CLINICAL VIGNETTE

Normal Serum Uric Acid Levels During Acute Gout Attacks

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Case Report

A 62-year-old male presented after the sixth day of an acute polyarthritis. His symptoms were acute in onset, characterized by pain and swelling of the right first MCP joint and right MTP joint. He had no associated fevers during his attacks. He had experienced similar attacks over the course of the last decade, however, there had been an increased frequency in the number of attacks over the past year. In the past, when they would occur, he would present to his local emergency room. His only treatment had been week-long rapid tapering courses of oral steroids. He had not had joint aspirations performed, and while his serum uric acid levels had been normal, he was given the tentative diagnosis of acute gouty arthritis. No other medications had been prescribed, and no additional follow-up was sought. He had no history of renal disease, diabetes or family history of gout. He did not consume alcohol on a regular basis.

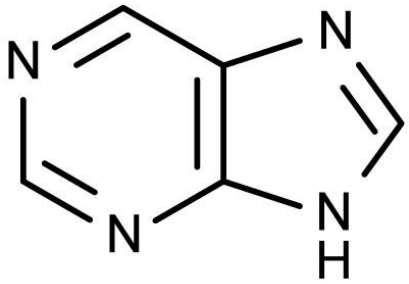
On examination, there was active swelling and tenderness of the joints described above. A soft, palpable mobile nodule, consistent with a ganglion cyst was noted adjacent to the first MCP joint. No obvious tophacious deposits were appreciated. His Body Mass Index was 23, and vital signs were normal. Serum uric acid levels at the time of presentation were 6.6 milligrams per deciliter (mg/dl) (4.0-9.0mg/dl). Urinalysis showed no crystals, with a pH of 5.5. A non-fasting glucose was 117 mg/dl (65-100mg/dl). A sedimentation rated was elevated to 39 (0-15 millimeters per hour, mm/hr). Serum creatinine was 0.8 mg/dl (0.5-1.3mg/dl). Serum Rheumatoid factor was <17 international units per milliliter, IU/ml (<25 IU/ml). The ganglion cyst was aspirated. The fluid was otherwise hazy yellow. The length of the viscous string of joint fluid dropped from the syringe was less than 1 centimeter (cm). Classic monourate crystals were appreciated within leukocytes, as well as free floating throughout the field. Symptoms had occurred for over 5 days, so empiric treatments were started, which consisted of a week-long oral steroid taper in addition to daily doses of colchicine 0.6 milligrams (mg).

At a three-week follow-up appointment, the patient remained on only daily colchicine dosing, and was asymptomatic. Sedimentation rate was now down to 8 mm/hour. Repeat serum uric acid level was now 11.9 mg/dl. Radiographs of the previously affected joints demonstrated erosive and subcortical cystic changes along the lateral aspects of the first metatarsal heads, and amorphous soft tissue densities suggesting tophacious deposits were noted surrounding the first affected metatarsophalangeal (MTP) joint. Metacarpophalangeal (MCP) joint findings showed minimal narrowing of the 3rd and 4th proximal interphalangeal (ITP) joints on the right with tiny subcortical cysts and minimal osteophyte formation, consistent more with osteoarthritis. Over the course of the next month, allopurinol was gradually escalated to reduce uric acid levels, while colchicine was continued. The patient remained asymptomatic, without recurrent acute gouty flare-ups in follow-up at 6 months. At that point, colchicine was discontinued, and the patient was maintained on allopurinol only.

Discussion

The overall incidence of gout is 1% in Western countries. The male to female prevalence ratio is ranging from 7:1 to 9:1.[1] Eighty to ninety percent of patients who suffer from gout are inefficient at excreting uric acid through the kidneys. The remaining ten to fifteen percent of patients over produce uric acid due to either inherited mutations in the regulation of purine metabolism, abnormalities in adenosine triphosphate (ATP) synthesis, or to excessive cellular turnover, as is classically seen in acute leukemia.[2]

Purines are a group of molecules that include the nitrogenous bases adenine, guanine, hypoypoxanthine, xanthine, theobromine, caffeine, and isoguanine. They all share in common a basic pyrimidine ring fused to an imidazole ring.



