Abstract
Ulcers resulting from tophaceous gout are uncommon and very difficult to heal. Here we report a case with chronic refractory tophaceous gout, not responding to conventional treatment modality for several months in a 39-year-old man with a 12-year history of gout with recurrent acute arthritis attacks. Two times after treatment with autologous platelet-rich gel (APG), the ulcer healed finally for 2 months. This is the first study to confirm that APG can improve tophus ulcer healing. Based on conventional medical therapy and standard debridement, APG might be a novel and effective method to stimulate tophus ulcer healing.

Key Words: Autologous platelet-rich gel, gout, platelet-rich plasma, tophus ulcer

Introduction
Hyperuricemia is a common metabolic disorder resulting from overproduction or underexcretion of uric acid. Gout is a chronic inflammatory disease of joints caused by hyperuricemia, which results in tissue deposition (joints and the tissues surrounding the joints) of monosodium urate crystals and intermittent inflammatory attacks.

Tophi refers to nodular masses of uric acid crystals depositing in different soft tissues of the body, which can destroy the joint and become ulcerated and infected. Delayed or ineffective treatment leads to chronic tophaceous gout. Tophus ulceration, due to long-standing inflammation caused by the deposition of monosodium urate crystals and tophi particularly vulnerable to breakdown, can be regarded as chronic wound. Patients with gout are more likely to have other comorbidities that predispose them to impaired wound healing, including diabetes, obesity, and peripheral vascular disease. Therefore, it is hard to heal because the repair of the wound is slowed or even stopped, and especially ulcers on the feet at sites of joint deformity and weight bearing are prone to delayed healing. The other main reasons responsible for delayed healing include wound infection or continued existence of necrotic tissue, insufficient blood supply and disturbances of local microcirculation, decreased quantity and bioactivity of multiple growth factors, excessive apoptosis, and structural changes in the cell membrane receptors of growth factor leading to loss of coupling between growth factor and its receptor.

Conventional surgical debridement of the tophaceous lesions carries the risk of skin necrosis, tendon, or joint exposure. Thus, treating these ulcers is an important clinical challenge.

Autologous platelet-rich gel (APG), containing platelet-rich plasma (PRP), leukocytes, thrombin (derived from human/calf), and calcium, has been extensively used to promote wound healing of different types. However, it has not been reported about APG accelerating tophus ulcer healing. Here, we report a case with ulcerated tophaceous gout cured by APG.

Case History
A 39-year-old man with an ulcerated tophi on the back of his left foot was referred to the Diabetic Foot Care Center, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

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West China Hospital, Sichuan University, in December 2007. He had been suffering from chronic tophaceous gout for more than 12 years in multiple joints of his hands and feet with recurrent acute arthritis attacks several times a year. Two months before admission, the patient felt severe pain with local redness and increased skin temperature on the back of his left foot. He found the soft tissue breakdown overlying tophi and ulceration on the back of his left foot. He was admitted to a local hospital and took some drugs such as allopurinol and benz bromarone tablets, conservative debridement, and got dressings changed. However, the size of the ulcer gradually increased over time.

Physical examination on admission included the following: temperature 37°C, respiration 18 beats/min, heart rate 80 beats/min, and blood pressure 104/60 mmHg. His body mass index was 23.7 kg/m² and abdominal circumference was 101 cm. Nodules of sizes of a soybean or egg were on both sides of tibial, knee, wrist, elbow, and interphalangeal joints, with redness, swelling, and different degrees of deformity of the above-mentioned joints. There was an ulcerated nodule about 3 cm × 4 cm in size on the back of his left foot, which was discharging white chalky material and pus [Figure 1a].

Laboratory tests showed that white blood cell count was 11.82 × 10⁹/L, serum uric acid level was 532.1 µmol/L (normal range: 240–490 µmol/L), urinary uric acid of 24 h was 2.72 mmol (normal range: 2.4–5.9 mmol/24 h), blood urea nitrogen was 1.6 mmol/L (normal range: 2.4–7.2 mmol/L), and serum creatinine was 62.8 µmol/L (normal range: 53–140 µmol/L). Liver function test and serum lipid profiles were normal. Urine pH was 6.5. The results of oral glucose tolerance test showed that fasting blood glucose was 5.5 mmol/L and blood glucose level at 2-h after 75 g of glucose loading was 10.35 mmol/L.

X-ray of all the affected joints revealed osteoporosis with multiple bug chisel-like bone destruction, soft tissue swelling, and protruding masses with multiple high-density patches. Narrowing of the joint space was found in wrists and interphalangeal joints. Abdominal ultrasonography showed fatty liver and echo enhancement at bilateral renal pyramids. Both bacterial and fungal cultures were sterile. Overall, the clinical spectrum was consistent with destruotive gouty arthritis.

