Late-Onset Posttraumatic Skin and Soft-Tissue Infections Caused by Rapid-Growing Mycobacteria in Tsunami Survivors

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Background. In the tsunami catastrophe in Thailand in 2004, several thousand Swedish tourists were injured, with contaminated crush trauma of the legs being the main cause of injury among the survivors.

Methods. Patient and laboratory data for those who received hospital care in Stockholm and Gothenburg and contracted late-onset infections due to rapid-growing mycobacteria were reviewed retrospectively. Also, concomitant infections were recorded.

Results. Fifteen patients with late-onset skin and soft-tissue infections due to rapid-growing mycobacteria are described here. Mycobacterium abscessus was isolated in 7 cases, Mycobacterium fortuitum was isolated in 6 cases, and Mycobacterium peregrinum and Mycobacterium mageritense were isolated in 1 case each. The infections appeared after a delay of 20–105 days (median, 60 days) after the trauma, targeting undamaged skin located near primary sutured wounds or skin grafts. Antimycobacterial drugs were given to 9 (60%) of the patients. The course of infection was protracted, but all infections due to rapid-growing mycobacteria healed within 12 months. Concomitant subcutaneous infections due to other microorganisms, such as Burkholderia pseudomallei or Cladophialophora bantiana, appeared early or late after the trauma.

Conclusions. Repeated cultures of abscess and wound specimens for Mycobacterium species may be needed to find the etiologic agents causing contaminated skin and soft-tissue infections, such as those that developed after traumas that occurred during the tsunami. These cultures are especially necessary when symptoms appear late and when conventional bacterial culture results are negative. A biopsy is recommended for the best yield and for complementary histopathological examination.

On 26 December 2004, an earthquake triggered a huge tsunami wave that flooded the coastal areas of southern Asia. The tsunami killed >200,000 persons, and many more were severely injured. On the coast of Thailand, ∼500 Swedish tourists died, and >2000 experienced serious crush injuries, mostly in connection with enforcing by contaminated water. The early- or late-onset infectious complications in traumatic wounds that were caused by unusual pathogens have been one of the clinical challenges after the tsunami catastrophe. Various uncommon bacterial or fungal infections caused by environmental organisms that have occurred in tsunami survivors have been reported [1–5]. However, few reports have included infections due to rapid-growing mycobacteria (RGM), a group of organisms known to sometimes cause skin and soft-tissue infections in immunocompetent patients (e.g., after inoculation during surgical procedures or after penetrating trauma) [6, 7]. Antimycobacterial treatment is difficult because of the natural resistance of RGM to many antibiotics, and relapses are common. We describe 15 patients who experienced traumatic injuries during the tsunami and who thereafter developed delayed-onset RGM infections; these infections were frequently associated with concomitant bacterial or fungal infections.

STUDY DESIGN

The study was retrospective and included patients with infections caused by RGM, identified at the Microbiology Laboratories in Stockholm and Gothenburg, the
2 largest cities in Sweden. Data were collected from the patient charts after informed consent was obtained. Infection characteristics and site, clinical description of the lesions, antimicrobial therapy, surgical procedures, other treatment, and outcome were registered. Culture results for swab and biopsy specimens, drug susceptibility patterns, and findings of histopathological examination of biopsy specimens were reviewed.

Definite infection was established by a positive culture result combined with clinical symptoms of protracted skin ulcer or abscess. Treatment failure was defined as the lack of clinical improvement during therapy or relapse of infection during the follow-up period.

**RESULTS**

**Initial clinical course.** The patients’ clinical data are shown in table 1. Ten patients underwent primary surgical debridement with sutting in Thailand. After arrival in Sweden, 12 patients were treated for early-onset bacterial infections. All patients, except for patient 8, were discharged within 1.5 months. Nine of the patients received skin grafts during their hospital stay. The median duration from the trauma to the appearance of new wounds or abscesses was 60 days (range, 20–105 days). The lesions started as tender erythematous nodules, which tended to perforate and secrete a yellowish fluid. They were most often localized in nontraumatized, virtually intact skin and were located outside the area where the skin was transplanted (figures 1 and 2). In 14 patients, the lesions were localized on the lower extremities, and 1 patient (patient 8) had a lesion on the arm. In 2 of the patients whose wounds had been primary sutured, foreign material was subsequently observed; in one patient (patient 7), sand particles were seen by microscopic examination, and in the other patient (patient 15), a small piece of wood was found during revision of the infected site. Twelve months after patient 7’s trauma, large amounts of sand particles could be demonstrated by MRI of the subcutaneous tissue. There were no clinical signs of disseminated mycobacterial infection in any of the patients.

