Mycobacterial Infection of the Upper Extremities

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Background and purpose: Mycobacterial infection of the upper extremities is extremely rare. To make an early accurate diagnosis is often difficult, and the treatment is, therefore, frequently delayed in clinical practice. This paper describes the diagnosis and treatment of mycobacterial infection of the upper extremities in a series of patients treated at National Taiwan University Hospital.

Methods: The medical records of 15 patients with mycobacterial infection of the upper extremities treated between 1985 and 1998 were retrospectively analyzed. The diagnosis of mycobacterial infection was established by positive culture results, the presence of acid-fast bacilli, or characteristic histopathologic findings.

Results: Mycobacterial infection was suspected on initial examination in only two patients. The duration between the onset of symptoms and correct diagnosis averaged 37.5 months (range, 3 wk to 209 mo). The involved sites of mycobacterial infection included the wrist in nine patients, the elbow in two, the hand in two, the humerus in two, the forearm in one, and the shoulder in one. Three patients suffered from multifocal musculoskeletal mycobacterial infection. Microbiologic studies identified Mycobacterium tuberculosis in four patients and nontuberculous mycobacteria (NTM) in four. Characteristic histopathologic findings of mycobacterial infection including caseation, granulomatous inflammation, eosinophilic epithelioid cells, Langhan's giant cells, and lymphocytic aggregates were noted in all 15 patients. All patients received chemotherapy and 14 patients underwent surgical treatment. The mean duration of followup was 46 months (range, 15-97 months). Treatment failed in two of the patients with multifocal NTM infection and in one patient whose mycobacterial infection was identified by histopathology.

Conclusions: Mycobacterial infection should be included in the differential diagnosis of infection of the upper extremities. Treatment failures are more frequent in patients with multifocal NTM infection.

Mycobacterial infection of the musculoskeletal system is uncommon in developed countries [1–3]. However, the incidence of extrapulmonary mycobacterial infection and musculoskeletal mycobacterial infection has gradually increased in recent years due to the increased numbers of immunocompromised individuals and drug-resistant bacterial strains [1, 2]. Extrapulmonary tuberculosis (TB) accounts for 18.5% of all TB cases, and musculoskeletal TB accounts for 10% of extrapulmonary TB cases [1]. The most common sites involved in musculoskeletal TB include the spine (51%), pelvis (12%), hip and femur (10%), knee and tibia (10%), and ribs (7%) [2].

Mycobacterial infection of the upper extremities is extremely rare [3]. The onset of clinical symptoms is insidious and there may not always be simultaneous involvement of other organs such as the lungs. Therefore, early accurate diagnosis is often difficult and treatment is frequently delayed, resulting in irreversible osteoarticular destruction by the time of diagnosis [4–12]. Here, we report the characteristics of diagnosis and treatment of mycobacterial infection of the upper extremities.
Patients and Methods

The medical records of 15 patients with mycobacterial infection of the upper extremities treated at National Taiwan University Hospital from 1985 to 1998 were retrospectively analyzed. The diagnoses of these patients were established by positive culture results in tissue or synovial fluid specimens, the presence of acid-fast bacilli in tissue specimens or in synovial fluid smears, or characteristic histopathologic findings including caseation, granulomatous inflammation, eosinophilic epithelioid cells, Langhan's giant cells, and lymphocytic aggregates. Patients whose diagnoses were not based on these findings were excluded from this survey, although antimycobacterial chemotherapy was prescribed in some of these cases.

Details of clinical manifestations, laboratory and radiographic findings, treatment, and outcome were recorded. The radiographic findings were classified into four stages according to the criteria proposed by Martini et al in 1986 [3], as follows: stage 1, localized osteoporosis without bony lesions; stage 2, one or more erosions or cavities in the bone; stage 3, involvement of the whole joint without gross destruction; and stage 4, gross destruction of the bones and joints.

Mycobacteria were isolated and identified using conventional methods [13]. The medium for primary isolation during 1985 to 1995 was the Lowenstein-Jensen slant (BBL, Becton Dickinson, Sparks, MD, USA). From 1996 onwards, Middlebrook 7H10 agar (BBL, Becton Dickinson) was also used for isolation. Drug susceptibility testing of Mycobacterium spp to isoniazid, ethambutol, rifampin, and streptomycin was performed using the modified proportional method recommended by the US National Committee for Clinical Laboratory Standards [14].

