CASE REPORT

Bimalleolar pathological fracture in a patient with chronic tophaceous gout

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Abstract

Gout is one of the most common types of inflammatory arthritis. Four stages have been described in its evolution: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. Monosodium urate crystals deposits are more frequently encountered in hyaline cartilage, tendon sheaths, articular bursae, bone epiphysis, synovium, and skin. Pathological fractures that occur at the formation sites of gout tophi have been rarely described in gout. Bimalleolar fractures often occur following a trauma. We present the case of a 56-year-old patient, diagnosed with chronic gout for over 12 years, with tophi in the upper and lower limbs, who presented accusing mechanical pain in the left tibio-tarsal joint and impaired function of the hands. The clinical examination showed bilateral multiple destructive gout tophi in the hands, forearms, elbows, feet, ankles, and lower legs, while the left ankle exhibited an important varus deformity. Computed tomography examination of the left ankle showed multiple gout tophi with bone erosions and a bimalleolar pathological fracture. The patient underwent pharmacological treatment, physical therapy and the ankle was immobilized in a knee-ankle-foot orthosis, with subsequent orthopedic surgical treatment for fracture fixation, to improve functional status. We have chosen to present this case given the multiple disabilities of the patient, which have improved following the rehabilitation treatment.

Keywords: gout tophi, fracture, bone erosions, rehabilitation.

Introduction

Gout is a chronic condition, characterized by the formation of deposits of monosodium urate crystals in the joints or soft tissue. It is one of the most common types of inflammatory arthritis. From a clinical point of view, it is characterized by four progressive stages: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and, if left untreated, chronic tophaceous gout [1, 2]. The deposition of monosodium urate crystals is more frequently encountered in the synovium, hyaline cartilage, joints, periarticular soft tissues, and it leads to the development of bone erosions [1, 3, 4].

Intraosseous tophi are a rare presentation, but if they occur, they have a subchondral bone and metaphyseal location, and may lead to pathological fractures following minor trauma or even in the absence of a traumatic event [4, 5]. Long-term complications include joint damage and renal stones, and it is associated with an increased prevalence of chronic renal disease. In advanced stages, gout is associated with severe disability, mainly if complicated by the presence of bone fractures [1].

Biologically, hyperuricemia is defined as a uric acid level in the blood that exceeds its physiological solubility

limit of 6.8 mg/dL, elevated values above this threshold leading to the formation and deposition of monosodium urate crystals [6]. Uric acid is the final product of purine metabolism and excess consumption of purine rich foods and alcohol results in hyperuricemia [3, 6]. Most of the uric acid is excreted by the kidneys and a smaller proportion is eliminated through the gastrointestinal tract. A decreased renal excretion causes uric acid accumulation, with subsequent deposition and tophi formation [6, 7].

Gouty tophi represent a chronic inflammatory granulomatous reaction secondary to the presence of monosodium urate crystals [8, 9], with various pro-inflammatory factors being expressed, among them interleukin (IL)-1 β , IL-6, and tumor necrosis factor-alpha (TNF- α). These cytokines can stimulate osteoclasts and chondrocytes, which are implicated in bone erosions [6, 8–10]. Furthermore, monosodium urate deposits decrease osteoblastic activity, contributing to the production of bone lesions and preventing healing, resulting in bone fragility and fractures [9].

The treatment of asymptomatic hyperuricemia and gout consists of patient education, hygienic-dietary regime, steroidal and nonsteroidal anti-inflammatory medication, urate lowering therapy and means of medical rehabilitation

through which the effects of disability are minimized, and attempts are made to increase functionality.

Aim

We present a rare case of pathological fracture due to gout tophi, which imposed a diagnostic challenge, and showed the importance of multidisciplinary management in such conditions. Usually, gout is not associated with an increased risk of fracture, but our patient had fractures of the upper and lower limbs and multiple disabilities, which have improved following the complex rehabilitation treatment.

Case presentation

A 56-year-old patient with known chronic tophaceous gout and a history of surgical removal of bilateral elbow and dorsal forearm tophi, surgical neck fracture of the left humerus (August 2018), high blood pressure and duodenal ulcer surgery (2002) was referred to the Department of Physical and Rehabilitation Medicine within the Clinical Rehabilitation Hospital, Cluj-Napoca, Romania, in September 2019, complaining of mechanical left ankle pain, functional impairment of the hands and impaired joint mobility of the left shoulder.

