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Gout in the course of systemic lupus erythematosus: Literature review and case study report

ABSTRACT

Gout is one of the relatively common inflammatory diseases of the joints. It is caused by the deposition of uric acid crystals in the tissues, which induces an acute or chronic inflammatory process. Elevated serum uric acid levels are usually found long before symptoms appear, and it is worth emphasizing that not every hyperuricemic patient will ever develop gout symptoms. The onset of gout is characterized by periodic joint inflammation, which may be triggered by various stress factors (trauma, infection), certain medications, dietary mistakes, and excessive exercise. Over time, repeated joint inflammation causes permanent joint damage. Most often, deposits of urate crystals are located in places with poorer blood supply and exposed to increased pressure, such as joints and soft tissues (e.g., auricles). The coexistence of gout and autoimmune diseases is relatively rare. While for many years it was believed that gout was not associated with other systemic connective tissue diseases, gout has been described in the course of systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis. The presented systematic review also describes a case of a patient with long-lasting systemic lupus erythematosus who was diagnosed with gout.

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KEY WORDS: gout; systemic lupus erythematosus; diagnosis; treatment

INTRODUCTION

The awareness of the co-occurrence of autoimmune and inflammatory diseases of a different origin implies the need to broaden the scope of diagnostics and verify diagnoses. The following paper presents a systematic review regarding the prevalence of the co-occurrence of gout in patients with previously diagnosed autoimmune diseases. Furthermore, it outlines the case of a patient with systemic lupus erythematosus (SLE) who was additionally diagnosed with gout. Particular attention was paid to the clinical changes that formed the basis for extending the scope of diagnostics in the patient.

MOLECULAR MECHANISMS IN THE DEVELOPMENT OF GOUT

Gout is one of the inflammatory joint diseases caused by the presence of crystals in the tissues. While it is well known that uric acid crystallisation occurs in the course of gout, so far, the underlying factor inducing this process has not been conclusively identified. The main contributors to the formation of urate deposits in tissues include increased serum uric acid concentrations, ischaemia and decreased tissue pH [1]. The presence of urate crystals in the periarticular tissues induces an inflammatory process of an acute or chronic nature, which ultimately leads to progres-

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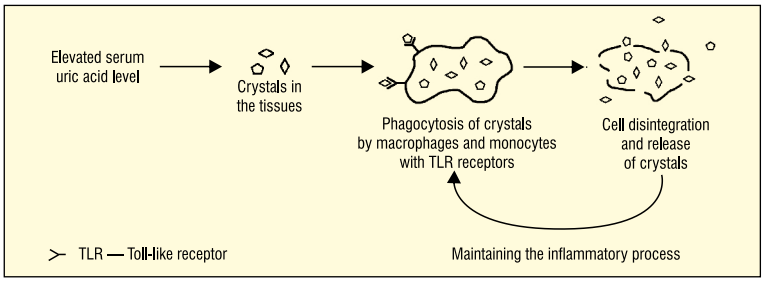

Figure 1. Mechanism of the inflammatory reaction in tissues during the course of gout

sive cartilage and bone damage (Fig. 1). The crystals tend to form conglomerates in areas suffering from poorer blood supply and those more frequently exposed to pressure, such as the elbow joints. Gout is not merely a joint disease — urate deposits located in various tissues lead to their progressive destruction. Its course changes over time. Initially, it involves seizures and later progresses to a chronic phase associated with the development of gouty arthritis [2].

Although the exact mechanism causing inflammation in the course of gout is not known, there are many hypotheses related to the aetiopathogenesis of this disease. An elevated serum uric acid level (above 6.8 mg/dL) is recognised to be an important factor in the formation of sodium urate deposits in tissues [1]. Moreover, uric acid-like molecules are also released when the body cells die [3].

Sodium urate crystals have a potent immunogenic effect, but its basis is not yet fully understood. Studies have shown that blockade of CD16 and CD11b receptors results in selective activation of neutrophils by sodium urate particles. This suggests that membrane receptors play an important role in the induction of the inflammatory process [4]. An important group of receptors contributing to the development of inflammation in gout are pattern recognition receptors, which combine with activating pathogen-associated molecular patterns. They include, among other things, toll-like receptors (TLRs) and NOD-like receptors (Fig. 1). TLRs are the most well-studied and often regarded as a possible contributor to the development of inflammation in gout [5]. They are commonly found in the membranes of immune cells and many other tissues and are critical in the initiation of the non-specific immune response. In the presence of unknown abnormal factors, such as urate crystals in tissues, they are activated and thus play an important role in the local inflammatory process.