Results

Clinical manifestations

Fifteen patients, including eight males and seven females, met the entry criteria of this retrospective study. The mean age at the onset of symptoms was 38.8 ± 20.4 years (mean ± standard deviation; range, 2–65 yr). Nine were referred from local practitioners because of failure to respond to initial treatment. The initial presentations included chronic inflammation, swelling and pain in eight patients, tumor mass in seven, limitation of range of motion in five, abscess or sinus formation in five, axillary lymphadenopathy in one, and carpal tunnel syndrome in one. None of the patients suffered from systemic symptoms such as fever, fatigue, night sweating, or weight loss.

Mycobacterial infection was suspected at the first visit in only two patients. One of these two patients suffered from chronic inflammation with the formation of abscesses and bony destruction in the arm; the other had axillary lymphadenopathy and a family history of pulmonary TB. Initial clinical impressions of the other 13 patients included noninfectious arthritis in six, noninfectious tenosynovitis in three, suppurative tenosynovitis in two, felon in one, and lipoma in one. The duration from the onset of symptoms to correct diagnosis averaged 37.5 ± 55.0 months (range, 3 wk to 209 mo).

The clinical characteristics of the 15 patients are shown in the Table. The involved sites of mycobacterial infection included the wrist in nine patients, the elbow in two, the hand in two, the humerus in two, the forearm in one, and the shoulder in one. Three patients suffered from multifocal musculoskeletal mycobacterial infection. All patients underwent chest radiographic study, which showed inactive pulmonary TB in three patients, and a calcified lymph node on the left upper portion of the mediastinum without pleural reaction in one other patient. None of the 15 patients had detectable active pulmonary lesions. The underlying diseases included adrenal insufficiency in one patient, and systemic lupus erythematosus (SLE) in two patients receiving long-term steroid therapy. One patient had a previous local wound over the right fourth finger, injured by broken china, followed by contamination with dirty water. One patient had a previous local wound over the right middle finger due to puncture by a fish fin [15]. Only one patient had a family history of pulmonary TB.

Laboratory investigations

All patients underwent laboratory examinations including complete blood cell count, erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP) concentration. The initial white blood cell (WBC) count averaged 7.84 ± 2.13 x 10³ cells/ L (range, 4.80–11.67 x 10³ cells/ L). The initial ESR averaged 32 ± 34 mm/ 1 hour (range, 5–122 mm/ 1 hour) and 69 ± 48 mm/ 2 hours (range, 19–155 mm/ 2 hours). The initial CRP concentration averaged 4.7 ± 6.5 x 10⁴ µg/ L (range, < 0.4–20.2 x 10⁴ µg/ L). Most patients had a normal WBC count and mildly elevated ESR. Marked elevation of ESR was noted only in the two patients (patients 13 and 14) with concomitant pyogenic infection (Staphylococcus aureus) and the two patients with underlying SLE. Only patient 15 received a tuberculin purified-protein derivative (PPD) skin test, and the result was strongly positive (1.7 ± 2 cm induration).
### Table. Clinical characteristics, treatment, and outcome in 15 patients with mycobacterial infection of the upper extremities

