Gout – Practicable Interdisciplinary Insights for the Clinician on a Surgeon's Perspective

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Abstract

Gout is a common systemic metabolic disease caused either by increased uric acid production or by decreased uric acid excretion potentially leading to crystal deposition of monosodium urate in various tissues and resulting in acute gouty attacks mainly initially presenting as mono arthritis of joints. The further course can be accompanied with development of chronic tophaceous gout with or without complications such as skin perforation of tophi accompanied with occurrence of chronic fistula and overlying bacterial infection. When the diagnostic management was early and sufficiently done, it can be successfully treated by specific drugs in most cases, and approximately in up to 5% of cases only surgical intervention becomes necessary that includes various extremity- and motion-preserving procedures, but in life threatening conditions primary amputation as well. The aim of this article is to present practicable interdisciplinary insights of the disease for clinicians on a view of a surgeon.

Key words: Gout; Diagnosis; Clinical presentation; Differential diagnoses; Treatments;

List of Abbreviations

GA: gouty arthritis

MTPJ: metatarsophalangeal joint

MSU: monosodium urate

HU: hyperuricemia

CTG: chronic tophaceous gout

UA: uric acid

CT: computed tomography

MRI: magnetic resonance imaging

OA: osteoarthritis

RA: rheumatoid arthritis

What is gout?

Gout is a common systemic metabolic disease affecting up to 2% of the Western population with an increase of prevalence up to 7% in patients aged 65 years and older, associated with an overall male-to-female ratio of 3.6:1, and the prevalence peaked

in men between the ages of 75 and 84 years (7.3%), while in women its prevalence continued to rise beyond the age of 85 years (being about 2.8%) [1,2]. This entity was first identified by the ancient *Egyptians* in 2640 BC, *Hippocrates* was the first who used the term “podagra” referred to it as “the unwalkable disease” and as an “arthritis of the rich” in the 5th century BC for acute Gouty Arthritis (GA) occurring in the 1st Metatarsophalangeal Joint (MTPJ), 6 centuries later Galen first described the term “tophi” for the crystallized Monosodium Urate (MSU) deposits following longstanding Hyperuricemia (HU), and the alkaloid colchicine, derived from the seeds of the autumn crocus (*Colchicum autumnale*) (Figure 1), was introduced as a selective and specific treatment for gout by the Byzantine Christian *Alexander of Tralles* [3].

Figure 1: The autumn crocus (*Colchicum autumnale*), found in the Forest of Thuringia (Germany) near by the “big isle’s mountain” on Sept. 16_2018.

Gout is to be classified in 4 four clinical phases: (1) symptomatic or asymptomatic HU, (2) acute GA (initially presented as monoarthritis in up to 90% of cases, mostly

podagra), (3) intercritical gout (intervals between acute attacks), and (4) Chronic Tophaceous Gout (CTG) [4,5]. Uric Acid (UA) mainly exists as the urate ion, and as the more acidic un-ionized UA. Humans do not express the enzyme urate oxidase (uricase), because of a mutation during evolution of the uricase gene, which converts urate to the more soluble and easily excreted compound allantoin. Among mammals, only humans and other primate species excrete UA as the end product of purine metabolism [6]. HU may occur either by increased UA production that is found in 5 to 10% of patients (genetic enzymatic defects or acquired causes such as dietary indiscretions with purine-rich meat and fish, alcohol abuse, obesity, or excessive muscle activities accompanied with an increased purine metabolism) or by decreased UA excretion that is found in 90 to 100% of patients (genetic causes or acquired various kidney diseases leading to impaired renal function), and approximately 80% of the gout patients have a positive family history of gout or HU [6,7]. An increased serum UA level may exceed the solubility of the urate and imparts the risk of its crystal deposition as MSU which activates the monocytes producing the NALP3 inflammasome and subsequently leading to the liberation of various inflammatory mediators such as the interleukin 1 in soft tissues surrounding joints at the upper and lower extremity, nerves often firstly presented as peripheral nerve compression syndrome, cartilage, bones, but also in the eye and heart valve, and at the ear from the supersaturated fluids (Figures 2A-2C, 4, 5A-5C, 6A-6D, and 7A-7B) [7-17].