The main mediators of inflammation within tissues containing uric acid deposits are interleukins IL-1β and IL-18 (Fig. 2). Their elevated concentrations occur in systemic connective tissue diseases and a number of other non-rheumatic diseases. Studies have shown that the use of IL-1β inhibitors decreased the frequency and severity of gout attacks and improved the condition of patients with elevated levels of this interleukin who were previously diagnosed with, for example, type 2 diabetes, heart failure or multiple myeloma [6].

GOUT AND SYSTEMIC CONNECTIVE TISSUE DISEASES

The co-occurrence of gout and autoimmune diseases is relatively rare. Such instances have been described in a small number of cases of systemic sclerosis in patients exhibiting features of relapsing-remitting arthritis. In patients with systemic sclerosis, the possibility of developing gout should be taken into account if inflammatory joint changes and serous hyperuricaemia have been found. In turn, the differential diagnosis should address the metabolic syndrome, the side effect of diuretics and other drugs, diagnosed renal failure and cardiovascular disease [7].

The specific mechanism distinguishing the formation of gout in patients with previously diagnosed systemic sclerosis has not been established. Elevated serum uric acid levels in these individuals constitute a predictive factor for the occurrence of pulmonary arterial hypertension — one of the components of the systemic sclerosis clinical picture. In patients diagnosed with pulmonary hypertension, high levels of uric acid correlate with the deterioration of certain cardiovascular parameters, such as DLCO (diffusing capacity for carbon monoxide). Unfortunately, this group of patients is characterised by a high mortality rate [8].

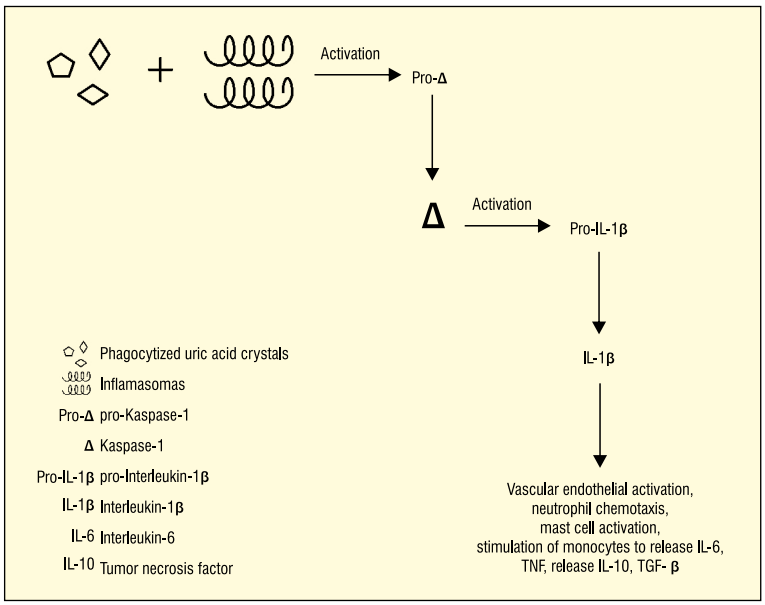

Figure 2. Intracellular mechanism of the inflammatory response in gout

The literature on the subject contains few descriptions of the co-occurrence of gout, mixed connective tissue disease and other overlap syndromes [9]. They occur mainly in women, and the diagnosis of overlap syndrome precedes the diagnosis of gout by several years. On the other hand, chronic arthritis, malar rash, photosensitivity, haematological disorders, serositis and neurological disorders are more frequently diagnosed [10].

The literature also contains descriptions of the co-occurrence of gout and Sjögren's syndrome, which suggests that patients with a history of gout are more prone to develop Sjögren's syndrome. According to existing analyses, this relationship is statistically significant only in the case of older patients [11].

For many years, it was believed that rheumatoid arthritis (RA) ruled out the possibility of the occurrence of gout, however, retrospective analyses reassessing the likelihood of RA indicate that the presence of these two conditions is rare but feasible. It has also been shown that when features of both diseases are found in the same joints, gout symptoms are more prone to predominate [12]. Although no clear association between drugs administered to treat RA and the development of gout has been proven, patients with gout lesions were more often treated with sulphasalazine and less often with non-steroidal anti-inflammatory drugs (statistically insignificant data) [13]. It is also worth emphasising that individuals with RA who have been simultaneously diagnosed with gout are often characterised by high serum levels of the rheumatoid factor [14].