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, yr/ Involved sites</th>
<th>X-ray staging</th>
<th>Chest x-ray</th>
<th>Mycobacterial culture</th>
<th>AFB</th>
<th>Chemotherapy/ duration (mo) of treatment</th>
<th>Surgery</th>
<th>F/U, mo</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/F Humerus</td>
<td>2</td>
<td>Negative</td>
<td>M. tuberculosis</td>
<td>Not done</td>
<td>INH, RMP, EMB/ 12</td>
<td>Debridement, curettage, kanamycin irrigation, allografting of bone</td>
<td>20</td>
<td>Cured</td>
</tr>
<tr>
<td>2</td>
<td>65/M Wrist</td>
<td>4</td>
<td>Inactive</td>
<td>M. tuberculosis</td>
<td>+</td>
<td>INH, RMP, EMB/ 6</td>
<td>Debridement, total carpectomy, wrist arthrodesis</td>
<td>75</td>
<td>Cured</td>
</tr>
<tr>
<td>3</td>
<td>2/M Wrist</td>
<td>2</td>
<td>Negative</td>
<td>M. tuberculosis</td>
<td>+</td>
<td>INH, RMP, EMB/ 6</td>
<td>Debridement, curettage</td>
<td>34</td>
<td>Cured</td>
</tr>
<tr>
<td>4</td>
<td>37/M Wrist, elbow</td>
<td>2</td>
<td>Negative</td>
<td>M. tuberculosis</td>
<td>-</td>
<td>INH, RMP, EMB, STM/ 11</td>
<td>Debridement, synovectomy</td>
<td>27</td>
<td>Cured</td>
</tr>
<tr>
<td>5</td>
<td>52/F Wrist</td>
<td>1</td>
<td>Negative</td>
<td>No growth</td>
<td>-</td>
<td>INH, RMP, EMB/ 7</td>
<td>Synovectomy, release of transverse carpal ligament, tendon repairs</td>
<td>57</td>
<td>Cured</td>
</tr>
<tr>
<td>6</td>
<td>47/F Wrist</td>
<td>4</td>
<td>Inactive</td>
<td>No growth</td>
<td>-</td>
<td>INH, RMP, EMB, PZA/ 24</td>
<td>Debridement, wrist arthrodesis</td>
<td>63</td>
<td>Cured</td>
</tr>
<tr>
<td>7</td>
<td>46/M Wrist</td>
<td>2</td>
<td>Negative</td>
<td>No growth</td>
<td>-</td>
<td>INH, RMP, EMB/ 6</td>
<td>Debridement, wrist arthrodesis</td>
<td>15</td>
<td>Cured</td>
</tr>
<tr>
<td>8</td>
<td>50/F Wrist</td>
<td>4</td>
<td>Negative</td>
<td>No growth</td>
<td>-</td>
<td>INH, RMP, EMB/ 10</td>
<td>Debridement, wrist arthrodesis</td>
<td>18</td>
<td>Cured</td>
</tr>
<tr>
<td>9</td>
<td>58/M Wrist</td>
<td>4</td>
<td>Negative</td>
<td>Not done</td>
<td>-</td>
<td>INH, RMP/ 12</td>
<td>Debridement, Darrach procedure, wrist arthrodesis</td>
<td>42</td>
<td>Cured</td>
</tr>
<tr>
<td>10</td>
<td>46/F Shoulder</td>
<td>1</td>
<td>Calcified</td>
<td>med. LN</td>
<td>Not done</td>
<td>INH, RMP, EMB/ 11</td>
<td>Debridement</td>
<td>77</td>
<td>Cured</td>
</tr>
<tr>
<td>11</td>
<td>36/F Forearm</td>
<td>1</td>
<td>Inactive</td>
<td>Lung TB</td>
<td>Not done</td>
<td>INH, RMP, EMB/ 48</td>
<td>Synovectomy</td>
<td>48</td>
<td>Not cured</td>
</tr>
<tr>
<td>12</td>
<td>52/F Hand</td>
<td>2</td>
<td>Negative</td>
<td>M. marinum</td>
<td>+</td>
<td>RMP, EMB, doxycycline, clarithromycin/ 19</td>
<td>Debridement, synovectomy, neurolysis</td>
<td>37</td>
<td>Cured</td>
</tr>
<tr>
<td>13</td>
<td>32/M Hand</td>
<td>1</td>
<td>Negative</td>
<td>Scotochromogens</td>
<td>-</td>
<td>INH, RMP, EMB/ 6</td>
<td>Synovectomy</td>
<td>53</td>
<td>Cured</td>
</tr>
<tr>
<td>14</td>
<td>48/M Humerus, wrists, ankle, ribs, lower limbs, mandible</td>
<td>2</td>
<td>Negative</td>
<td>M. chelonae</td>
<td>+</td>
<td>INH, RMP, EMB, kanamycin, amikin/ 41</td>
<td>Nil</td>
<td>41</td>
<td>Not cured</td>
</tr>
<tr>
<td>15</td>
<td>4/M Elbow</td>
<td>3</td>
<td>Negative</td>
<td>M. scrofulaceum</td>
<td>+</td>
<td>INH, RMP, EMB, PZA, amikin, ciprofloxacin, clarithromycin/ 97</td>
<td>Curettage</td>
<td>97</td>
<td>Not cured</td>
</tr>
</tbody>
</table>

AFB = acid-fast bacilli on microscopy; F/ U = follow-up; INH =isoniazid; RMP = rifampin; EMB = ethambutol; STM = streptomycin; PZA = pyrazinamide; med. LN = mediastinal lymph node. All 15 patients had characteristic histopathologic findings of mycobacterial infection.
Radiographic findings
All patients underwent radiographic examination of the lesion sites. The initial radiographic findings were stage 1 in four patients, stage 2 in six patients, stage 3 in one patient, and stage 4 in four patients (Table).

