Concise Report

Gout complicated with necrotizing fasciitis—report of 15 cases


Objective. To analyse the clinical features and outcomes of gout complicated with necrotizing fasciitis.

Methods. From the database of our hospital, we identified 15 hospitalized cases of gout complicated with necrotizing fasciitis from 1987 to 2001. The medical records of the patients were analysed in detail.

Results. Mean patient age was 54.7 ± 12.8 yr. Fever was found in only 10 (66.7%) patients, while the remaining five patients were afebrile on presentation. The peripheral blood white count was raised in only nine (60%) patients. The median time from the onset of symptoms to hospital visit was 4 days (range 2 to 25). Formation of bullae occurred in 60% of patients. Six patients had previous wound infection, two patients had concomitant septic arthritis and the remaining seven patients had no obvious source of infection. Diabetes mellitus and iatrogenic Cushing syndrome were each found in three patients. The identified causative microorganisms were Gram-positive cocci (eight cases) and Gram-negative bacilli (four cases); but in three patients the causative organisms were unknown. Thirteen patients received surgery, including amputation in four cases. Finally, six patients suffered septic shock, three of whom died as a result.

Conclusions. Necrotizing fasciitis in gout patients represents a surgical and medical emergency, and is associated with a high mortality rate. Prompt diagnosis and treatment is imperative and may be lifesaving. Early diagnosis requires a high level of suspicion, even in patients without fever or leucocytosis.

Key words: Gout, Necrotizing fasciitis, Amputation, Mortality.

Gout is a disease of purine metabolism or the renal excretion of uric acid, and is assumed to have four different phases characterized by asymptomatic hyperuricaemia, recurrent attacks of acute arthritis, intercritical gout and chronic tophaceous gout. Tophaceous deposits are well known to cause joint destruction, gouty nephropathy, spinal cord compression and concomitant tophaceous gout. Tophaceous deposits are well known to cause joint destruction, gouty nephropathy, spinal cord compression and concomitant gouty nephropathy and spinal cord compression [1] and concomitant septic arthritis [2]. Necrotizing fasciitis is a rare, life-threatening, invasive soft-tissue infection characterized by widespread, rapidly developing necrosis of the subcutaneous tissue and fascia [3, 4]. Necrotizing fasciitis causes high mortality and is prevalent in immunocompromised patients, but may also occur spontaneously [5]. Gout patients complicated with necrotizing fasciitis have been reported from other medical centres in Taiwan during the past 10 years, and are associated with high morbidity and mortality [6–8]. This study presents 15 cases of gout complicated with necrotizing fasciitis encountered in our hospital from 1987 to 2001, and provides detailed clinical analysis.

Materials and methods

Taiwan is a small island in southeastern Asia with a population of over 23 million people. Chang Gung Memorial Hospital, located at Lin-Kou, is a medical centre in Taiwan. This study searched the database of our hospital for patients with both gout and necrotizing fasciitis between 1987 and 2001. Fifteen patients were identified, accounting for 4.8% of the total number of necrotizing fasciitis patients (15 out of 331 cases). All patients fulfilled the 1977 American Rheumatism Association clinical criteria for gout [9]. Bacteriological diagnosis was established based on blood and wound cultures.

Clinical data were analysed, including duration of gout, tophi, co-morbid conditions, presumed source of infection, presence of fever (defined as an oral temperature over 37.8°C within 24 h of admission), duration of symptoms before the hospital visit, white blood cell count (WBC), differential count, bacteriological diagnosis, surgical treatment and patient outcome.

