an *M. chelonae* fitting the rapid positive mycobacterial culture. Thereafter, therapy was narrowed down to clarithromycin (500 mg twice daily) and levofloxacin (750 mg once daily), for which the *M. chelonae* was susceptible.

The skin lesions improved within several weeks of treatment (Figure 1B). The patient had no signs of hepatitis and no pulmonary infiltrates, and blood and bone marrow cultures were negative for mycobacterial growth. Bone marrow morphology showed complete remission of her acute myeloid leukemia in the months after chemotherapy.

Antimicrobial susceptibility was tested using the agar proportion method, using a pure culture from primary isolation in broth media. Resistance was demonstrated against primary antituberculosis agents such as isoniazid, rifampin, and ethambutol and susceptibility for clarithromycin (minimal inhibition concentration [MIC] of <2 mg/L) and ciprofloxacin (MIC 2 mg/L). Susceptibility for tobramycin was not tested.

**DISCUSSION**

Although this patient experienced 3 long neutropenic periods, it is remarkable that she developed a disseminated cutaneous *M. chelonae* infection, because numerous patients with hematological malignancies are treated with comparable chemotherapy regimens and do not develop mycobacterial infections. Perhaps the addition of clofarabine, in combination with her prolonged granulocytopenia, rendered her more susceptible. Clofarabine is a nucleoside analog that inhibits DNA synthesis and ribonucleotide reductase. It induces direct apoptosis resulting in toxicity to both nonproliferating human lymphocytes and rapidly proliferating cells [10]. This mechanism of action is similar to its analogs cladribine and fludarabine, which are capable of inducing T-cell depletion. At the time of the mycobacterial infection, the CD4 and CD8 counts in this patient were 304 and 45 × 10^6/L, respectively, indicating that a certain degree of T-cell depletion had occurred. Unfortunately, the source of the *M. chelonae* remains unknown. The patient did not use any new skin products in the period before her skin lesions appeared, nor was there any clinical suspicion of colonization of her central intravenous catheter.

The fact that a disseminated *M. chelonae* infection often only presents with skin manifestations and no signs of pulmonary and/or liver involvement, could be explained by the preference of some NTM (*M. chelonae, M. marinum, M. ulcers*, or *Mycobacterium haemophilum*) for lower temperatures (30°C) and therefore tropism for the skin [1].

After making the correct diagnosis, the clinical challenge persists in choosing the most appropriate therapy. NTM species, like *M. chelonae*, are associated with extensive resistance to antimicrobial drugs. Treatment of disseminated infections with NTM will remain a matter of discussion, because their low incidence precludes that randomized controlled trials will provide evidence-based guidance for best treatment modalities. According to expert opinion [11], it is recommended to use a macrolide...
(eg, clarithromycin) for the treatment of \textit{M. chelonae} infection, with addition of a quinolone (eg, levofloxacin or ciprofloxacin). The only clinical treatment trial for \textit{M. chelonae} skin disease used clarithromycin monotherapy, without a comparator. Of the 14 patients treated with 500 mg of clarithromycin twice daily for 6 months, all were cured except for 1 patient who relapsed with an isolate that developed mutational resistance to clarithromycin [12]. Because these patients were not as severely immunocompromised as our patient, and there was the possibility of inducible resistance to macrolides, we chose to treat our patient with duo therapy. In an ideal setting, therapy should be based on susceptibility data, although reports show that clinical response is not always compatible with in vitro susceptibility to antibiotics. When the infection is progressive under oral antibiotic therapy, addition of a parental antibiotic such as tobramycin should be considered. Another antimicrobial drug that could be used is linezolid. This remedy was not an option for our patient because of in vitro resistance and the possible adverse event of bone marrow suppression. Besides initiating appropriate anti-mycobacterial treatment, reconstitution of adequate immune responses is considered to be a key element in reaching the intended clinical endpoint. Duration of treatment is based on clinical response, with a range of 6 to 12 months.

This patient, together with other case series, demonstrates that no single specific immune deficiency alone, ie, T-cell, humoral, or granulocyte-related, predisposes for a disseminated \textit{M. chelonae} infection. However, it is unknown whether a combination of malfunction of different parts of the immune system or a certain level of either T-cell or granulocyte dysfunction provides sufficient opportunity for \textit{M. chelonae} to cause disseminated infection. Diagnosis of disseminated \textit{M. chelonae} infection often requires multiple sampling and perseverance of the treating physicians, whereas the often slow response to treatment in a setting of severe underlying morbidity requires perseverance of both the patient and the medical team.

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**References**