Crystal-Induced Arthritis

Simon H.K. Huang, MD, FRCPC, *Clinical Associate Professor, Division of Rheumatology, Faculty of Medicine, University of British Columbia, Vancouver, BC.*

Ian K. Tsang, MB, FRCPC, *Clinical Professor Emeritus, Division of Rheumatology, Faculty of Medicine, University of British Columbia, Vancouver, BC.*

The two most common forms of crystal-induced arthritis among older adults are gout and calcium pyrophosphate dihydrate (CPPD) deposition disease. Gout in older adults has unique clinical features. The new case incidence is the same in males and females over age 60. Upper limb and polyarticular involvement are not unusual. CPPD deposition disease may present as asymptomatic chondrocalcinosis on radiographs and symptomatically as pseudogout, pseudo–rheumatoid arthritis, or pseudo-osteoarthritis. Other crystals may cause periarthritis or arthritis. Management of crystal-induced arthritis among older adults requires special considerations due to comorbid conditions and concomitant medications. Nonsteroidal anti-inflammatory drugs may be contraindicated. Steroids taken either orally or intra-articularly are often an alternative.

Key words: *gout, chondrocalcinosis, pseudogout, pseudo–rheumatoid arthritis, pseudo-osteoarthritis*

Introduction

The most common forms of crystal-induced arthritis are caused by deposition of monosodium urate (MSU), as in gout, and calcium pyrophosphate dihydrate (CPPD), as in pseudogout, pseudo–rheumatoid arthritis, and pseudo-osteoarthritis). Other crystals, such as basic calcium phosphate, primarily hydroxyapatite, and calcium oxalate, may induce an inflammatory reaction in and around the joint. This article discusses the clinical characteristics of gout, CPPD deposition disease, and other crystal-induced arthritis/periarthritis among older adults.

Gout

Incidence and Prevalence

The prevalence of gout in the US population is <1% for both men and women, with more cases among men. After age 65, the prevalence increases to 5% for men and 2% for women. However, new case incidence of gout after 60 years of age is equal among men and women.[1] Furthermore, the incidence of gout appears to be increasing over the past decade, especially among older individuals.[2] This increase in incidence of gout may be related to the increased longevity in the general population, the increased use of medications such as diuretics and low-dose acetylsalicylic acid (ASA), and changes in dietary habits.

Factors Responsible for the Inflammation

Monosodium urate crystals have the ability to induce an inflammatory reaction after binding with immunoglobulins and other proteins. This includes the recruitment of phagocytic cells, ingestion of the crystals, and release of different mediators of inflammation.[3] The acute inflammation is usually self-limited, related to the removal and dissolution of the MSU crystals or the loss of binding of immunoglobulin to the crystals.

Unique Clinical Features of Gout among Older Adults

The classic clinical manifestation of gout is well known. Acute gout presents as acute intermittent monoarthritis. Intercritical gout presents as more frequent, intermittent, less severe monoarthritis or oligo- or polyarthritis. Chronic, or tophaceous, gout presents as low-grade, persistent inflammatory mono-, oligo-, or polyarthritis. Among older adults, several clinical differences have been observed. These include an increase in polyarticular presentation, upper limb involvement, an increase incidence in women, and the finding of tophi.[4] In our opinion, this early development of tophi may be due to a delay in the recognition of gout and from atypical, milder presentations of acute attacks.

Diagnosis

The gold standard for the diagnosis of gout is the identification of MSU crystals in joint aspirate during an acute attack. However, it is often impractical, particularly among older individuals, to aspirate the involved joint(s). Several criteria for the classification of gout have been developed. The 1977 American College of Rheumatology (ACR) criteria are the most frequently used (Table 1).[5]

In clinical practice, physicians should consider the possibility of crystal-induced arthropathy, including gout or CPPD deposition disease, in any older men or women who present with acute, subacute, or chronic inflammatory joint disease. The application of the ACR criteria is helpful in further establishing the diagnosis. A pilot study has suggested that dual-energy computed tomography may be useful in the identification of tophi, the specific diagnosis of gout, and the monitoring of disease progression.[6]

Three points cannot be overemphasized in the diagnosis of gout: first, always consider the possibility of septic arthritis, especially with mono- or oligoarticular arthritis. If clinically suspected, aspiration of the joint for examination is mandatory. Second, among older adults, the presence of osteoarthritis should not exclude gout as

osteoarthritis is almost universally present in older persons. Third, the presence or absence of hyperuricemia does not establish or exclude the diagnosis of gout.