The physical examination revealed multiple gout tophi on fingers, hands (Figure 1, A and B), forearms and elbows and an inferior subluxation of the left shoulder with associated pain and limited range of motion in all planes (Table 1).

The disabilities of the arm, shoulder and hand (DASH) score at admission was 70 points.

The lower extremities exhibited multiple gout tophi on toes, soles, heels, Achilles' tendons and calves, and a varus deformity of the left ankle was noted (Figure 2, A–D).

Table 1 – Active range of motion in the left shoulder

Flexion	75°
Extension	45°
Abduction	75°
Internal rotation	75°
External rotation	50°

Figure 1 – Gout tophi on fingers and hands: (A) Hands in prone posture; (B) Hands in supine posture.

Figure 2 – Gout tophi on lower extremities: (A–C) Anterior view showing multiple gout tophi on toes, soles, and calves; (D) Posterior view – varus deformity of the left ankle and multiple gout tophi on heels and Achilles' tendons.

Laboratory data revealed: erythrocyte sedimentation rate (ESR) 20 mm/h; triglycerides 255 mg/dL; alkaline phosphatase (ALP) 137 U/L; creatinine 1.2 mg/dL; urea 52 mg/dL; creatinine clearance (Cockcroft–Gault equation) 68 mL/min; glomerular filtration rate (GFR) [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for GFR] 67 mL/min/1.73 m² – CKD stage 2, according to Kidney Disease Outcomes Quality Initiative (KDQOI) Guidelines; urinary uric acid 120 mg/24 h – decreased excretion.

The patient had a very low fluid intake (approximately

500 mL/24 h) and, after one week of oral hydration (2000–2500 mL/24 h), the repeated laboratory data showed a slight improvement regarding renal function (creatinine clearance 73 mL/min, GFR 72.1 mL/min/1.73 m²) and renal excretion of uric acid (urinary uric acid 236 mg/24 h).

X-rays of both hands showed severe destructive bone changes of the phalanges, metacarpophalangeal and radio-carpal joints (Figure 3).

The computed tomography (CT) examination of the left foot revealed changes in bone structure, with sub-chondral tibio-tarsal and intertarsal bone erosions, as well

as a bimalleolar fracture, soft tissue infiltration and the presence of gout tophi (Figure 4, A and B).

Because gait and ambulation were very painful, and the patient presented a high risk of severe complications like necrosis or vascular ruptures, orthopedic surgery was advised. An internal fixation with a centro-medullary rod and nails was carried out, with good functional outcome (Figure 5, A and B).

Figure 3 – Hand X-ray, bilateral antero-posterior view showing severe destructive bone changes of the phalanges, metacarpophalangeal and radio-carpal joints.

Figure 4 – Left foot CT: (A) Coronal plane bone window shows bimalleolar fracture; (B) 3D VRT shows the presence of gout tophi. 3D: Three-dimensional; CT: Computed tomography; VRT: Volume rendering technique.

Figure 5 – Left foot X-ray: (A) Antero-posterior view after the surgery; (B) Lateral view after the surgery. Internal fixation with a centro-medullary rod and nails.

After removal of the tophi from the elbows and dorsal forearms, the excised tissue was fixed in 10% neutral buffered formalin, then washed with water, dehydrated, included in paraffin blocks, and sectioned, followed by histological and immunohistochemical (IHC) analysis of the slides obtained. Standard Hematoxylin–Eosin (HE) staining was used for histological analysis (Figure 6), and anti-cluster of differentiation 68 (CD68) antibody (Dako, clone PG-M1, 1:100 dilution, antigen retrieval – seven cycles citrate buffer) was used for IHC analysis (Figure 7, A and B).

Figure 6 – Urate deposits bounded by enlarged multinuclear macrophage. Hematoxylin–Eosin (HE) staining, $\times 200$.

We noticed on all the slides obtained from our patient that the tophus contained a monosodium urate core surrounded by inflammatory cell complexes, most of them being multinucleated and having very large dimensions and adjacent fibrovascular tissue. The monosodium urate crystals of are water-soluble and thus are dissolved during routine tissue processing, so the inside of the tophus has an anucleated, necrotic appearance. Cells that bordered the anucleated nucleus of tophus showed an intense positive reaction to CD68, which proves that they are inflammatory cells. In the fibrovascular area, we also noticed cells that showed a positive immunoreaction, but weaker and in small numbers.

