Mod Rheumatol (2008) 18:630–633
DOI 10.1007/s10165-008-0105-5

CASE REPORT

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome following spontaneous rupture of a gouty tophus

Kota Sugisaki · Taro Hirose

Received: 1 May 2008 / Accepted: 24 June 2008 / Published online: 8 August 2008
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Abstract A 70-year-old man with a 30-year history of gout presented with a ruptured gouty tophus over the right lateral malleolus. After the debridement of the tophus, bilateral arthralgia and pitting edema were observed in his extremities. Treatments with antibiotics and nonsteroidal antiinflammatory drugs were ineffective. However, prednisolone therapy was highly effective, and the patient's symptoms were rapidly ameliorated. Thus, we presume that rupture of a gouty tophus or its surgical treatment might contribute to the occurrence of RS3PE syndrome; however, in our case, the etiology of the syndrome remained unknown.

Keywords Debridement · Gout · Remitting seronegative symmetrical synovitis with pitting edema syndrome · Tophus rupture

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome was first described in 1985 [1], and since then, approximately 100 cases of RS3PE have been reported. The etiology of this syndrome remains unidentified; however, the administration of low doses of steroidal agents is known to considerably improve the symptoms of RS3PE. Here, we present the case of RS3PE syndrome that occurred following spontaneous rupture of a gouty tophus in a 70-year-old man with a 30-year history of gout.

K. Sugisaki (✉)
Division of Rheumatology, Jusendo General Hospital,
1-8-16 Ekimae, Koriyama, Fukushima 963-8585, Japan
e-mail: kota_sugisaki@mbc.nifty.com

T. Hirose
Division of Plastic and Reconstructive Surgery,
Jusendo General Hospital, Koriyama, Fukushima, Japan

Case report

On December 8, 2007, a 70-year-old man visited the Division of Plastic and Reconstructive Surgery of our hospital with a complaint of a painful ruptured tophus over the right lateral malleolus that had occurred spontaneously on December 2. He had been diagnosed with gout 30 years ago by his family physician, and since then, he was under medication; however, he was noncompliant with respect to medicine and diet. His plasma uric acid (UA) levels were unstable and widely ranged from 7 to 11 mg/dL (normal, <7 mg/dL). He occasionally experienced episodes of gout, mainly in the right first metatarsophalangeal joint, and was treated each time by oral administration of naproxen and diclofenac sodium suppositories. The gouty tophus was first observed approximately 10 years ago over the right first metatarsophalangeal joint, and gradually, tophi spread along both his extremities. At the time of the patient's first visit to our hospital, the tophus had already ruptured spontaneously and white powdery UA crystal discharges were observed. However, no hemorrhage or pus discharge was noted. Laboratory data recorded on the same day were as follows: white blood cell (WBC) count, 9,300/μL (normal, 3,900–9800/μL); UA level, 10.0 mg/dL (normal, 2.5–7.0 mg/dL); and C-reactive protein (CRP) level, 1.6 mg/dL (normal, <0.3 mg/dL). Debridement of the tophus was performed (Fig. 1), and the wound was carefully disinfected everyday.

On December 17, the patient suddenly complained of pitting edema in both the hands and feet. He also complained

of severe pain in his wrists and ankles; moreover, the mobility of the wrist and ankle joints was restricted because of the pain. On December 18, he was admitted to the Division of Plastic and Reconstructive Surgery of our hospital. On admission, he was unable to stand unaided. His body temperature was 38.4°C, and the cardiopulmonary function indices were within normal limits. Pitting edema without redness and tenderness was observed in both his hands and feet (Fig. 2). On the other hand, no symptoms of a gout episode, such as severe monoarticular arthritis accompanied by redness and local swelling, were observed. Chest and abdominal X-ray revealed no abnormal findings. Laboratory data at admission were as follows: CRP, 16.8 mg/dL; erythrocyte sedimentation rate, >140 mm/h (normal, <20 mm/h); WBC, 8,810/μL; total protein, 5.7 g/dL (normal, 6.1–8.0 g/dL); albumin, 2.9 g/dL (normal, 3.9–5.1 g/dL); and UA, 10.5 mg/dL. No hepatorenal damage or abnormality in glucose tolerance was observed.