Management

The management of gout can be divided into the management of acute gout, intercritical gout, and tophaceous gout, and the management of risk factors associated with gout or hyperuricemia.

Acute Gout

Colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) are the standard pharmacological treatment for acute gout. However, due to comorbid conditions experienced by older adults, such as renal insufficiency, hypertension, and cardiovascular disease, and the use of concomitant medications such as antihypertensives and anticoagulants, NSAIDs should be avoided or used with great care. If NSAIDs cannot be used, an intra-articular steroid or a short course of tapering oral prednisone may be an alternative. While there are many dosage schedules, in our experience, a short course of prednisone starting at 30 mg tapering by 5 mg every 2 days is usually very effective. On the rare occasion when a steroid is contraindicated, such as when labile diabetes is present, analgesics including opioids may be used until the acute inflammation settles.

Intercritical Gout

The management of acute episodes of intercritical gout is the same as that for acute gout. However, if the frequency of acute episodes exceeds three over a 12-month period, efforts should be taken to lower the serum uric acid to prevent further attacks as the uric acid level correlates with the frequency of acute episodes. We have found that the optimal serum uric acid level to be achieved is between 250 and 300 μmol/L. To lower the serum uric acid level, attention should be directed toward eliminating or avoiding risk factors. As most of these factors are difficult to modify, especially among older adults, pharmacotherapy to lower the serum uric acid level is often necessary.

Table 1: 1997 Criteria for the Classification of Acute Arthritis of Primary Gout

1.	More than one attack of acute arthritis
2.	Maximum inflammation developed within 1 day
3.	Monoarthritis attack
4.	Redness observed over joints
5.	First metatarsophalangeal joint painful or swollen
6.	Unilateral first metatarsophalangeal joint attack
7.	Unilateral tarsal joint attack
8.	Tophus (proven or suspected)
9.	Hyperuricemia
10.	Asymmetrical swelling within a joint on radiograph*
11.	Subcortical cysts without erosions on radiograph
12.	Monosodium urate monohydrate microcrystals in joint fluid during attack
13.	Joint fluid culture negative for organisms during attack

*This criterion could logically be found on examination as well as on radiographs. However, the protocol did not request this information in regard to examination.