In primates, uric acid is the final product of purine degradation through the enzyme xanthine oxidase. At that point, uric acid must be excreted through the bowels or kidneys. Approximately one-third is passively secreted by the intestine, and degraded further by enteric bacteria, while the majority is released by the kidneys.[3,4]

When uric acid precipitates out of serum it forms monosodium urate crystals (MSU). It is likely that immunoglobulin may facilitate the crystallization of uric acid.[5] MSU crystals can be observed on light microscopy but is more easily appreciated with the assistance of a polarizing filter due to its

negative birefringence. The needle-shaped crystals will split light into two wave fronts that travel at different velocities: the ordinary and resultant extraordinary rays. This double refraction, or birefringence, is negative in monosodium urate crystals, because the rotated-extraordinary ray-travels more rapidly than the ordinary ray.[6] MSU crystals can deposit in joints, bones, and soft tissues. The phagocytosis of these crystals by neutrophils plays a critical role in the subsequent inflammatory gout attack and likely also affects level of urinary excretion of uric acid, and consequently, serum uric acid levels.

Hyperuricemia is directly linked to the progression of gout.[7] It sets in motion a series of progressively severe disease stages that can end with radiographically unique joint findings, as well as chronic arthritis, and massive collections of MSU crystals in tophi throughout the body.

Uric acid is no longer soluble and may precipitate at serum concentrations as low as 6.8 mg/dl.[8] In its earliest stage, asymptomatic hyperuricemia has only recently been identified to result in pathophysiological changes to the body.[7] At the time of the first acute gouty attack, microscopically visible tophi are identifiable in the affected joint. It is thought therefore, that in patients with hyperuricemia, the tophi antedated the onset of the first attack.[9]

The second stage is characterized by acute flares, 50% of which will be monoarticular arthritis of the 1st MTP, or podagra. The flares stimulate measurable elevations in cytokines IL6, and CRP. During this acute phase, serum uric acid levels measurably decline by a similar percentage increase found in the fractional excretion of uric acid (FEua). Elevations in interleukin 6 (IL6) and C-reactive protein (CRP) correlate directly with declines in serum uric acid.[10] In the

patient described above, the repeatedly low levels of uric acid obtained during the acute phase of his gout attacks, are explained by increased urinary release of uric acid by this actively inflammatory process.

Acute flares can last from several hours to several weeks. Typically, the initial acute flares subside over 3 to 10 days in the absence of pharmacologic therapy. This happens because, in the final stages, a variety of mechanisms are initiated that lead to eventual spontaneous resolution. These mechanisms include an increase in the amount of anti-inflammatory factors and, conversely, the degradation of inflammatory factors. Even though the flare has subsided, the patient is not cured of this chronic disease. Following the first acute flare, 66% of patients will experience a second flare within 1 year. Furthermore, once clinical gout is established, these flares become more frequent if the disease remains untreated.[11] The intercritical time (time between gouty flare-ups) will gradually shorten if hyperuricemia is not corrected. In the patient described, the frequency of attacks has gradually escalated because of his undiagnosed chronic hyperuricemia. In the later stage of hyperuricemia, chronic tophacious gout and chronic arthritis even felt between intercritical times are common. The duration of acute flares tend to be longer. Attacks are more likely to be polyarticular.[12] Bony erosions with characteristic sclerotic margins or overhanging edges are unique radiographic changes seen in the affected joints of patients who are in this later stage of chronic hyperuricemia.[13]

Treatment of acute gout flairs is dependant upon the time frame of their presentation. If started within the first 24 hours of the attack, repeated dosages of oral colchicine can result in response in 60% of patients.[14] The patient presented in this case had suffered symptoms for six days prior to being seen. Because he was felt to still be in an acute flare, a brief course of oral steroids were used to alleviate symptoms. There is, however, a high incidence of rebound attacks of gout if corticosteroids are used alone.[15] To reduce the risk of such rebound attacks, the patient was also treated with low dose colchicine.[16,17] In an effort to reduce the progression of his disease, and because of the increased frequency and severity of his intercritical times between attacks, the xanthine oxidase inhibitor allopurinol was gradually introduced to achieve a goal reduction of serum uric acid to below 6.7mg/dl.[18] To reduce the risk of allopurinol induced gout flares due to shifts in uric acid from treatment, low dose colchicine was continued in this patient for an additional 6 months.[19]

It is important to recognize hyperuricemia as a chronic progressive state that can ultimately lead to significant degenerative arthritis, as well as increased risk of nephrolithiasis 10 to 30 fold higher than those with a history of gout.[1,20] During the acute phase, uric acid levels drop due to increased fractional excretion of uric acid, and so normal uric acid levels during an acute flair should be expected when evaluating a patient during such flares. If aspiration of an affected joint or tophi is not feasible, repeat uric acid levels should be sought weeks after the attack has subsided. In the later phases of gout, unique radiographic findings may also assist in the establishment of a diagnosis of gout.

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