Chapter

Introductory Chapter: Gout

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1. Introduction

Gout is a disease known since before the Common Era. There are reports of urate crystal deposition in the big toe joints of an excavated mummy in ancient Egypt. There are records of many figures throughout Western history who experienced the painful suffering of gout, for example, Alexander the Great of Macedonia, King Carlos V of Spain, Frederick the Great of Prussia, Louis XIV of France, Martin Luther of the Reformation, Oliver Cromwell of the Puritan Revolution, the artist Michelangelo, Leonardo da Vinci, the poets Dante and Milton, the physicist Isaac Newton, and the biologist Charles Darwin, among others. In contrast, there is little historical evidence of gout in Asia. Yet the disease has become common in modern society [1–3]. The prevalence of gout in the past has generally been higher among middle-aged men, but in recent years, the number of young people and women with gout has been increasing.

2. Pathophysiology

Gout is a metabolic disorder caused by hyperuricemia [4, 5]. Uric acid is the final metabolite of purine in humans. Uric acid is produced via hypoxanthine and xanthine by the action of xanthine oxidase on purine. Two-thirds of uric acid is excreted in the urine and one-third in feces. The amount of serum uric acid is determined by the amount produced and the amount excreted in the kidneys. Hyperuricemia occurs when the level of serum uric acid rises. In hyperuricemia, when urate crystals precipitate in the joint cavity and are phagocytosed by leukocytes, crystal-induced gouty arthritis develops. The symptoms of crystal-induced arthritis are similar to those of rheumatoid arthritis, infectious arthritis, and many collagen diseases, among others. Therefore, it is necessary to distinguish among these conditions. Gouty arthritis develops as acute monoarthritis, with pain, swelling, redness, and fever, peaking in 12–24 h. The initial strong inflammation improves in about 2 weeks but can relapse if hyperuricemia remains unchecked. If hyperuricemia continues, urate crystals are deposited in the joints and connective tissues, activating monocytes or macrophages via the Toll-like receptor pathway and innate immune response. Inflammatory cytokines including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) are secreted, leading to endothelial activation and attraction of neutrophils to the site of inflammation. Neutrophils secrete inflammatory mediators that create an acidic environment, which causes further precipitation of urate crystals.

3. Classification

Causes of hyperuricemia are classified into primary and secondary hyperuricemia. Primary hyperuricemia is idiopathic. Secondary hyperuricemia can involve

hereditary metabolic diseases such as Lesch–Nyhan syndrome, phosphoribosyl-pyrophosphate synthetase hypertrophy and congenital myogenic hyperuricemia, malignant tumors such as malignant lymphoma and breast cancer, psoriasis vulgaris, hemolytic anemia, rhabdomyolysis, hypothyroidism, and others. In addition, drug-induced hyperuricemia owing to anticancer agents, low-dose aspirin, loop diuretics, ethambutol, theophylline, and others can be involved in secondary hyperuricemia [6, 7].

4. Symptoms

In gouty arthritis, severe pain attacks may also occur in the hallux metatarsophalangeal joints, ankle joints, Achilles tendon, knee joints, wrist joints, and other sites [8]. When urate crystals precipitate in the joints, acute inflammatory arthritis is produced, which causes recurrent episodes of red, tender, swollen joints and leads to bone and joint destruction. Gout nodules, or tophi, are most often found in the auricle but also form on the elbow, forearm, hallux, Achilles tendon, patella, and so on. Tophi are not painful, but if they progress, tophi can lead to joint deformation and bone destruction, seriously affecting quality of life. Urate crystal accumulation in the kidneys causes severe pain and deterioration of kidney function and renal failure. Furthermore, hyperuricemia might be associated with hypertension and ischemic heart diseases [9].

5. Management

For effective treatment of acute gout attacks, nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine are administered as soon as possible, as first-line treatment options [10]. For patients who do not respond to NSAIDs or colchicine, systemic corticosteroids generally may be applied. In addition, for gouty arthritis, joint injection of corticosteroids is often used. For the treatment of chronic gout, drugs are used that either promote uric acid excretion, such as probenecid, or prevent its synthesis via inhibition of enzyme xanthine oxidase, such as allopurinol and febuxostat. If serum uric acid levels fluctuate during gout treatment, arthritis may become exacerbated. In addition, if a gout attack occurs during drug treatment, the level of serum uric acid should be maintained, that is, the amount of uric acid-lowering drugs should not be increased. In such cases, NSAIDs, colchicine, and corticosteroids are used for treatment of a gout attack. Generally, renal function should be checked before drug treatment because gout often occurs in patients with renal impairment. Furthermore, as nondrug treatment, extracorporeal shock wave lithotripsy is used to break up kidney and ureteral stones. Large gout nodules may be surgically resected. Thus, other treatments for gout are often used in combination with drug therapy.

6. New treatment

Gout is classified within a group of autoinflammatory diseases that includes hereditary periodic fever, Muckle-Wells syndrome, familial Mediterranean fever, familial cold autoinflammatory syndrome, and pseudogout. In gout, innate immunity is said to act, and acquired immunity is not involved; there is a difference between gout and autoimmune diseases such as rheumatoid arthritis or juvenile idiopathic arthritis. Recently, newer treatment options have been extensively

studied, especially IL-1 inhibitors such as anakinra, canakimumab, and rilonacept. Although IL-1 inhibitors are less effective than TNF inhibitors in rheumatoid arthritis, they have become available as a treatment for gout in recent years. Although the inflammatory effects of IL-1 are diverse, owing to their therapeutic effect, IL-1 inhibitors are expected to be widely used in future clinical applications [11]. When combined with current traditional therapies, these new agents present more promising treatment options for clinicians and patients with gout that is difficult to treat.

7. Conclusion

Gout is not a life-threatening illness, but it is characterized by many lifestyle-related diseases such as obesity, hyperlipidemia, hypertension, and glucose intolerance [12]. All these diseases cause arteriosclerosis; therefore, it is necessary to treat gout carefully. All physicians in clinical practice should know about the treatment and prevention of gout. The treatment goal for gout is to provide effective methods of treatment and prevention and to provide patients with good health-related quality of life. However, long time is required to improve serum uric acid levels and to manage gout attacks. In this book, each expert reports on gout based on the evidence and their own research. It is my hope that this book will be helpful in your clinical practice.

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