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Journal
Dermatology Online Journal, 21(1)

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Publication Date
2015

DOI
10.5070/D3211025437

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Peer reviewed
Case Presentation

Gout nodulosis: report of a rare case and brief review

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Dermatology Online Journal 21 (1): 8

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Abstract

The development of tophi in the absence of prior episodes of gouty arthritis is unusual. We hereby present a case of a non-alcoholic, normoglycemic, and normotensive middle-aged man, who presented with multiple nodules distributed bilaterally over the dorsum of hands, feet, and elbow joints without any prior history of arthritis. Serum uric acid level was found to be normal. Histology was consistent with features of tophi. On the basis of clinical and histological findings, the nodules were diagnosed as gouty tophi and the patient was diagnosed with gouty nodulosis. Gouty nodulosis is a very rare presentation of gout and only a few reports exist in the medical literature.

Introduction

Gout usually passes through four sequential stages of asymptomatic hyperuricemia, acute intermittent arthritis, inter-critical stage, and chronic gout. Chronic tophaceous gout classically occurs after 10 years of recurrent attacks of polyarthritis. However, it can be the first manifestation of the disease in the absence of arthritis. Gouty nodulosis is a rare presentation of the disease in which nodular subcutaneous tophi form in the absence of gouty arthritis [1].

Case synopsis

A 55-year-old man was referred to us with multiple asymptomatic nodules on the hands, feet, soles, and elbow joints of 15 years duration. His past medical and surgical history, including drug history were unremarkable. Family history was non-contributory. There was no history of pain and/or swelling of the joints, fever, or any other constitutional symptoms. He had not received any treatment for this condition. On cutaneous examination, there were multiple, firm, skin-colored nodules distributed bilaterally over the dorsal as well as plantar surface of both feet, around the lateral and medial malleoli, over dorsum of fingers, and around the elbow joints (Figures 1, 2, and 3). The lesions were firm to palpation, non-tender, and mobile. They were of variable size, ranging from 1 centimetre to approximately 6 centimetres in diameter. Systemic review was within normal limits. Tuberous xanthoma, calcinosis cutis, erythema elevatum diutinum (late fibrotic lesions), histoid leprosy, and rheumatoid nodules were included in the differential diagnosis.
Routine laboratory investigations were carried out. Erythrocyte sedimentation rate was raised (82 millimeters in the 1st hr), but hemoglobin, total leukocyte count, differential blood count, platelets, blood sugar, serum calcium, phosphate, albumin, electrolytes, urea, creatinine, parathyroid hormone, thyroid-stimulating hormone, rheumatoid factor and anti-nuclear antibody titers were within normal range. Lipid profile showed total cholesterol 290 mg/dl, high density lipoprotein (HDL) cholesterol 46 mg/dl, low density lipoprotein (LDL) cholesterol 216 mg/dl and triglycerides 141 mg/dl. Serum uric acid level was 3.9 grams/deciliter. 24-hour urine analysis did not reveal any abnormality. Chest X ray, X ray of hands and feet, and ultrasonography of the abdomen were unremarkable. Hepatitis B virus, Venereal Disease Research Laboratory (VDRL) and Human immunodeficiency virus (HIV) serology were non-reactive. Samples for histological examination were collected from a nodule on the dorsum of feet and from a plantar growth. Histological findings from both lesions were similar and showed nodular aggregates of amorphous material in the dermis, surrounded by a palisading arrangement of histiocytes (Figures 4, 5 and 6). Polarized microscopy could not be done owing to unavailability in our institute. Based on the clinico-pathological correlation, the nodules were diagnosed as tophaceous gout and the patient was diagnosed with gouty nodulosis.
**Discussion**

Gout is a chronic metabolic disorder characterized by hyperuricemia (serum urate > 7.0 mg/dl in men and > 6.0 mg/dl in women) and deposition of monosodium urate monohydrate (MSU) crystals in joints and within the peri-articular soft tissues. Predisposing factors include heavy alcohol intake, overzealous use of diuretics and analgesics (mainly acetylsalicylic acid), purine-rich diet, obesity, hypertension, and renal compromise [2]. The hyperuricemia in gout may be primary and secondary. Primary hyperuricemia is either the result of inborn errors of purine metabolism (urate over-producers) or related to a reduction in the renal excretion of uric acid (urate under-excretors). The secondary causes of hyperuricemia include systemic diseases with extensive cell turnover including malignancies and renal disease [3].