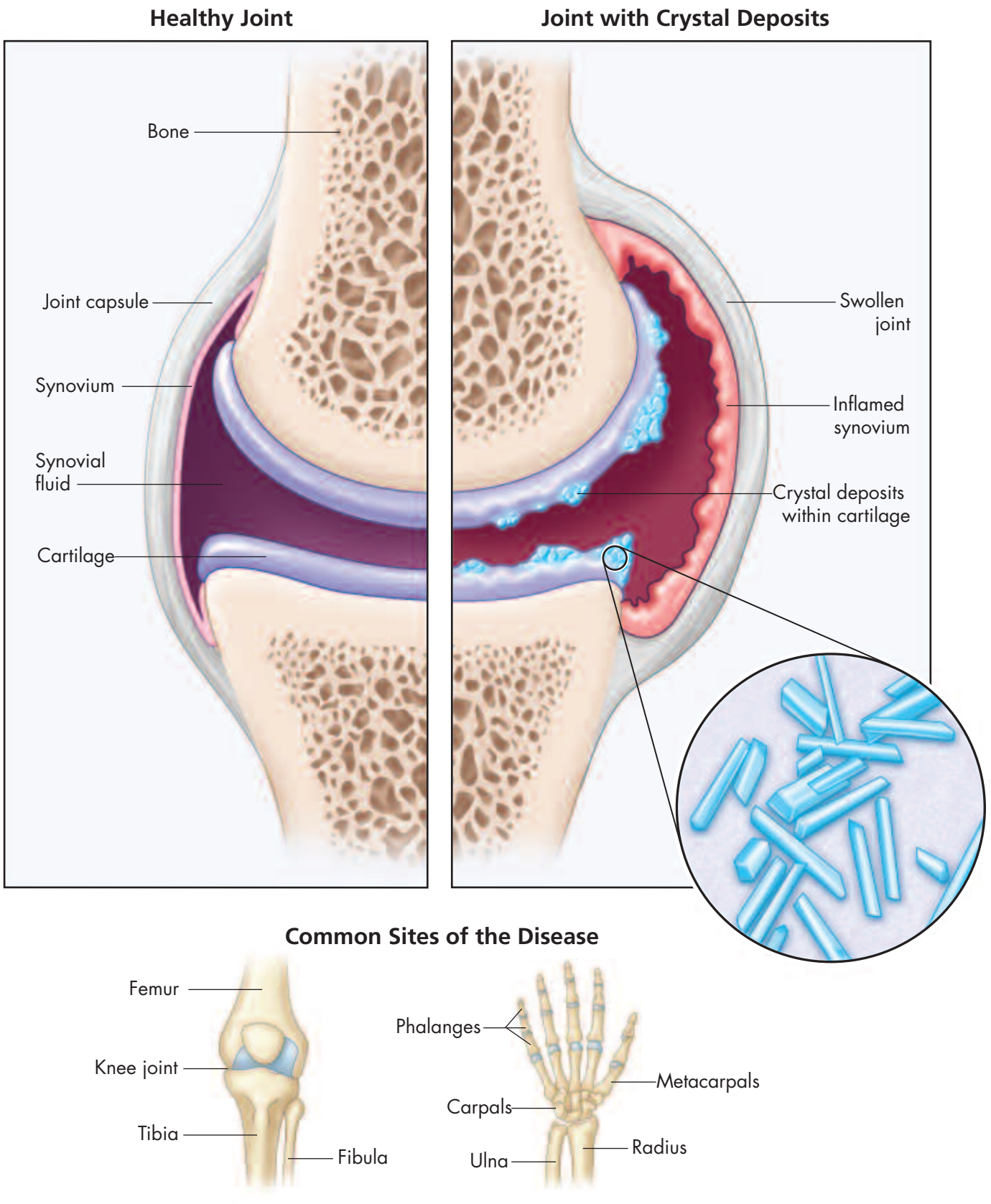
Source: Adapted from Wallace SL et al., 1997.[5]

Two classes of medications are currently available to accomplish this—uricosuric agents and allopurinol, a xanthine oxidase inhibitor. Uricosuric agents are most effective for those with normal renal function with a high urine output, and in the absence of renal calculi; they are therefore difficult to use, especially among older adults. Thus, allopurinol becomes the hypouricemic drug of choice. As a rapid change in the serum uric acid level may precipitate an acute attack, this drug should be started at a low dose, 50–100 mg daily, titrating upwards every 3–4 weeks by 50–100 mg until the optimal uric acid level is achieved (between 250 and 300 μmol/L). As the serum uric acid level and the metabolism of allopurinol are dependent on the glomerular filtration rate of the kidney, periodic assessments of renal function and uric acid are required. For those who are allergic to allopurinol, the use of uricosuric agents or a trial of allopurinol desensitization may be appropriate.[7] Newer hypouricemic drugs, for example, febuxostat, are currently under study but not yet available. Finally, agents to lower the serum uric acid level should only be initiated or altered after the acute attack has settled as lowering the uric acid during an acute phase may prolong the attack.

Tophaceous Gout

The management goals in tophaceous gout are to control the ongoing or recurrent joint inflammation and to lower the serum uric acid level to prevent acute episodes, decrease the chance of renal dysfunction, and reduce or eliminate the tophi. The management of tophaceous gout is the same as that of intercritical gout. However, due to the ongoing inflammation, it is often necessary to keep the patients on low-dose colchicines such as 0.6 mg once or twice per day or less, depending on the renal function; an optimal dose of NSAID (if not con-

Figure 1:
CPPD Deposition Disease



Key Points

- Septic arthritis should always be considered, with acute mono- or oligoarticular arthritis.
- Physicians should consider the possibility of crystal-induced arthropathy, including gout or CPPD deposition disease, in any older men or women who present with acute, subacute, or chronic inflammatory joint disease.
- Pharmacological treatment for crystal-induced arthritis in older adults deserves special attention due to comorbid conditions and the use of concomitant medications.

traindicated); or low-dose prednisone such as 5 mg/d. If steroid use is anticipated to be >12 weeks, osteoporosis prevention should be initiated.