Results

Demography

The study included 15 gout patients with necrotizing fasciitis (Table 1). All were male and nine had subcutaneous tophi. The mean age was 54.7 ± 12.8 yr (range 30 to 77 yr) and the mean duration of gout was 10.2 ± 5.1 yr (range 3 to 20 yr). The serum urate level ranged from 6.1 to 12.6 mg/dl (normal reference range 2.7–8.0 mg/dl). All patients presented to the emergency department. The brief drug history disclosed they used to take non-steroidal anti-inflammatory drugs (NSAIDs) or herbal drugs, which commonly contain corticosteroids, for pain relief during acute gouty attacks. None had been regularly treated with hypouricaemic agents before they visited our hospital. Three patients (cases 1, 5 and 9) had diabetes mellitus and three patients (cases 3, 13 and 15) had iatrogenic Cushing syndrome, which probably resulted from internixture of corticosteroids in some
### Table 1. Clinical and laboratory data for 15 patients with necrotizing fasciitis and gout

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Organism Presenting site</th>
<th>Time to Hospitalization (ER days)</th>
<th>Time to Admission (days)</th>
<th>WBC count (10^9/L)</th>
<th>Differential count (B/S)</th>
<th>Blood culture</th>
<th>Fever</th>
<th>Shock</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>ORSA</td>
<td>Left leg</td>
<td>3</td>
<td>9.8</td>
<td>4.85</td>
<td>Z Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>OSSA</td>
<td>Right leg</td>
<td>7</td>
<td>8.9</td>
<td>8.68</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td></td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>OSSA</td>
<td>Left hand</td>
<td>4</td>
<td>10.3</td>
<td>2.23</td>
<td>Z Z Z Z Y</td>
<td>Z</td>
<td>Y</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>OSSA</td>
<td>Right thigh and leg</td>
<td>2</td>
<td>12.6</td>
<td>8.85</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td></td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>Group A streptococcus</td>
<td>Left leg</td>
<td>3</td>
<td>14.4</td>
<td>7.08</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>Group A streptococcus</td>
<td>Right thigh and leg</td>
<td>3</td>
<td>14.4</td>
<td>7.08</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td></td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Pseudomonas aeruginosa</td>
<td>Right leg</td>
<td>8</td>
<td>12.6</td>
<td>8.85</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>Group A streptococcus</td>
<td>Right leg</td>
<td>14</td>
<td>12.0</td>
<td>8.85</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>N</td>
<td>Amputation</td>
</tr>
<tr>
<td>9</td>
<td>83</td>
<td>Pseudomonas aeruginosa</td>
<td>Right leg</td>
<td>5</td>
<td>1.5</td>
<td>1.95</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>Enterobacter cloacae</td>
<td>Right leg</td>
<td>4</td>
<td>8.7</td>
<td>4.83</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>Not found</td>
<td>Left forearm</td>
<td>4</td>
<td>8.7</td>
<td>4.83</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>Not found</td>
<td>Right leg</td>
<td>19</td>
<td>8.7</td>
<td>4.83</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>13</td>
<td>30</td>
<td>Not found</td>
<td>Left leg</td>
<td>25</td>
<td>8.7</td>
<td>4.83</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>14</td>
<td>83</td>
<td>Not found</td>
<td>Left leg</td>
<td>4</td>
<td>8.7</td>
<td>4.83</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>Y</td>
<td>Died</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
<td>Not found</td>
<td>Left leg</td>
<td>2</td>
<td>9.2</td>
<td>9.77</td>
<td>Z Z Z Z Y</td>
<td>Y</td>
<td>N</td>
<td>Survived</td>
</tr>
</tbody>
</table>

ORSA, oxacillin-resistant *Staphylococcus aureus*; OSSA, oxacillin-sensitive *Staphylococcus aureus*; ER, emergency room; N, no or no growth; P, positive; Y, yes; B/S, band and segment percentage.

### Symptoms and laboratory data at presentation

Fever was observed in only 10 (66.7%) patients, while the remaining five patients were afebrile on presentation. The median time from onset of symptoms to hospital visit was 4 days (range 2 to 25). Bullous formation occurred in 60% of patients. The mean peripheral blood white cell count was (16,160 ± 9195) × 10^9/L (range 7700 to 40,000), and was normal in six patients (40%). The mean percentage of polymorphonuclear cells in the differential count was 86%, of which 8% were of mean band form. All but one patient had more than 3% band form neutrophils. Five patients (cases 2, 4, 9, 10 and 11) had positive blood culture, two in the normal white blood count group and three in the leucocytosis group. Additionally, two blood culture-positive patients developed septic shock.