Gout usually passes through four sequential stages of asymptomatic hyperuricemia, acute attacks of arthritis, inter-critical stage, and chronic gout, as mentioned earlier. Gout typically involves joints, peri-articular tissue, and sometimes, viscera. Involvement of the metatarsal-phalangeal joint of the great toe (podagra) is often the earliest manifestation and is highly suggestive (but not pathognomonic) of gout. Gout attacks begin abruptly and typically reach a maximum intensity within 8-12 hours. Affected joints are red, hot, and exquisitely tender. Untreated, the first attacks resolve spontaneously in less than 2 weeks. Other than the great toe, the common sites of gouty arthritis are the instep, ankle, wrist, finger joints, and knee. In early gout, only 1 or 2 joints are usually involved. The pattern of symptoms in untreated gout changes over time. The attacks can become polyarticular. Attacks tend to occur more frequently and last longer. Eventually, patients may develop chronic polyarticular arthritis [1, 2, 3].

Dermatological features include gouty tophi and gouty panniculitis. Tophus results from deposition of MSU crystals in dermis and subcutaneous tissue [3]. Gouty panniculitis is an extremely rare dermatological manifestation of gout, characterized by the deposition of MSU crystals in the hypodermis and may precede or appear subsequently to the joint involvement. It is characterized by indurated, erythematous, and irregular subcutaneous nodules or plaques that are mostly found on the lower extremities and often ulcerate. Histology is consistent with lobular panniculitis with deposition of needle crystals, consistent with urate deposits [4, 5]. Other uncommon cutaneous features include hyperpigmented skin nodules, pustules, vesico-bullous lesions, and deep ulcerations mimicking vasculitis [6, 7, 8].

Tophi generally form in peri-articular soft tissue, sub-articular regions of bone, in bursae, tendon sheaths, articular cartilage, synovial tissue of flexor tendons, outer helix of the ear, or the pinna. However, they can involve any part of the body including vocal cords, artenoids cartilage, myocardium, mitral and aortic valves, eyes, spinal cord, tail of pancreas, breast, and penis [2, 3, 9]. When the tophi enlarge, the nodules may break spontaneously (or on minor trauma) through the skin and discharge white or yellowish-white chalky material [2, 3]. Clinical differential diagnoses for chronic tophaceous gout include tuberous xanthoma, erythema elevatum diutinum, histoid leprosy, rheumatoid nodules, ganglion cysts, pigmented villonodular synovitis, and Heberden's or Bouchard's nodes [1, 2, 3].

Tophi usually develop after about a decade in untreated patients who develop chronic gouty arthritis. However, it may develop earlier in older women, particularly those receiving diuretics. However, in exceptional cases, it can manifest in the absence of prior history of any acute attack or history of the disease, thus being the first clinical sign of the disease [3, 10, 11, 12, 13, 14].

Other uncommon dermatological manifestations of gouty tophi are gouty nodulosis [12, 14] and miliarial gout [15]. Gouty nodulosis, as mentioned earlier, is a rare presentation of tophi in which nodular tophi develop in the absence of gouty arthritis. Miliarial gout is another extremely rare manifestation and presents as grouped, tender, yellowish-red papules that occur in crops over the metatarsophalangeal joints of hands, knees, abdomen, and extensor forearms, as described by Mireku et al [15]. Interestingly, most of the reported cases of gouty nodulosis, as well as miliarial gout, have normal uric acid levels, thus necessitating high index of suspicion and histopathology for diagnosis.