Risk Factors Associated with Gout or Hyperuricemia

Risk factors such as age, gender, and ethnicity are not modifiable. Modifiable factors include obesity, diet, alcohol consumption, and medications.[8] A high-protein, purine-rich diet and alcohol consumption are associated with hyperuricemia and gout. Fruit, vegetables, nuts, and legumes are neutral, while plant oils and multiple vitamins may decrease the uric acid level. Common medications that increase serum uric acid include diuretics and low-dose ASA. As fluctuating uric acid levels often induce acute gouty arthritis, a steady serum uric acid level should be maintained.

Calcium Pyrophosphate Dihydrate Deposition Disease

The hallmark of CPPD deposition disease is the deposition of CPPD crystals within hyaline or fibrocartilage within joints (chondrocalcinosis) (Figure 1). It may present as acute arthritis as in gout (pseudo-gout), chronic low-grade inflammation resembling rheumatoid arthritis (pseudo–rheumatoid arthritis), or chronic noninflammatory arthritis resembling osteoarthritis (pseudo-osteoarthritis), or as asymptomatic articular cartilage deposition found incidentally on radiographs.

Incidence and Prevalence

As the presentation of CPPD deposition disease is variable, the true incidence and prevalence are not available. However, the prevalence of knee chondrocalcinosis on radiographs in a US population was 3% for those <70 years old, rising to 27% for those >85 years of age.[9]

Factors Responsible for the Inflammation

Calcium-containing crystals have been shown to induce collagenase and metalloproteases, leading to the generation of proinflammatory prostaglandins and other cytokines.[10] It has been suggested that CPPD deposition disease may play a role in an advanced form of osteoarthritis.[11]

Clinical Features

As mentioned, the prevalence of chondrocalcinosis increases with increasing age; thus, CPPD deposition disease primarily occurs among older adults. It may be asymptomatic or present with clinical features resembling gout, rheumatoid arthritis, or osteoarthritis; however, subtle differences may distinguish CPPD-induced arthritis from true gout, rheumatoid arthritis, and osteoarthritis.[12]

Pseudogout

Unlike gout, the most common sites of acute arthritis are the knees, wrists, and, to a lesser degree, shoulders and hips.

Pseudo–rheumatoid Arthritis

Unlike classic rheumatoid arthritis, the most common sites of chronic low-grade inflammatory arthritis from CPPD deposition are the wrists and metacarpal phalangeal joints, particularly the second and third, usually sparing the proximal interphalangeal and metatarsal phalangeal joints, which are commonly affected in classic rheumatoid arthritis.

Pseudo-osteoarthritis

Unlike typical osteoarthritis, pseudo-osteoarthritis associated with CPPD deposition often presents with low-grade synovial inflammation. Calcium pyrophosphate dihydrate deposition disease is more commonly seen in a number of metabolic conditions, including hemochromatosis, hyperparathyroidism, and possibly gout and hypothyroidism.

Diagnosis

Asymptomatic CPPD deposition disease is usually discovered incidentally by the finding of chondrocalcinosis on radiographs. Clinically, because CPPD-induced arthritis may present with different clinical features, a high index of suspicion is the key to establish the diagnosis, especially for those who have metabolic conditions associated with CPPD deposition. The gold standard for the diagnosis of CPPD-induced arthritis is the finding of CPPD crystal in the joint aspirate. However, it may not be practical to perform joint aspiration in all patients. The diagnosis may therefore rely on the clinical presentations, together with the finding of chondrocalcinosis on radiographs. It should be pointed out that the acute and chronic inflammatory arthritis associated with CPPD deposition disease may occur without the radiographic finding of chondrocalcinosis as the deposit may not be visible on radiographs. Finally, it must be emphasized again that the possibility of septic arthritis should be considered, especially with mono- or oligoarticular arthritis. If infection is clinically suspected, aspiration of the joint for examination is mandatory.