Diagnosis of Gout

One problem is that a majority of patients with gout present to and are being cared for by nonspecialists, and the management remains suboptimal [18-23]. For diagnosis of gout in routine clinical practice the New York criteria from 1966 are still helpful when 2 of these criteria are present: (1) at least 2 acute attacks of painful joint swelling with complete resolution within 2 weeks if untreated, (2) a clear history of podagra, (3) the presence of a tophus, and (4) a rapid response to colchicine within 48 hours of starting treatment; in comparison to the formerly introduced Rome criteria the response of colchicine was added and the serum UA level (>7 mg/dl in men / >6 mg/dl in women) was removed [6]. Under clinical aspects, a tophus is defined as a draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity [24]. Noted that the serum UA level is primarily increased when starting first symptoms of an acute attack, and then, it often early decreases to normal value within approximately 2 to 3 days later, hence, measuring of the serum UA level during the initial attack and at least 2 weeks later is required, and if its level at this time later is not increased (if untreated by drugs) then the diagnosis of gout is unlikely [25-27]. However, probably the best investigation for establishing a definite diagnosis of gout is the presence of MSU crystals in aspirated joint fluids or tophus, but joint fluids should ideally be examined within 6 hours after its aspiration to minimize the risk of artefactual results [6,9,28,29]. Noted that MSU crystals are not radio opaque and are identified on polarized microscopy as negatively birefringent, and MSU crystals in synovial fluid are observed in more than 95% of patients with acute GA, but

in some asymptomatic patients, MSU crystals are also detected in joints in which there is no inflammation [6,30,31,32]. MSU crystals in soft tissues around joints are well identified by dual energy computed tomography and Computed Tomography (CT) can clearly demonstrate tophi growing into the adjacent bones, ultrasound with Doppler imaging and Magnetic Resonance Imaging (MRI) with contrast showing increased vascularity with inflammation surrounding crystal deposits, and MRI is the only clinical imaging which accurately shows bone marrow edema [7].

Clinical presentation and differential diagnoses of gout

Typically, the acute attack of GA often begins at night mostly presenting in up to 50% of cases as monoarthritis of the 1st MTPJ (Figure 2A-C). In decreasing order, other joints can be involved such as ankle and insteps, knees, wrist (Figure 3), fingers, and the olecranon or prepatellar bursae [33,34,35]. Symptoms are agonizing pain around the swollen and reddened joint, fatigue, fever, and chills, but noted that GA is often less severe in elderly than in younger patients potentially leading to the misdiagnosis as having a non-specific Osteoarthritis (OA) especially at the finger joints (Heberden OA) [36,37]. The further course can be associated with polyarticular involvement which tends to be less abrupt in onset and less severely painful [30,38]. Primary acute polyarticular GA attacks are uncommon, more often observed in elderly patients, and often associated with a positive family history [39]. CTG usually develops 10 or more years after the first gout episode, and tophi may be the initial manifestation of the disease as well [6,40].

Figure 2: (62-year-old male): (A) Advanced stage of CTG at his left 1st MTPJ (clinical photograph after surgical incision). **(B)** A resection arthroplasty was performed, note the severe cartilage destruction associated with multiple crystal deposits on the particular surface of the 1st metatarsal head. **(C)** The postoperative course was uneventful.

Generally, gout must be demarcated from the also crystal-induced arthropathy pseudogout following deposition of calcium pyrophosphate dihydrate, first described as "pseudogout syndrome" by Kohn et al. in 1962 [41], which is probably the

Figure 3: (49-year-old male): Acute GA monoattack at his right wrist with painful swelling

acutest form of arthritis in the elderly, but associated with a relatively rare monoarticular involvement [42-45]. Pseudogout includes at least 6 presentations: (1) acute pseudogout, (2) asymptomatic chondrocalcinosis, (3) pseudo-OA (with or without acute attacks), (4) pseudo-Rheumatoid Arthritis (RA), (5) pseudo-polymyalgia rheumatica, and (6) pseudo-neuropathic arthropathy that can resemble a neuropathic Charcot's joint [46]. The prevalence of pseudogout among younger people is unknown, a major gender pre-dominance do not exist, attacks of acute pseudogout appear more commonly in men, and women more frequently exhibiting the pseudo-OA pattern of the disease [47,48]. The knee is most commonly involved, followed by the wrist, ankle, elbow, toe, shoulder and hip. Compared with true GA, pseudogout attacks may take longer to reach peak intensity and may persist for up to 3 months despite therapy [49]. Noted that acute pseudogout attacks can be provoked postoperatively by abrupt changes in serum calcium levels such as observed after parathyroidectomy, and after partial thyroidectomy as well [42,50].