The diagnosis is based on the correlation of clinical suspicion, serum uric acid level, imaging studies (X-ray, ultrasonography, and computed tomography scan), histopathology, and arthrocentesis with joint fluid analysis of the affected joint and polarized microscopy [1, 2, 3]. According to the European League Against Rheumatism (EULAR) recommendations, classical intermittent monoarthritis of the first metatarsophalangeal joint (podagra) and presence of tophi have the highest clinical diagnostic value for gout [16]. Although increase in uric acid level is a major risk factor for gout, serum uric acid levels do not confirm or exclude...
gout; many people with hyperuricemia do not develop gout and during acute attacks serum levels may be normal. In fact, the levels can be normal even during the chronic tophaceous stage, as noted in many cases including our case. Thus, serum uric acid levels cannot be considered a sensitive marker for the diagnosis of gout [3, 16, 17]. Also, McCarty et al reported the possibility of normal uric acid levels in diabetics and alcoholic gout patients [17]. However, our patient was neither diabetic nor alcoholic, yet the serum uric acid was within normal limits (3.9 milligrams/deciliter). Gout is often associated with hyperlipidemia (usually hypertriglyceridemia) and insulin resistance syndrome (IRS) [3]. The serum triglyceride and blood sugar levels both were normal in our patient. 

The gold standard for diagnosis is the demonstration of urate crystals in synovial fluid or in a tophus by polarized light microscopy [1, 3, 16]. Crystals of monosodium urate (MSU) are needle-shaped and exhibit negative birefringence on polarized microscopy [3].

Plain radiographs may show findings consistent with gout, but these findings are not diagnostic. Punched-out erosions or lytic areas with overhanging edges are considered characteristic of gout, but usually do not appear early. Such punched out erosions with overhanging edges may be seen in some other conditions too, but some additional findings including location outside the joint capsule, maintenance of the joint space, absence of peri-articular osteopenia, and sclerotic borders favor the diagnosis of gout. “Double-contour” sign and “Wet clumps of sugar,” representing tophaceous material are classical ultrasonographic findings in established gout. Dual-energy CT, using a renal stone color-coding protocol, is useful for assessing chemical composition, and labels urate deposits red [1, 3].

Chronic tophaceous gout may be diagnosed with reasonable certainty by histopathological findings. In alcohol-fixed samples, urate crystals appear as well-demarcated deposits of closely arranged, brown, needle-shaped crystals. In formalin-fixed material, the crystals usually dissolve during routine processing and there are characteristic large pale pink acellular areas, which represent dissolved urate crystals, surrounded by histiocytes and multinucleated giant cells. However, if there are a large number of crystals, some may survive processing and appear as pale brown-gray refractile material, which may even be seen on unstained sections [1, 3, 10, 12]. Similar histopathology findings (pale pink areas surrounded by histiocytes and multinucleated giant cells) are also seen in pseudogout, but on higher-power views, the crystals in pseudogout appear purple and are rhomboid, allowing differentiation from gout on routine histology [3]. The differentiating findings in gout and pseudogout have been summarized in Table 1.

<table>
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<th>Table 1. Gout and Pseudogout</th>
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<td><strong>Gout</strong></td>
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<td>Composition of the deposits</td>
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Fine needle aspiration cytology (FNAC) is another useful method of diagnosing gouty tophi and is favored over histopathology on account of being rapid, less invasive, and highly sensitive in the diagnosis of tophi [18, 19].

Treatment involves a multidisciplinary approach including dermatologists, rheumatologists, nutrition experts, and internists. General measures include weight reduction, reduction of alcohol intake, modification of diet, and proper exercise. Pharmacological therapies include analgesics, steroids, colchicine, and allopurinol [1, 3, 20]. Surgical treatment may be needed depending on the extent of the patient’s disabilities and compression of surrounding structures. Widespread and numerous lesions limit the utility of surgical treatment modalities; however, surgical excision may be an option in cases refractory to medical
therapy [20,21]. Recently, pegloticase, a pegylated mammalian recombinant uricase, has been shown to be beneficial in lowering urate levels and rapidly reducing tophus size in patients with chronic tophaceous gout [22].

Because the first clinical presentation of gout, in the complete absence of any acute attacks of arthritis, may be tophi, dermatologists should be aware of this atypical presentation in order to facilitate timely diagnosis and intervention. Very few cases of gouty nodulosis i.e. nodular subcutaneous tophi in the absence of gouty arthritis, have been reported from India. The uniqueness and rarity of our case prompted the present report.

References