Microbiology and pathology
The results of microbiologic studies including mycobacterial culture and acid-fast stains are shown in the Table. Characteristic histopathologic findings of mycobacterial infection were noted in all 15 patients.

Treatment and outcome
The regimens and duration of chemotherapy in the 15 patients are shown in the Table. The mean duration of chemotherapy was 20.3 ± 24.9 months (range, 6–97 mo). Fourteen patients underwent surgical treatment, including debridement, synovectomy, and curettage. Four patients underwent arthrodesis of the wrist because of severe destruction of joints (Table).

The mean duration of follow-up from the beginning of treatment was 46.0 ± 24.4 months (range, 15–97 mo). Treatment failed in two of the patients (patients 14 and 15) with multifocal nontuberculous mycobacteria (NTM) infection, and in one other patient (patient 11) whose mycobacterial infection was identified by characteristic histopathologic findings. The other 12 patients were cured after treatment, without relapse during a mean follow-up period of 43 months (Table). Their joints were painless with acceptable functional outcome, except in four patients who had a wrist joint fusion.

Fig. 1. A 2-year-old boy (patient 3) suffered from tuberculosis of the wrist for 6 months with delayed diagnosis. Radiographic examinations (A and B) revealed osteolytic cavities in the distal radius (stage 2). After debridement, curettage, and combined chemotherapy for 6 months, the bony lesions healed (C and D) with minimal functional deficit.

Fig. 2. A 58-year-old man (patient 9) suffered from mycobacterial infection of the wrist for 101 months with delayed diagnosis. The initial plain radiographs of the wrist (A and B) showed advanced destruction of the bone and joint (stage 4). Darrach procedure and wrist arthrodesis using modified Gill's procedure were performed (C and D). He received chemotherapy with isoniazid and rifampicin for 12 months. The wrist joint was finally fused with acceptable functional outcome.
Discussion

The high incidence of delayed diagnosis and treatment in mycobacterial infection of the upper extremities is usually due to the rarity of this disease and the lack of physician experience [16]. In addition, the clinical symptoms frequently are not manifested for up to 18 months after the onset of infection [1, 17]. Detectable pulmonary lesions or systemic symptoms of mycobacterial infection occur in only about one-third of patients with active musculoskeletal mycobacterial infection [2]. Therefore, early correct diagnosis is often difficult and treatment is frequently delayed, so that irreversible osteoarticular destruction is often present at the time of diagnosis [4–12]. In the present study, the initial impression was correct in only two patients (13%). The lack of typical clinical manifestations of mycobacterial infection led to various incorrect initial impressions. Nevertheless, some clinical characteristics have been reported to be useful in differentiating mycobacterial infection from acute pyogenic infection, such as the absence of notable systemic symptoms, nearly-normal WBC count, and mildly elevated ESR [1, 17]. The present study supports these findings.

The diagnosis of mycobacterial infection of the upper extremities is established by positive culture results, the presence of acid-fast bacilli, or characteristic histopathologic findings. Surgery is often utilized as a diagnostic tool in order to obtain an adequate tissue specimen or tissue fluid [2]. Because of the uncertainty in the diagnosis, patients whose diagnoses were not based on the above findings were excluded from this study. This may have resulted in underestimation of the incidence of mycobacterial infection of the upper extremities in our hospital.

There have been few studies concerning the treatment of musculoskeletal mycobacterial infection. Previous studies have shown that treatment with combination chemotherapy for 6 to 24 months with agents includingisoniazid and rifampin with or without pyrazinamide, ethambutol, or streptomycin resulted in satisfactory cure rates for musculoskeletal TB [18–23]. The current recommended regimen in the treatment of adult musculoskeletal TB is a combination of isoniazid 300 mg/day, rifampin 600 mg/day, and pyrazinamide 20 to 30 mg/kg·d (discontinued after 2 mo) [24, 25]. Ethambutol or streptomycin should be included in the initial regimen until the results of drug susceptibility tests are available. For NTM infection, the chemotherapeutic regimen is selected on the basis of the species, in vitro drug susceptibility, host immune status, and location and extent of disease [26–30]. Children should be treated essentially the same as adults, but with adjusted doses.