Three patients (patients 2, 3, and 7) developed recurrent lesions on the lower extremities, despite long-term antibiotic treatment. The lesions were excised, and they subsequently healed.

**Cultures and biopsies.** Seven RGM infections were determined on the basis of positive results of culture of swab specimens. Eight RGM infections were found on the basis of positive results of culture of skin biopsy specimens, often after several swab culture attempts. Results of smears for acid-fast bacteria were negative for 8 patients, and microscopic examination of smear specimens was not performed for 7 patients. The median duration from onset of skin symptoms caused by cutaneous mycobacterial infection to microbiological diagnosis was 33 days (range, 13–116 days). All isolated mycobacteria were rapid growing; 7 were *M. abscessus*, 6 were *Mycobacterium fortuitum*, 1 was *Mycobacterium peregrinum*, and 1 was *Mycobacterium mageritense*.

Histopathological examinations were performed for the 8 biopsy specimens that were positive for RGM by culture, and all showed granuloma formation; in 1 specimen, fungal hyphae were also observed. In one specimen (from patient 7), foreign material interpreted to be sand particles was observed. Biopsy specimens obtained from recurrent lesions in patients 2, 3, and 7 had negative culture results but showed histopathological signs of granuloma formation.

**Drug susceptibility tests.** In vitro drug susceptibility testing
Late-Onset Mycobacterial Infections

Figure 1. Multiple abscesses caused by Mycobacterium fortuitum in the skin outside the wound in a tsunami survivor.

Table 1. Clinical data on tsunami survivors who contracted late-onset skin and soft-tissue infections due to rapid-growing mycobacteria.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age, years</th>
<th>Primary suture</th>
<th>Graft</th>
<th>Symptoms (no. of days after trauma)</th>
<th>Culture yield (no. of days after symptom onset)</th>
<th>Antimycobacterial treatment (duration of treatment, months)</th>
<th>Concomitant infection or colonization</th>
<th>Time from onset of mycobacterial infection to healing, months</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>55</td>
<td>Yes</td>
<td>No</td>
<td>Abscesses (44)</td>
<td>Mycobacterium abscessus (31)</td>
<td>Rifabutin (0.5) and Clm (0.5)</td>
<td>...</td>
<td>8.5</td>
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<td>2</td>
<td>M</td>
<td>39</td>
<td>Yes</td>
<td>Yes</td>
<td>Abscesses (58)</td>
<td>M. abscessus (20)</td>
<td>Amikacin (8) and Clm (8)</td>
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<td>3</td>
<td>M</td>
<td>42</td>
<td>Yes</td>
<td>Yes</td>
<td>Abscesses (47)</td>
<td>M. abscessus (116)</td>
<td>Amikacin (8) and Clm (6)</td>
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<td>9</td>
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<tr>
<td>4</td>
<td>M</td>
<td>28</td>
<td>Yes</td>
<td>Yes</td>
<td>Wound (100)</td>
<td>M. abscessus (13)</td>
<td>...</td>
<td>MRSA</td>
<td>6</td>
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<tr>
<td>5</td>
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<td>Yes</td>
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<td>M. abscessus (15)</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>C. bantiana</td>
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<tr>
<td>8</td>
<td>F</td>
<td>29</td>
<td>Yes</td>
<td>Yes</td>
<td>Wound (100)</td>
<td>Mycobacterium fortuitum (13)</td>
<td>...</td>
<td>C. bantiana, Scardapropium apospenum, Saksena vasiformis</td>
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<tr>
<td>9</td>
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<td>33</td>
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<td>Yes</td>
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<td>Doxycyclin (3) and ciprofloxacin (5)</td>
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<td>40</td>
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<td>Yes</td>
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<tr>
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<td>No</td>
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<td>Actinomyces neui</td>
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<td>No</td>
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<td>...</td>
<td>6</td>
</tr>
<tr>
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<td>M</td>
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<td>No</td>
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<td>Mycobacterium mageritense (83)</td>
<td>...</td>
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</tbody>
</table>

NOTE. Clm, clarithromycin; MRSA, methicillin-resistant Staphylococcus aureus.

of M. abscessus and M. fortuitum revealed species-specific susceptibility patterns. All 7 strains of M. abscessus were susceptible to clarithromycin (median MIC, 0.064 mg/L; range, 0.064–0.125 mg/L), and 6 were susceptible to amikacin (median MIC, 12 mg/L; range, 0.75–32 mg/L). All 7 strains were resistant to ciprofloxacin (MIC, >32 mg/L), doxycycline (MIC, >250 mg/L), and sulfamethoxazole (MIC, >32 mg/L).