The main differential diagnosis for CTG is Rheumatoid Arthritis (RA). However, GA tends to be less symmetric than typical RA, and the non-chalk-like rheumatoid nodules typically appear polyarticular at the wrist and/or finger joints accompanied with its specific OA-related severe dislocations in volar and ulnar direction (Figure 8A-8C) [6,51]. Other differential diagnoses for CTG are various subcutaneous tumors arising directly from bones, joints or its surrounding tissues (Figures 9A-9H, 10) [52-55]. Chalk-like draining is observed as well from nodules of trichilemmal cysts (Figure 11A-11E), but its appearance at hairless regions such as the fingers is very uncommon, and it was probably first described by Ikegami et al. in 2003 [56-60]. Non-traumatic painful swelling around the wrist and finger joints are also observed by avascular osteonecrosis; furthermore, non-traumatic disruption of the scapholunate ligament can also be initially caused by gout; and moreover, a carpal tunnel syndrome can be the first manifestation of GA as well [8,11,12,13,14,15,61].

Intraosseous appearance of gout presenting as lytic lesions is challenging in diagnostic management [62]. For demarcation of osteomyelitis or intraosseous tumors dual energy computed tomography and/or MRI is the method of choice [7,63,64]. However, histological examination of intraoperatively taken specimens before definite surgical treatment is strictly recommended in order to avoid a failed treatment (Figure 7A-7B) [65].

How is gout treated?

Treatment of gout is based on 3 main pillars: (1) dietary modification or restriction, (2) medical treatment, and (3) surgical treatment. In 1876, *Garrod* was among the first to suggest that HU could be controlled by lowering the intake of purine-rich food, and later, *Haig* confirmed this in a series of clinical experiments he conducted on himself from 1894 to 1897 [3]. In acute GA attack, medical treatment that involves the application of the mitosis inhibitor colchicine which also has an anti-inflammatory effect based on the ability to impair the mobility and activity of neutrophil leucocytes, non-steroidal anti-inflammatory drugs, and maybe also prednisolone should be initiated immediately within 12 to 24 hours that often leads to relief of symptoms within 24 hours [66]. But noted that an overdose of colchicine can be associated with an intoxication presenting as severe nausea, vomiting, and diarrhea; and in single cases with lactic acidosis leading to multiorgan failure with rhabdomyolysis, and death by cardiac arrest [67]. Uricosuric agents, first used at the end of the 19th century, are contraindicated in this phase because its application can provoke further acute attacks [3,68]. For the intercritical phase or CTG, the use of the xanthine oxidase inhibitor allopurinol, developed by Rundless et al. in 1963 [69], which acts by inhibiting the synthesis of UA from hypoxanthine and xanthine, is the treatment option of choice. The aim of allopurinol is to decrease the serum UA level below 6,8 mg/dl in order to avoid deposition of MSU crystals [70,71].

Figure 4: (53-year-old male with a longstanding history of alcohol abuse): Typical chalk-like CTG at the distal interphalangeal joint of his left little finger that led to ulcerations at the fingertip.

Figure 5: (83-year-old male): (A) Typical CTG with ulcerations and super infection around the proximal interphalangeal joint of the index and distal interphalangeal joint of the little finger at his right hand, noted that there are no joint dislocations. (B) Intraoperative clinical photograph showing the crystal deposits at the index involving the extensor tendon sheath. (C) Primary amputations were done at the metacarpophalangeal joint of the index and proximal interphalangeal joint of the little finger because the patient needed immediately a pacemaker.

Figure 6: (A 57-year old male presented with a history of drug-resistant arthritis at his left wrist over a period of 2 years [15]): (A) Initial radiograph showing a collapsed and sclerotic lunate bone with surrounding bony fragments (arrow) that suggests Kienböck's disease with its typical stress fractures. (B) Same findings in CT (arrow). (C) Intraoperatively, the severe destructed lunate bone was confirmed (light blue arrow), but there were crystal deposits on the same bone (white arrow), and the diagnosis of gout was confirmed by histological examination. (D) A non-cemented motion-preserving total wrist replacement was performed.

Figure 7: (A 38-year-old male presented with right chronic wrist pain over a period of 2 years): (A) Initial radiograph showing lytic intra osseous lesion at the ulnar styloid (arrow), and MRI showing tumor-like infiltrations of the surrounding soft tissue (arrows) that led to the diagnosis of a possible osteosarcoma with stage T4 by the radiologist, but histological examination of primarily taken specimens revealed gout. (B) A motion-preserving non-cemented ulnar head replacement was performed.

Figure 8: (Typical clinical presentations of RA): (A) Polyarticular non-chalk-like nodules at the finger joints. **(B)** Typical dislocations at the metacarpophalangeal joints in volar and ulnar direction. **(C)** Severely arthritic destructions of all joints at the hand with typical dislocations in ulnar direction at the proximal interphalangeal joints II-IV [51].