In the case of psoriatic arthritis (PsA), the diagnosis of gout is described to occur extremely rarely. Typically, PsA is detected first and may entail the development of gout, whose timing of presentation is positively correlated with age [15]. Such correlations are not observed in another seronegative spondyloarthropathy — ankylosing spondylitis (AS). In the case of AS, the prevalence of gout has been shown to occur at a comparable level to that in the general population [16].

In SLE patients, the diagnosis of gout is also rare and is usually made in patients with a long history of lupus. Patients with nephritis in the course of SLE appear to be particularly predisposed [17]. Most SLE patients who are diagnosed with gout are on a long-term diuretic therapy, and the diagnosis of lupus precedes the diagnosis of gout by several years. Moreover, characteristic gout attacks occur in patients during a period of reduced SLE activity [10].

Although gout is diagnosed more frequently in patients with lupus nephritis, the onset of the first gout attack itself is preceded by a rapid deterioration of renal function that is not clearly related to SLE activity [17]. Serological tests additionally indicate a higher prevalence of anti-Sm and U1RNP antibodies (less frequently reduced C3 levels) in patients with coexisting renal disease [18]. Elevated serum uric acid levels in patients with a diagnosis of SLE were found to be an additional predictor of the development of lupus nephritis, as well as neurological, respiratory and cardiovascular complications. Therefore, this is associated with an overall worsening of the disease course [19].

TREATMENT OF GOUT IN THE COURSE OF AUTOIMMUNE RHEUMATIC DISEASES

When discussing the development of gout in the course of systemic connective tissue diseases, it is worth emphasising that commonly used drugs in the treatment of rheumatic diseases affect serum uric acid levels in different ways and modulate the body's inflammatory response. It was found that glucocorticosteroids (GCS) and non-steroidal anti-inflammatory drugs as medications to reduce the inflammatory response, also used in the treatment of gout, can reduce the risk of a first attack. Methotrexate (MTX), which has the effect of inhibiting purine synthesis, and leflunomide, which causes an increase in urinary excretion of uric acid, also appear to have a protective effect [14].

The treatment of gout is two-pronged: there is a distinction between management of its acute attack and treatment between attacks to normalise serum uric acid levels. Non-steroidal anti-inflammatory drugs and oral corticosteroids are most commonly used for the treatment of gout attacks. If a small number of joints are involved, intra-articular injections with GCS are also possible. In contrast, treatment of hyperuricaemia aims to reduce the incidence of attacks. The above-mentioned methods of treatment are used particularly in patients with chronic kidney disease and gout nodules. Drainage of the joint and antibiotic therapy are also used for septic arthritis in the course of gout [20].

In this paper, a case of a patient with a long-term diagnosis of SLE was described. The patient had co-morbidity in the form of gout, which increased joint pain and was accompanied by septic arthritis of the elbow.

CASE STUDY

In February 2021, a 37-year-old patient with a diagnosis of SLE was admitted to the Clinic of Rheumatology, Rehabilitation and Internal Medicine due to persistent pain in the left wrist and elbow joint, lasting for approximately 4 weeks. The patient was diagnosed with SLE in 2004, at which time he reported muscle and joint pain, recurrent fevers, headaches, a sore throat, weight loss and acute pericarditis. Tests performed found ANA in a titer of 1/1280 and an anti-Sm in the profile. Treatment with GCS and chloroquine was initiated. Intravenous cyclophosphamide (total dose 9600 mg) was used after one year of treatment due to high disease activity. Proteinuria was first diagnosed in 2018 and since then methylprednisolone and mycophenolate mofetil were used for treatment. The patient reported pain in the right arm and physical examination revealed generalised joint deformities of the arm with Jaccoud arthropathy. X-ray findings described multiple joint deformities, most severe within the wrist. The patient was selected for surgical treatment after orthopaedic consultation.

After 6 months, the patient reported experiencing pain in the left arm and left elbow joint for the first time. Physical examination revealed signs of hypercorticism and generalised joint deformities of the arm with Jaccoud arthropathy, skin lesions on the extensor surface of the elbows with the presence of bursitis (Fig. 3A, 3C). Laboratory tests revealed elevated baseline inflammatory parameters, increased lactate dehydrogenase activity and high serum uric acid levels. Material taken from a skin nodule near the left elbow revealed sodium urate crystals (assessed using polarised light microscopy). X-rays of the elbow and wrist joints revealed signs of periarticular osteoporosis, lytic foci in the head of the left elbow as well as in the carpal bones and the bases of the metacarpal bones, destruction of the distal end of the right radius and subluxation of the proximal series (bones) of the right wrist (Fig. 3B, 3D). Furthermore, an ultrasound scan revealed significant inflammatory lesions and suspected tendon rupture within the left wrist and left elbow.