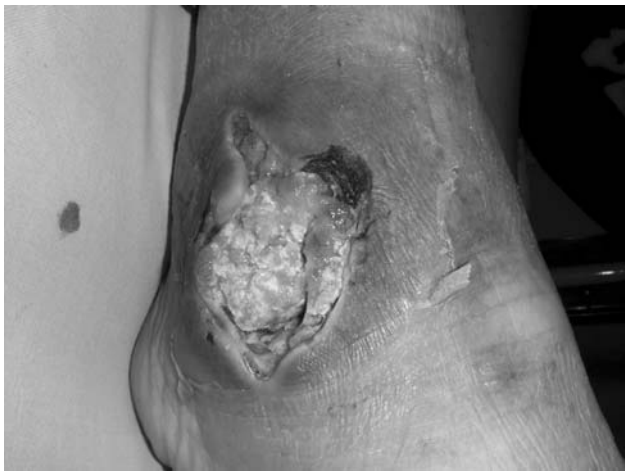

Fig. 1 Ruptured gouty tophus in the right lateral malleolus after debridement. The distal fibula is exposed

The patient was initially diagnosed with bacterial panniculitis and osteomyelitis. Magnetic resonance imaging performed on December 18 revealed the accumulation of synovial fluid in the right ankle joint and soft tissue swelling in the dorsal aspect of the joint; however, no abnormal signal intensity was observed in the bone marrow region. Tenosynovitis was also not distinctly evident in the flexor hallucis longus and gastrocnemius muscles. Further, no subcutaneous abscess formations were detected. The patient was administered intravenous antibiotics and antifungal drugs, including pazufloxacin mesilate, vancomycin, and fluconazole; however, the symptoms persisted, and laboratory data remained abnormal. The effusion culture obtained from the wound samples was negative. Nonsteroidal antiinflammatory drugs (NSAIDs) such as loxoprofen sodium and diclofenac sodium suppositories were mostly ineffective in alleviating the symptoms. With the suspicion of a rheumatic disease, he was readmitted to our division on December 25, 2007. On admission, he had a high fever and complained of severe arthralgia in his wrists and ankles; however, there were no respiratory or gastrointestinal symptoms. Although debridement cleared the wound of the ruptured tophus, the pitting edema in his hands and feet persisted. The laboratory data obtained on the same day were as follows: CRP, 21.6 mg/dL; UA, 9.0 mg/dL; ferritin, 178 ng/mL (normal, 22–275 ng/mL); IgG, 891 mg/dL (normal, 600–1,700 mg/dL); IgA, 400 mg/dL (normal, 360–350 mg/dL); IgM, 56 mg/dL (normal, 35–230 mg/dL); and total hemolytic component (CH_{50}),

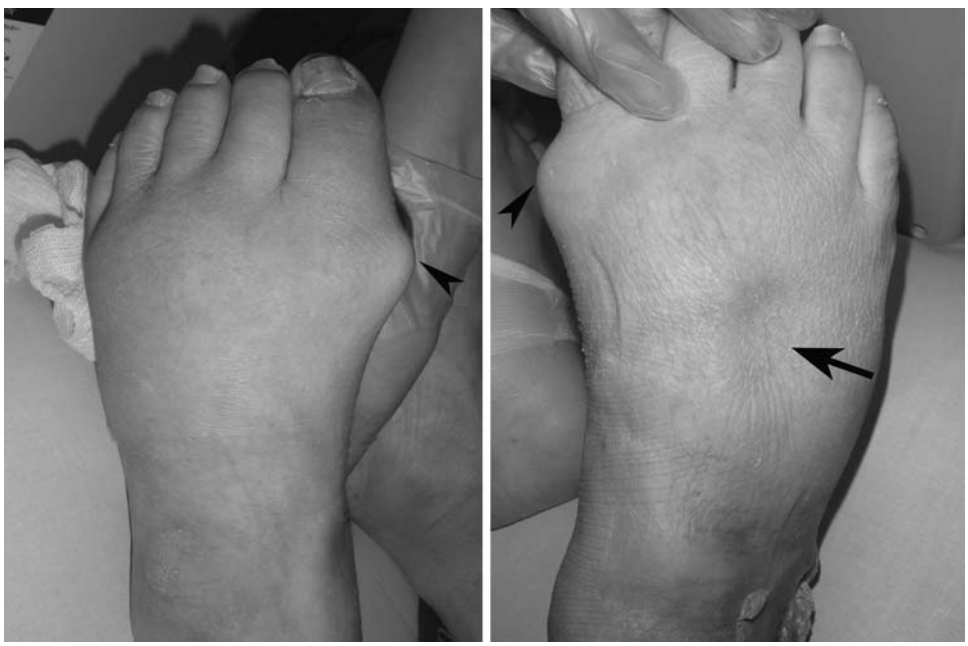

Fig .2 Both feet with pitting edema. Note the impression of the thumb (*arrow*). Gouty tophi are seen in the bilateral first metatarsophalangeal joints (*arrowheads*)

60.7 IU/mL (normal, 25–48 IU/mL). The patient's serum was negative for rheumatoid factor (RF), antinuclear antibody (ANA), myeloperoxidase–antineutrophil cytoplasmic antibody (MPO–ANCA), and proteinase 3–antineutrophil cytoplasmic autoantibody (PR3–ANCA). Although a small amount of UA crystals was detected in the urine, there were no findings of microhematuria or urinary tract infection.