Figure 9: (Painful swellings around joints caused by various tumors): (A) Ganglion cyst of the ankle that led to an entrapment of the posterior tibial nerve (i.e. tarsal tunnel syndrome). **(B)** Volar wrist ganglion. **(C)** Giant cell tumor at the volar aspect of the metacarpophalangeal joint (arrow). **(D)** Ganglion cysts of the tibialis anterior tendon (arrows). **(E)** Ganglion cyst of the thumb's saddle joint (arrows). **(F)** Ganglion cyst of the proximal tibiofibular joint (arrows). **(G)** Schwannoma of the common peroneal nerve (arrows). **(H)** Chronic granuloma at the volar aspect of the ring finger caused by a previously incorporated foreign body.

Figure 10: (64-year old female): Monstrous subcutaneous tumor at the volar aspect at her left wrist that led to an entrapment of the median nerve (i.e. carpal tunnel syndrome). A radical debridement of all flexor tendon sheaths was done, and histological examination revealed a giant cell tumor. The postoperative course was uneventful associated with full recovery of neurological deficits.

Figure 11: (51-year-old male): (A) Initial findings, the patient reported a history of longstanding progressive growth of subcutaneous tumors at the volar aspects of the metacarpophalangeal and proximal interphalangeal joints of his left index (arrows) over a period of approximately 22 years. **(B)** Primarily, specimens were taken and there was a white viscous mass resembling chalk-like CTG, but histological examination revealed a trichilemmal cyst. **(C) – (E)** After correct diagnosis by the pathologist, the 2 trichilemmal cysts were en bloc rejected, and the postoperative course was uneventful.

Figure 12: (43-year-old male): (A) Massive phlegmonous bacterial superinfection caused by ulcerating CTG of the overall right little finger. (B) The extremity-preserving radical surgical debridement of all tophi involving all flexor and extensor tendon sheaths was performed. (C) The further course was complicated by development of soft tissue necrosis at the distal phalanx. (D) After removal of the necrosis and wound conditioning the resulting defect could be covered by a skin graft. (E) At the 6-months follow-up there was marked functional loss with an incomplete fist conclusion due to adhesions of the tendons with overlying skin.

Figure 13: (58-year-old male): (A) Painful advanced stage of OA at his right 1st MTPJ (i.e. hallux rigidus), there was a longstanding history of multiple acute gout attacks (i.e. podagra). (B) A motion-preserving non-cemented total joint replacement was performed. (C) Dynamic radiographs demonstrating the well gait

Figure 14: (57-year-old female): Painful advanced stage of OA at her right 1st MTPJ (i.e. hallux rigidus), there was a longstanding history of multiple acute gout attacks (i.e. podagra). Primarily, a motion-preserving total joint replacement was performed, but it has been failed 2 years postoperatively. Therefore, the motion-restricting arthrodesis utilizing a non-vascularized corticocancellous iliac crest bone graft and a titanium plate had to be performed.

When GA is primarily diagnosed, only 5% of patients may not respond to medical treatment and surgical treatment at the wrist and hand becomes necessary [23]. The most important indications for surgery are longstanding drug-resistant painful joint OA and pronounced tophi with or without its ulceration potentially leading to chronic fistula and bacterial super infection. Extremity-preserving surgery, that includes radical debridement of tophi with or without coverage of resulting soft tissue defects, should generally be sought, but noted that complete functional recovery often cannot be achieved especially when the tendon sheaths are affected by the gouty inflammation (Figure 12A-12E). Motion-preserving joint surgery can be achieved utilizing partial or total joint replacements (Figures 6A-6D, 7A-7B, and 13A-13C) or resection arthroplasty (Figure 2A-2C), and another option is the motion-restricting joint arthrodesis (Figure 14). Which of these procedures had to be done depends on the patient's claim in activities of daily living. Primary amputation becomes necessary in patients with life-threatening conditions (Figure 5A-5C).

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Declarations

The author declares that he has none conflict of interests concerning this article content.

Notification

The author of this article content is "Winner of the World Academic Championship-2018 in Rheumatology (metacarpophalangeal joints) and Fellow" among 5657

nominations from 53 countries based on the subject "A 10-Year Follow-Up of Uncemented Constrained Metacarpophalangeal Joint Arthroplasties Using the RM Prosthesis in a Patient with Rheumatoid Arthritis" (published in: *J Rheumatol Arthritic Dis.* 2017;2(1):1-5. [51]), awarded by the Directorate of the International Agency of Standards and Ratings (IASR), and the IASR recognized him among "World's 500 Most Influential Experts in Rheumatology for the year 2018 on earth" [72-75].

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