While waiting for the arm surgery date, the patient's health status deteriorated and he reported a significant increase in pain in the knee, left elbow and right shoulder joints. For this reason, the patient was hospitalised urgently in the department of internal medicine, where he received pulse methylprednisolone, achieving temporary improvement in his general health status and reduction in joint pain. After the patient was transferred to the Clinic of Rheumatology, Rehabilitation and Internal Medicine, joint fluid was collected and found to contain bacteria. Despite the empirical antibiotic therapy implemented, septic shock developed. The culture grew MRSA (methicillin-resistant *Staphylococcus aureus*). As the patient's health status deteriorated, his treatment was continued in the ICU setting, where targeted antibiotic therapy and renal replacement therapy were included.

Based on the overall picture, a diagnosis of gout accompanied by SLE was made. A factor in the development of gout in the patient in

question was renal involvement, which is often described in cases of co-morbidity of gout and other systemic connective tissue diseases with a long-term course.

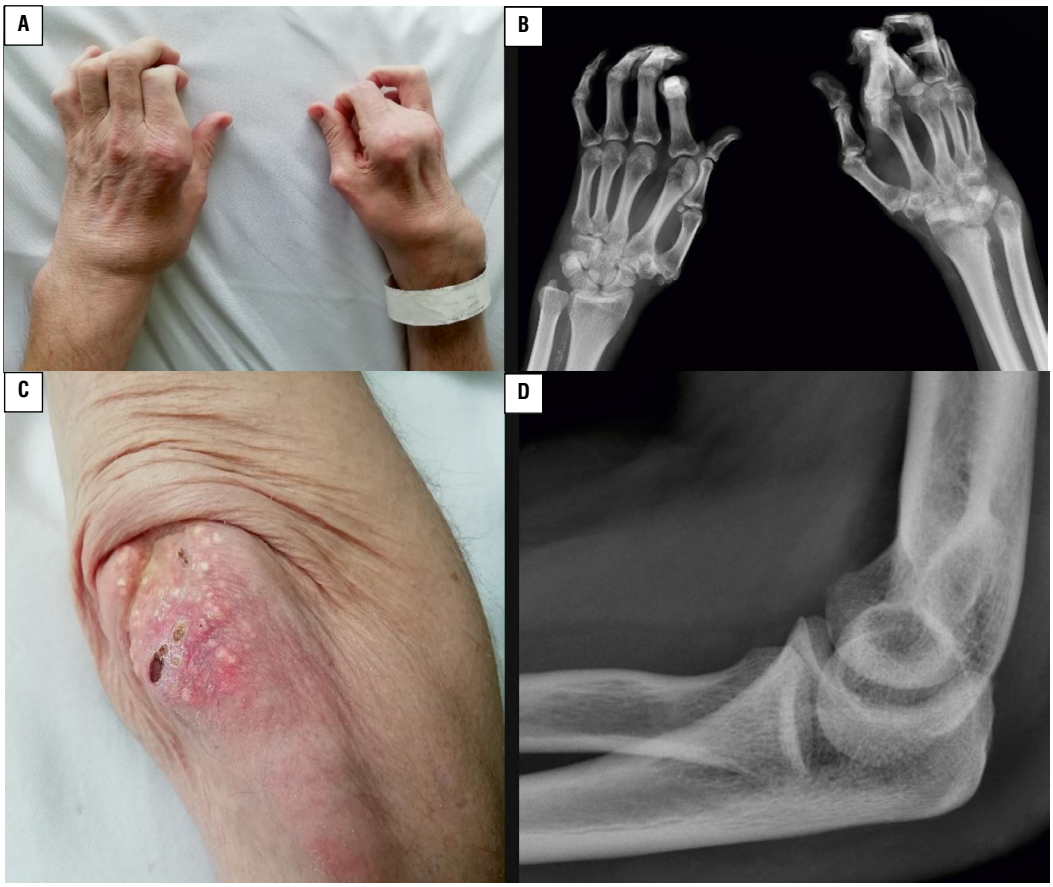

Figure 3. Joint deformations and gouty changes in hands and elbows of patient with systemic lupus erythematosus and gout: **A.** Hand joints deformities; **B.** X-ray of hands — multiple deformations of hands; **C.** Gouty lesions in the elbow area; **D.** X-ray of left elbow

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