The optimal duration of chemotherapy for musculoskeletal mycobacterial infection is still controversial. Some investigators suggest that treatment for as long as 12 months may be necessary [2]. In the present study, the duration of chemotherapy was at least 6 months. Among the 11 patients who had TB or no growth in the mycobacterial culture or whose mycobacterial culture was not done, the regimens included isoniazid and rifampin with or without pyrazinamide, ethambutol, or streptomycin. Treatment failed in only one patient, whose mycobacterial culture was not done. Among the four patients with NTM infection whose drug susceptibility tests other than to traditional anti-TB drugs were not available, the prescription of drugs was based on regimens recommended in the literature [1, 26–29]. The two patients with infection due to Mycobacterium marinum and Scotchochromogens were cured after treatment; however, treatment failed in the two patients with multifocal Mycobacterium chelonae and Mycobacterium scrofulaceum infection.

Adequate chemotherapy does not eliminate the need for surgical treatment in some patients with musculoskeletal mycobacterial infection. In patients with TB of the shoulders and elbows without abscess formation, chemotherapy and immobilization followed by rehabilitation can often result in a satisfactory outcome [3, 31]. However, patients who have extensive, advanced lesions or who do not respond adequately to chemotherapy usually require surgical interventions such as debridement, synovectomy, or curettage. Excision of the relatively avascular tissues that antimycobacterial drugs cannot access is often necessary for the clearance of pathogens. Resection of joints, resection of bones, arthrodesis, and even amputation may be required if destruction is very extensive [3, 7]. In addition, surgical intervention is needed for those who suffer from tenosynovitis of the flexor and extensor tendons in the wrist, which may result in secondary carpal tunnel syndrome or de Quervain’s disease [6, 32–34]. Antimycobacterial chemotherapy should be started before surgery to decrease the likelihood of dissemination of the disease during the procedure [17]. In the present study, 14 patients received surgical treatment, with wrist arthrodesis performed in four patients. Their joints were painless with acceptable functional outcome after surgical interventions, at a mean postoperative follow-up of 50 months.

In conclusion, mycobacterial infection, which is rare and difficult to diagnose accurately at an early stage, must be considered in the differential diagnosis of infection of upper extremities. Early diagnosis and treatment are important to prevent permanent destruction and disability, and are possible only through a combination of good history taking, complete physical examination, and a high degree of suspicion. Con-
continued efforts to educate clinicians on how to make an accurate diagnosis and provide appropriate management for the disease may improve rates of early diagnosis and good functional outcome. Adequate chemotherapy and surgical interventions can result in satisfactory cure rates for mycobacterial infection of the upper extremities. Failures in treatment are more frequent in patients with multifocal NTM infection.

R eferences


Background and purpose: Mycobacterial infection of the upper extremities is extremely rare. To make an early accurate diagnosis is often difficult, and the treatment is, therefore, frequently delayed in clinical practice. This paper describes the diagnosis and treatment of mycobacterial infection of the upper extremities in a series of patients treated at National Taiwan University Hospital. METHODS: The medical records of 15 patients with mycobacterial infection of the upper extremities treated between 1985 and 1998 were retrospectively analyzed. The diagnosis of mycobacterial infection was Atypical mycobacterial infections of upper extremity synovial-lined structures are often misdiagnosed and unrecognized. Despite an increasing incidence, lack of physician awareness of these pathogens may result in considerable delay in diagnosis and management, potentially leading to permanent disability. The authors conducted a literature review and analyzed 31 cases of penetrating atypical mycobacterial infection to better understand the clinical characteristics and to evaluate their posttreatment complication rate compared with available literature. Medical records for culture-positive case Atypical Mycobacterial Infections of the Upper Extremity. Kevin P. Smidt, Peter J. Stern, Thomas R. Kiefhaber. Published: 26 March 2018. by SLACK, Inc. in Orthopedics. Orthopedics, Volume 41; doi:10.3928/01477447-20180320-06. Publisher Website. Google Scholar.