Among the M. fortuitum strains, 3 of 6 were susceptible to clarithromycin (median MIC, 16 mg/L; range, 1–64 mg/L), 5 of 6 were susceptible to amikacin (median MIC, 2 mg/L; range, 1–64 mg/L), 5 of 5 were susceptible to ciprofloxacin (median MIC, 0.25 mg/L; range, 0.25–0.75 mg/L), 4 of 5 were susceptible to doxycycline (median MIC, 16 mg/L; range, 0.5–24 mg/L), and 3 of 3 were susceptible to sulfamethoxazole (median MIC, 0.075 mg/L; range, 0.047–0.094 mg/L) [14]. There is a lack of established breakpoints for in vitro susceptibility testing of the rare species M. peregrinum, and treatment of infection due to this bacterium was therefore given according to clinical practice [6, 14].

**PFGE.** To determine strain identity, DNA from 7 M. abscessus isolates from 7 different patients was digested by a restriction enzyme, Ase I [11], and was examined by PFGE. All patients had isolates displaying unique PFGE patterns, indicating an environmental origin (figure 3).

**Concomitant infections.** Various bacteria and fungi were concomitantly recovered from the patients’ abscesses. In 3 cases, 1 of which appeared 12 months after the trauma, Cladophialophora bantiana was detected (in patients 6, 7, and 8). Ac-
tinomycyes neuii and Scedosporium apiospermum were observed in 1 case each (in patients 13 and 8, respectively). Burkholderia pseudomallei was found by culture of a wound specimen and was also the cause of septicemia in patient 5. Three patients were infected with methicillin-resistant Staphylococcus aureus (patients 4, 5, and 10). It could not be concluded if mixed infection or only carriage was present.

Antimycobacterial treatment. Nine patients received antimycobacterial drug therapy. The median duration of treatment was 3 months (range, 0.5–9 months). The most frequently prescribed antimicrobial agents for treatment of M. abscessus infection were clarithromycin and amikacin (table 1). For 6 patients, a combination of parenteral and oral antibiotics was given for a median duration of 8 months (range, 2–9 months), and 3 patients received oral antibiotics only for 3 months (range, 0.5–6 months); 1 of these 3 patients received clarithromycin only.

Seven patients with multiple lesions were treated for a median duration of 5 months (range, 0.5–9 months), and 2 patients with single lesions were treated for a duration of 3 months. M. abscessus infections were treated for a median duration of 6 months (range, 0.5–9 months), and M. fortuitum infections required treatment for a median duration of 3 months (range, 2–3 months) (table 1). The patient with M. peregrinum infection was treated according to clinical practice. Two patients experienced reversible toxic effects caused by rifabutin (in one patient) and clarithromycin (in the other patient).

Outcome. Six patients healed spontaneously without antimycobacterial treatment after a median duration of 7 months (range, 5–12 months). The median time it took for the lesions to heal for the 9 patients given drug treatment was 8.5 months (range, 3–11 months). The median follow-up time for all of the patients was 4 months (range, 1–24 months) after treatment. The course of infection was protracted in several patients, but all symptoms of infection disappeared in all patients within 1 year. One patient infected with both M. abscessus and C. bantiana still had black scars at the end of the follow-up period. There were no treatment failures.

Case report (patient 8). A healthy 29-year-old Swedish woman was propelled into a concrete pool by the tsunami wave and contracted fractures of the pelvis, tibia, clavicle, rib, and manubrium sterni and an open fracture of the right ankle. She had deep crush wounds in the arms, legs, and buttocks. Primary revisions were performed in Thailand. She arrived in Sweden 1 week after the trauma with infected wounds and spent 2 months in the intensive care unit. Twenty-four operations were performed, and she contracted severe pneumonia. A great variety of gram-positive and gram-negative bacteria and fungi were recovered from airways and wounds (e.g., multidrug-resistant Acinetobacter baumannii with extended-spectrum β-lactamases). Among the identified fungi, S. apiospermum was recovered, various Candida species were identified in a wound specimen, and the zygomycete Saksenea vasiformis was found in a necrotic tissue specimen. The patient was treated with colistin for the acinetobacter infection, and voriconazole was given for 1 month to treat the mold infections. However, no specific drug was given for treatment of zygomycosis. The patient recovered gradually. Four months after the trauma, a granulomatous wound appeared on her arm, and culture yielded M. fortuitum. The wound healed without treatment. Eleven months after the trauma, C. bantiana was isolated from new
abscesses on her legs. These were excised, and they healed without antifungal therapy. After a 2-year follow-up period, the patient still had neurological sequelae.