After the surgery, gait and ambulation was possible with an ankle-walker orthosis. We considered useful the use of an assistive device, such as a cane for six weeks after the surgery to improve safety, gait and to reduce stress of the affected joint. The rehabilitation treatment consisted in soft tissue massage, stretching, strengthening, gait and balance exercises. Other therapeutic methods used were thermotherapy, ultrasound, electrical stimulation, and laser, to decrease pain and increase the functionality of the involved joints. Additionally, conservatory treatment was included, consisting of hydration with 2000–2500 mL liquids per day, a hypourinic diet and hypouricemia medication. Discharge DASH score was 63.3 points, showing an improvement in the functionality of the upper limbs.

Discussions

Monosodium urate deposits are commonly found in soft tissues, ligaments, or skin. Tophi have an organized structure, with a crystalline center consisting of a collection

of monosodium urate crystals, surrounded by a crown in which multinucleate giant cells, such as histiocytes,

fibroblasts, lymphocytes, and a fibrovascular area are most commonly present [11].

Figure 7 – (A and B) Intense positive immunoreaction in giant macrophage cells. Anti-CD68 antibody immunostaining: (A) $\times 40$; (B) $\times 100$. CD68: Cluster of differentiation 68.

In gout pathogenesis, the activation of the inflammasome, the caspase system and IL-1 synthesis play a central role. But the main event occurring in gout inflammation is the activation of inflammatory cells by the monosodium urate crystals. According to Danger's theory, the immune system constantly scans the cells and tissues to keep everything fully and normally functioning. If certain foreign substances are liberated from the cells, the Danger system detects them immediately and provides a response. These signaling molecules are called Danger-associated molecular pattern (DAMP) [12, 13].

It was previously demonstrated that monosodium urate crystals represent a DAMP signal for Toll-like receptors (TLR2 and TLR4). Also, besides natural immunity, adaptative immunity is also activated. The trigger for the adaptative immune response is the dendritic cells that carry the antibody of T-cells from lymphatic nodules. The monosodium urate crystals, as DAMP, activate dendritic cells and other immune reactions, creating an immunity cascade, where also the monocyte/macrophage, fibroblasts from the synovium and neutrophilic granulocytes are activated.

The proinflammatory cytokines that are synthesized (IL-1, IL-6, IL-8, TNF- α) create another immunity cascade, where prostaglandins, leukotrienes and reactive oxygen species take part. Cytokines induce the expression of adhesion molecules, like vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, on vascular endothelial cells, that facilitate the adherence of leukocytes to the endothelium and their release in the vascular system. The mediator of the sterile inflammation associated to cell necrosis on crystal induction is IL-1. This cytokine has two isoforms, IL-1 α and IL-1 β , but that bind to the same IL-1 receptor. Also, caspase-1 is activated by a cascade reaction. There are several factors that can inhibit the immunity cascade and inflammation. Phagocytosis induced by the crystals can be inhibited by apolipoprotein E and B. Also, inhibition of the synovial inflammation is facilitated by the anti-inflammatory cytokines, like tumor growth factor-beta (TGF- β), IL-10 and peroxisome proliferator-activated receptor gamma (PPAR- γ), and by the apoptotic cells and the exhaustion of proinflammatory mediators [13, 14].

In several histological studies, cells from the outside of the tophus showed a positive immunoreaction for CD68, indicating their monocytic/macrophage nature [10, 15]. CD68 is a protein highly expressed by cells in the monocyte lineage (monocytic phagocytes, by circulating macrophages, and by tissue macrophages). We used the anti-CD68 antibody precisely to highlight the immunoinflammatory reaction in the coronary area of gouty tophus, an aspect studied and noticed by other authors, as well as the presence of inflammatory cells in small numbers and with a much weaker reaction that can be found disseminated in the adjacent fibrovascular area [16].

Conclusions

We presented a patient with poorly controlled gout, with severe disability after a bimalleolar fracture due to intraosseous tophi. After orthopedic surgery and conservative treatment, the quality of life of the patient increased, as gait and ambulation were restored. But, due to coronavirus disease 2019 (COVID-19) pandemic and lockdown, clinical follow-up and additional laboratory tests could not be performed.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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