### Bacteriological investigations

Gram-positive cocci comprised 53.3% (eight cases) of infections. *Staphylococcus aureus* were cultured in five cases, including one oxacillin-resistant *Staphylococcus aureus* (ORSA). Moreover, group A *Streptococcus* infection was found in three patients. Two of these three patients experienced septic shock and one died. Gram-negative bacteria were found in four patients (two *Pseudomonas aeruginosa*, one *Enterobacter cloacae* and one *Aeromonas hydrophila*). The remaining three patients displayed no microorganism growth. Case 13 was assumed to have *Vibrio vulnificus* infection, based on the clinical history. This patient had severe right lower leg necrotizing fasciitis and presented to our emergency department with shock and disturbed consciousness. The patient underwent emergency above-knee amputation and resumed normal blood pressure and consciousness. However, fever recurred and was accompanied by multiple small pustules all over the body 6 days after surgery. A consultation with a rheumatologist obtained a history of exposure to seawater 5 days prior to admission and an incidental abrasion wound over the tophi on the right lower leg. The leg then displayed progressive swelling and fever occurred 1 day before presentation. Antibiotic treatment was changed to ceftazidime and doxycycline and the patient soon recovered. All patients received adequate antibiotic treatment according to drug sensitivity testing, although a mean antibiotic delay of 2.8 ± 2.6 days occurred in eight patients before bacterial drug sensitivities were available.

### Surgical treatment and outcome

The mean duration of hospitalization was 42.0 ± 4.0 days. Thirteen patients underwent surgery. The median time from admission to surgical debridement was 1 day (range 0 to 15). Five patients received immediate emergency surgery and five received surgical debridement within 24h. The remaining three patients received surgical debridement after medical treatment failed (3, 7 and 15 days later). Four patients (cases 4, 8, 13 and 14) received above-knee amputation on days 32, 1, 0 and 1 of hospitalization respectively. Myonecrosis occurred concomitantly with necrotizing fasciitis in 20% of patients (cases 2, 4 and 11). Two cases (cases 6 and 10) received medical treatment only. Case 6 displayed streptococcal toxic shock syndrome with septic
shock and swelling of the left thigh accompanied by subcutaneous bullae. The patient died 3 days after admission. Notably, case 10 had concomitant septic arthritis and necrotizing fasciitis. This patient refused surgery and was successfully treated with antibiotics. Six cases developed septic shock. Three of these cases (cases 11, 13 and 14) developed septic shock within 5 h of visiting the emergency department, and two other patients (cases 6 and 7) developed septic shock 2.5 and 3 days respectively after visiting the emergency department. Despite aggressive treatment, two patients died (cases 6 and 11). The other case of mortality was case 9, who developed septic shock 8 days after admission.

Discussion

Gout is a disease of purine metabolism characterized by deposition of crystals of monosodium urate. Subcutaneous tophi are usually a late manifestation of gout if left untreated. Gout is frequently encountered in general practice and represents around 20 to 25% of outpatients in rheumatology clinics in medically underserved areas in Taiwan; tophi remain a problem in our gout patients [10, 11]. While many regard gout as a decreasing problem, our previous study showed it instead to be a growing rheumatological problem in Taiwan. We found an increased incidence of gout with younger age of onset, high incidence of tophi, more frequent attacks and shortened interval from first gouty attack to formation of tophi [10]. The surprising increase in the number of gout patients in Taiwan has recently been noted [12–15]. The reason for the apparent increased frequency of tophaceous gout in Taiwan is unclear at the present time. It may be due to inadequate treatment of hypouricaemia, a westernized diet, an elevated lead burden or other environmental factors that contribute to hyperuricaemia and gout [10, 12–17].