**DISCUSSION**

Traumatic wound infections were among the most common acute medical problems after the tsunami catastrophe. In our patients, blunt and sharp trauma, as well as enforcement of contaminated water by high pressures, caused the inoculation of various microorganisms in soft tissues that spread under the surface of the intact skin. This was proved by the finding of sand particles in the subcutis peripheral to the transplanted skin, although the transplanted regions remained free from infection. It might be speculated that nosocomial spread of the bacteria had occurred after the trauma, but the isolated *M. abscessus* strains were all of different PFGE types, which provides evidence against a common-source nosocomial infection. Many of the identified microorganisms are known to be prevalent in soil, decaying vegetation, sewage, and natural waters in certain geographical areas; such microorganisms include *M. abscessus*, *C. bantiana* fungi, and the gram-negative *B. pseudomallei*. Trauma itself and the presence of foreign bodies predispose patients to long-term infections, often due to such low-pathogenic bacteria or fungi. These concomitant infections probably retarded the healing process and were, in some patients, clearly significant, such as in the patient infected with *B. pseudomallei* who developed septicemia. Also, *C. bantiana* infection in 1 patient resulted in a black scar, probably consisting of dead fungal hyphae, signifying its invasive growth in the skin. In the remaining patients, the clinical importance of the pathogens causing the concomitant infections was unclear.

Delayed onset of infection caused by bacteria or fungi has been commonly recognized [15–17]. However, the ways in which microbes remain latent are enigmatic, although the molecular mechanisms underlying dormant persister cells are now being unravelled. It seems that dormancy, in general, may be the default form of bacterial life [18]. Persistent forms of RGM may therefore explain the protracted onset of such infections in our patients.

Among the 126 hospitalized Swedish tsunami survivors, at least 15 had contracted RGM infections in the skin and soft tissue. Erythematous lesions appeared a median of 60 days (range, 20–105 days) after the trauma, a somewhat longer period than that observed in an outbreak of *M. abscessus* infection that resulted from persons bathing in a public pool [19]. The bacteriological diagnosis of RGM infection on the basis of testing of biopsy specimens proved to be more sensitive than diagnosis on the basis of testing of samples of secretions [14]. Moreover, the *M. abscessus* infections were more severe than those caused by other RGM and often involved multiple abscesses, and patients with *M. abscessus* infections received antibiotic treatment for longer periods. In *M. abscessus* skin and soft-tissue infections, the combination of surgical therapy and clarithromycin treatment reduced healing time by 50%, compared with surgical therapy or clarithromycin treatment alone [20]. Generally, the correlation between in vitro susceptibility testing and clinical outcome in RGM infection is poorly documented, with the exception of such testing of clarithromycin, which is the first-line drug [14]. However, a combination of at least 2 drugs is recommended to minimize the risk of development of drug resistance. Moreover, surgical resection is recommended, especially for small, single lesions.

Despite full in vitro susceptibility to amikacin and clarithromycin, recurrent lesions developed in 3 of our patients during their treatment and required additional surgical excision. In 1 patient, sand particles were present subcutaneously (visualized by MRI), probably facilitating the persistence of the infection. Overall, only 60% of our patients required antibiotic treatment. Thus, spontaneous healing was not uncommon, particularly for patients with infections caused by RGM other than *M. abscessus* and in the absence of foreign or necrotic material, which explains why the removal of all such debris is mandatory.

It is surprising that so few reports of RGM infections after the tsunami catastrophe are known. A few explanations may be the relative mildness of these infections (even if they were long term), the difficulties in diagnosing them, and the tendency of small lesions to spontaneously heal. Contaminated trauma, as in our tsunami survivors, may thus cause RGM soft-tissue infections after a latency period. Repeated specific cultures or biopsies supplemented by histopathological examination are recommended for the best diagnosis.

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**References**


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