After admission, indomethacin (50 mg, tid) and sodium bicarbonate tablet (900 mg, tid) were giving to alleviate his pain and to alkalinate the urine, respectively. Debridement and drainage with dressing change of the ulcer were performed everyday. However, the ulcer did not show any sign of improvement after 2 weeks with continuous drainage of pus and urate crystals [Figure 1b]. Partial amputation of the left foot was considered. But the patient and his family members refused. Hence, APG treatment was adopted after the patient gave informed consent.

APG was administered on the 15th day after admission. The volume of the ulcer on his left foot was about 2.6 mL. About 30 mL of peripheral venous blood was drawn into a sterile centrifuge tube from the patient’s elbow vein, which was mixed with 3 mL of EDTA (pH 8.0). After gradient centrifugation, we got PRP based on previous reports. The APG, produced by mixing the FRP with thrombin and calcium gluconate according to proper proportion (10:1, V/V), was injected on the ulcer through a three-way pipe [Figure 1c]. Then the wound was covered and fixed with Suile Wound Dressing (Hedonist Biochemical Technologies Co. Ltd., USA) and sterile gauze. The dressing was changed every 3 days for 2 weeks. Granulation tissue occurred on the ulcer on the third day and the volume of the ulcer decreased to 1 mL after 2 weeks [Figure 1d]. Then, the APG was used on the ulcer again [Figure 1e]. Finally, the ulcer healed about 1 month after the second administration of APG [Figure 1f]. The follow-up of the patient after 9 years showed that the patient is fully mobile again and the lesion had not flared till reporting [Figure 1g]. He had no pain at all in the foot and could wear closed, soft shoes.

**Discussion**

Gout is characterized by recurrent attacks of acute inflammatory arthritis caused by the deposition of urate crystals. Gout has been linked to major medical conditions such as heart attack, diabetes, and premature death. Chronic gout is the late stage of gout due to long-standing and untreated hyperuricemia lasting for about more than 5 years and leads to formation of tophi. The pathologic characteristics of tophi are cumulation of monosodium urate crystals encircled by chronic mononuclear and giant cell inflammation. Tophi can be formed in the joints, cartilage, bones, and other places throughout the body, and they usually occur at feet, knees, and finger joints. Local pain, joint destruction, soft tissue damage and deformity as well as nerve compression syndromes such as carpal tunnel syndrome are the possible manifestations. When breakdown of the soft tissue overlying tophi does occur, chronic ulcers with persistent discharge may develop and become infected.

This patient had chronic gout with intermittent acute attack and nonhealing ulcer. Although traditional nonsteroidal anti-inflammatory drug was quite effective to relieve the local inflammatory symptoms, his foot ulcer did not change by conservative debridement and dressing change for months together. Surgical treatment of tophaceous gout should be strongly considered in poorly controlled pain attributed to a tophus, nerve compression or entrapment, uncontrolled or recurrent infection, and significant skin ulceration. However, previous report revealed that there is a relatively high
rate of complications for the surgery of tophaceous gout. Therefore, tophaceous gout is an intractable problem for the plastic surgeon, on account of not only its high recurrence rate but also its delayed wound healing and the probability of skin necrosis and infection which often happen after surgery. Based on our previous experience of treating chronic refractory ulcers in patients with diabetes with APG, an attempt was made to use APG for chronic nonhealing tophaceous gout on this patient and the ulcer healed well after two administrations of APG.

Why was the APG effective in promoting the healing of ulcerated tophaceous gout? First of all, a relative lack of growth factors, such as platelet-derived growth factor, epithelial growth factor, and vascular endothelial growth factor, in the wound site could make the healing process delayed. Once activated, the platelets in APG can release plenty of proteins such as fibronectin, vitronectin, fibrinogen, the above-mentioned growth factors, insulin-like growth factor, transforming growth factor-β, and platelet-derived angiogenic factor, which can promote accelerate tissue regeneration. Furthermore, the gelatinous preparation can decrease the loss of the platelet and leukocyte, which can ensure wound healing and prevent the wound from bacteria infection. In addition, APG treatment may redress the proteolytic imbalance of refractory dermal wounds by suppressing the expression of matrix metalloproteinases and promoting tissue inhibitors of metalloproteinases in granulation tissues but the exact underlying mechanisms still need further study.

Although the application of APG showed high efficiency in the treatment of the tophus ulceration, basic principles should not been ignored, including standard debridement, proper coverage of soft tissue, urate lowering therapy, and systematic appropriate antibiotics if necessary.

To our knowledge, this is the first study to confirm that APG can improve tophus ulcer healing. Since it is a single case report, further properly designed, adequately powered, and high-quality randomized controlled trials are needed to assess the efficacy and safety of APG treatment for chronic tophus ulcers.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient have given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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