RS3PE syndrome was highly suspected, and the patient was orally administered a daily dose of 20 mg prednisolone (PSL) from December 27. All antibiotics, antifungal drugs, and NSAIDs were discontinued. The effect of the PSL treatment was dramatic, and the patient's symptoms completely disappeared by December 29. His symptoms did not aggravate even when the dose of PSL was tapered to 15 mg/day from January 5, 2008. The patient was discharged on January 13 with a normal CRP level. On February 14, he was readmitted to the Division of Plastic and Reconstructive Surgery, and lateral supramalleolar flap transfer was performed successfully. No pitting edema was observed over the course of admission, during which 10 mg/day of PSL was orally administered to the patient. To rule out internal neoplasm, abdominal computed tomography, esophagogastroduodenoscopy, and total colonoscopy were performed; none of them revealed any malignancies. Urological investigation detected only the known benign prostatic hypertrophy. On April 17, 2008, the patient's general condition was good with no arthralgia, myalgia, or pitting edema under medication with 5 mg/day of PSL. The CRP level remained normal, and the serum UA level was 7.2 mg/dL under oral medication with 100 mg/day of allopurinol.

Discussion

Since 1985 [1], when RS3PE syndrome was first described, it has been widely recognized as an idiopathic disorder characterized by sudden-onset symmetrical synovitis with pitting edema in the extremities. In this condition, patients test negative for RF and ANA. Although the etiology of RS3PE syndrome remains unclear, it is known that the administration of low doses of a corticosteroid such as PSL dramatically improves the condition. Recent studies have reported the co-occurrence of muscular symptoms resembling those of polymyalgia rheumatica (PMR) in patients with RS3PE syndrome [2, 3]; moreover, some patients with RS3PE syndrome exhibit the characteristics of paraneoplastic syndromes [4, 5]. Therefore, several reports have questioned the acceptance of the RS3PE syndrome as an autonomous disease entity [2, 6, 7]. Based on the results of the different studies on RS3PE and PMR, Cantini et al. [8] proposed that RS3PE syndrome and PMR may be different manifestations of the same disease. Additionally, Cimmino et al. [9] reported that RS3PE syndrome might merely be the clinical sign of recurrence of PMR. As mentioned above, the disease concept and etiology of RS3PE syndrome is rather controversial.

In our case, drug-induced angioedema should be ruled out. Our patient had frequently used oral naproxen and diclofenac sodium suppositories for at least 10 years. In addition, he used these agents daily for approximately 2 weeks before the edema and arthralgia occurred. It was difficult to accept that the medication that had not caused any adverse reactions thus far might have triggered off RS3PE syndrome-like symptoms at this time. As far as the other drugs are concerned, the patient was rarely administered 100 mg/day of allopurinol by his family physician; besides the above-mentioned drug, he did not take any medication. Furthermore, he was not administered any antibiotics before the edema and arthralgia occurred. Therefore, on the basis of the above-mentioned reasons we conclude that the possibility of drug-induced RS3PE syndrome is exceedingly low.

Several reports have indicated that RS3PE syndrome might occur following some inflammatory events such as formation of subcutaneous abscess [10], *Mycoplasma pneumoniae* infection [11], and intravesical bacillus Calmette-Guérin (BCG) instillation for the treatment of bladder carcinoma [12, 13]. Gout has generally been accepted as a disorder that causes severe inflammatory oligoarthritis. However, to the best of our knowledge, there have been few reports on the occurrence of RS3PE syndrome in the course of chronic gout. Palazzi et al. [14] reported a case of symmetrical pitting edema, resembling the edema seen in RS3PE, in a patient with gout; the disease manifested as high fever and elevated inflammatory markers. Their patient was successfully treated with meloxicam (15 mg/day for 10 days), and a complete remission of the condition was achieved without the administration of steroidal agents. Therefore, they presumed that the symmetrical pitting edema observed in their patient was strictly associated with the gout attack. Torres et al. [10] also reported the recovery of their patient without the administration of steroidal agents. Unlike these reported cases, our patient showed no response to the treatment with NSAIDs; therefore, we presumed that the condition of our patient was more similar to that of the patients originally reported by McCarty [1]. Additionally, although there are no reports of an association between physical stresses, such as external trauma, and the RS3PE syndrome, it might be supposed that tophus rupture and its surgical treatment might trigger the onset of the syndrome.

In conclusion, we reported a case of RS3PE syndrome that developed following spontaneous rupture of a tophus and was successfully treated with PSL medication. Thus,

the role of spontaneous rupture of a gouty tophus and its subsequent surgical treatment in causing RS3PE syndrome cannot be completely refuted.

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