Management

Management of the arthritis associated with CPPD deposition disease is directed to controlling pain and inflammation and treating any underlying metabolic diseases. Nonsteroidal anti-inflammatory drugs are the standard pharmacological treatment for the pain and

inflammation. Colchicines may be considered in acute pseudogout and to prevent flare up. When NSAIDs and colchicines are contraindicated, an intra-articular steroid or a short course of tapering oral prednisone can be an alternative, as in the management of gout. Among individuals with CPPD-associated chronic arthritis, hydroxychloroquine can be considered, particularly in those for whom NSAIDs and steroids are contraindicated.[13]

Other Crystal Deposition Diseases

A number of other crystals, predominantly hydroxyl apatite crystal (also known as basic calcium phosphate hydroxyl apatite) may cause periarticular or articular pathology. Two clinical syndromes, painful shoulder and Milwaukee shoulder, are briefly discussed.

Painful Shoulder

Calcification within the rotator cuffs is commonly seen. Occasionally, this condition may present with acute or subacute shoulder pain. Treatment should be primarily directed toward maintenance and improvement of range by active exercises and reduction of pain with nonpharmacological and/or pharmacological modalities, including steroid injection.

Milwaukee Shoulder

Occasionally, severe osteoarthritis of the glenohumeral joint with limited mobility and instability is associated with hydroxyl apatite deposition around the rotator cuff tendons: the so-called Milwaukee shoulder. Surprisingly, pain is not a prominent feature. No specific treatment is required outside of the maintenance of shoulder function.

Conclusion

Crystal-induced arthritis, especially gout and CPPD deposition disease, are more common in the older population. Clinically, crystal-induced arthritis may present as acute, subacute, or chronic mono, oligo, or polyarthritis. Therefore, physicians should consider the possibility of crystal-induced arthropathy in any older men or women who present with joint disease. Because of the frequent presence of comorbid conditions and the use of concomitant medications, pharmacological treatment for crystal-induced arthritis in older adults deserves special attention and care.

No competing financial interests declared.

References

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.
2. Wallace KL, Riedel AA, Joseph-Ridge N, et al. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol 2004;31:1582–7.
3. Schiltz C, Lioté F, Prudhommeaux F, et al. Monosodium urate monohydrate crystal-induced inflammation in vitro: quantitative histomorphometric analysis of cellular events. Arthritis Rheum 2002;46:1643–50.
4. Ter Borg E, Rasker JJ. Gout in the elderly, a separate entity? Ann Rheum Dis 1987;46:72.
5. Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1997;20:895–900.
6. Nicolaou S. Utilization of the dual source CT for musculoskeletal applications: confirming the pattern of distribution of gout. Paper presented at the 10th International Symposium Multidetector Row CT; 2008 May 13–16; Las Vegas, NV.
7. Fam AG, Dunne SM, Iazzetta J, et al. Efficacy and safety of desensitization to allopurinol following cutaneous reaction. Arthritis Rheum 2001;44:231–8.
8. Choi H. Epidemiology of crystal arthropathy. Rheum Dis Clin North Am 2006;32:255–73.
9. Felson DT, Anderson JJ, Naimark A, et al. The prevalence of chondrocalcinosis in the elderly and its association with knee osteoarthritis: the Framingham study. J Rheumatol 1989;16:1241–5.
10. Morgan MP, McCarthy GM. Signalling mechanisms involved in crystal-induced tissue damage. Curr Opin Rheumatol 2002;14:292–7.
11. Nalbant S, Martinez JA, Kitumnuaypong T, et al. Synovial fluid features and their relations to osteoarthritis severity: new findings from sequential studies. Osteoarthritis Cartilage 2003;11:50–4.
12. Doherty M. Hochberg, et al. Rheumatology, 3rd edition. Toronto, ON: Mosby; 2003:1939.
13. Wu WC, Terkeltaub R, Kalunian KC. Calcium-containing crystals and osteoarthritis: implication for the clinician. Curr Rheumatol Rep 2005;7:213–9.