Tophaceous deposits are well known to cause joint destruction, gouty nephropathy, spinal cord compression [1] and concomitant septic infection [2]. This study reports another important complication of gout that is associated with high morbidity and mortality. Necrotizing fasciitis is an invasive infection of the subcutaneous tissue and fascia with high morbidity and mortality. Formerly called streptococcal gangrene, necrotizing fasciitis is associated with various other Gram-positive, Gram-negative aerobic and anaerobic infections [18–22]. Only 20% of cases of necrotizing fasciitis in this study were caused by group A streptococcus infection. Despite different infectious microorganisms, the pathophysiology, clinical features and treatment approaches are all similar [23]. Morbidity and mortality are very high if treatment is delayed. Thus, necrotizing fasciitis must be promptly recognized and adequately treated.

The clinical features of necrotizing fasciitis are diverse, as illustrated in this study. One-third of the patients in this study were febrile on presentation, and 40% had normal peripheral blood leukocyte counts, even in the presence of concomitant shock (cases 6, 11, 13 and 14). A wide range and substantial overlap of values make the leukocyte count less helpful for diagnosis. Early diagnosis depends on a high index of suspicion, and necrotizing fasciitis should be included in the differential diagnosis whenever a patient appears acutely ill and toxic. Additionally, most of the subjects in this study had displayed an elevated percentage of band neutrophils (>3%) on differential counts, even in the presence of a normal blood white cell count. This elevated percentage of band neutrophils may be a useful clue for diagnosing severe soft-tissue infection.

Necrotizing fasciitis must be diagnosed based on clinical grounds [24]. The tissue inflammation may initially resemble erysipelas or cellulitis, but it proceeds rapidly to formation of bullae. Later the skin becomes friable and may exhibit ulceration or necrosis. Early diagnosis may be difficult. A previous study has reported that the most consistent clinical clue in the early stage of necrotizing fasciitis is unrelenting pain out of proportion to the physical findings [25]. Formation of bullae is a late manifestation of necrotizing fasciitis and occurred in 60% of patients in the present study. During the late stage, patients are toxic and frequently manifest shock, multiorgan failure and even death.

Necrotizing fasciitis frequently occurs in immunocompromised patients, such as those with uncontrolled diabetes, alcoholism, malignancy, severe malnutrition or severe peripheral vascular disease. Necrotizing fasciitis also has been reported to occur spontaneously [26–28]. In two recent studies from Taiwan [6, 7], a relatively high proportion (7.1–17.9%) of patients with necrotizing fasciitis had concomitant gout. In this study, the portal of entry of the microorganism may have been through a ruptured tophaceous wound or septic joint, although seven patients (40%) displayed no obvious source of infection. The breakdown of the skin overlying subcutaneous tophi carries an increased risk of soft-tissue infection and deserves the attention of doctors who are taking care of gout patients.

Case 13 was assumed to have *Vibrio vulnificus* infection based on the clinical history and was treated successfully. A helpful clue in diagnosing *Vibrio vulnificus* infection is a history of exposure to seawater or ingestion of raw seafood, especially in patients with liver cirrhosis [29]. The organism is highly susceptible to tetracycline but cefotaxime should be added to maximize therapeutic efficacy [30, 31]. Group A streptococcal infection of the fascia carries a mortality rate of 20 to 50% with penicillin treatment [32]. In experimental models of streptococcal necrotizing fasciitis, clindamycin has exhibited markedly superior efficacy and should be added to the regimen in critically ill individuals [32, 33]. The mortality rate of necrotizing fasciitis in our patients is 20%, but there is no previous report in the literature concerning gout patients for comparison.

In summary, necrotizing fasciitis is diverse in terms of clinical manifestations and severity. It presents a great challenge to clinicians. A high index of suspicion of this rare but potentially life-threatening infection is important for early diagnosis [27, 34–36]. Aggressive treatment with appropriate antibiotics and surgical debridement is imperative and may be lifesaving.


