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Tophaceous Gout – When the Skin Comes First

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ABSTRACT Gout represents a metabolic disorder with systemic echo, in which needle-like crystals of monosodium urate are deposited in various tissular structures. Crystals accumulation in the connective tissue (tophi) represents the late, chronic stage of this disease, usually emerging after an average of 10 years after disease onset. Herein we report three cases of patients aged 70, 33, and 53 who presented with painful subcutaneous nodules located on various body areas. All of them had hyperuricemia. Several conditions had to be investigated in order to establish the etiology of uric acid metabolism alterations. Laboratory and pathology findings established the diagnosis of gout, with tophi as the first symptom of the disease. Following patient education, diet and lifestyle changes, and medication, the outcome in all patients was favorable, with alleviation of the symptoms. Tophaceous gout as a first presentation of this disease is currently uncommon, but dermatologist should be aware of this rare finding for proper management of such cases and to prevent the resultant significant functional and quality of life impairment if not recognized early.

KEY WORDS: tophaceous gout, hyperuricemia, gout

INTRODUCTION

Gout, a clinical syndrome caused by a group of heterogeneous conditions, with potential systemic echo, is characterized by deposition of monosodium urate crystals in various tissues – first the bone and articular tissues, followed by soft tissues or the renal tract. It represents the most common type of inflammatory arthritis affecting elderly people, especially men over 40 years of age (1), and has a general estimated prevalence of 1-4% (2). Usually, the evolution of gout corresponds to four stages in the clinical picture: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout, and chronic tophaceous gout (3). Chronic tophaceous gout represents the late stage of this metabolic disorder, which normally develops after prolonged disease evolution following multiple years of recurrent gout attacks, usually in untreated or partly treated patients (4), more frequently in women (27%) compared with men (10%) (5).

Tophaceous gout as the first manifestation of gout with no previous gout attacks represents an uncommon presentation of this disease, with 96 cases described in the literature between 1970 and 2017, which were associated with certain risk factors such as increased age, female gender, chronic kidney disease, and diuretic treatment (4). Furthermore, it has been shown that tophi development without

previous gout attacks are also associated with lower serum levels of uric acid, compared with patients who develop tophi after many years of recurrent gouty attacks (6). Due to recent and continuous shifts regarding diet (increased fast food intake), lifestyle (lack of physical exercises associated with increased rates of sedentariness, increased incidence of obesity and metabolic syndrome) (2), medical care, and enhanced longevity, an increased prevalence of gout in general and chronic tophaceous gout in particular has been recorded worldwide (4); this represents an indicator of a need for an improved effort towards early identification of patients with gout as well as their disease process (7).

We present three cases of tophaceous gout as the first clinical presentation without previous gout attacks, in male patients aged 70, 33, and 53 years old, without any significant medical or drug intake history known to determine metabolic imbalance of the uric acid.

CASES

Case 1

A 70-year-old man presented with multiple painful erythematous nodules 5-15 mm in diameter located on the palmar and dorsal aspects of the fingers (Figure 1, a, b), which had been evolving for six weeks and were associated with impairment of daily activities. Many of these nodules were ulcerated, occasionally expressing a dense, white-chalky material. Significant dysfunction of the adjacent joints was present. The patient had no other conditions mentioned in his medical record and denied alcohol abuse.

Laboratory investigations revealed a moderate inflammatory syndrome and elevated levels of serum uric acid. The patient denied receiving treatment with diuretics or any other drugs that could be incriminated in increasing uric acid levels.

A biopsy of one of the nodules was performed, with the pathology report revealing granulomatous inflammation surrounding needle-like spaces in a radial arrangement, representing crystals dissolved during processing (Figure 1, c, d).

The pathology report, taken together with clinical and laboratory data, supported the diagnosis of tophaceous gout.

Therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and allopurinol was initiated (8), with a favorable evolution during treatment and gradual decreasing of the inflammation and associated pain (Table 1).

Case 2

A 33-year-old man was referred to our clinic for multiple painful erythematous nodules, with the biggest (35/20 mm) located on the dorsal aspect of the third metacarpophalangeal joint of the right hand (Figure 2, a). Other smaller nodules were present on helix of the left ear, the left elbow, the extension area of the left forearm (Figure 2, b), and the second digit of the left foot (Figure 2, d). The nodules had been growing over the past four years, and a week before hospital admission the patient experienced an episode of painful erythema and edema of the metacarpophalangeal joints of the left hand, with improvement of the symptoms after NSAIDs treatment. The

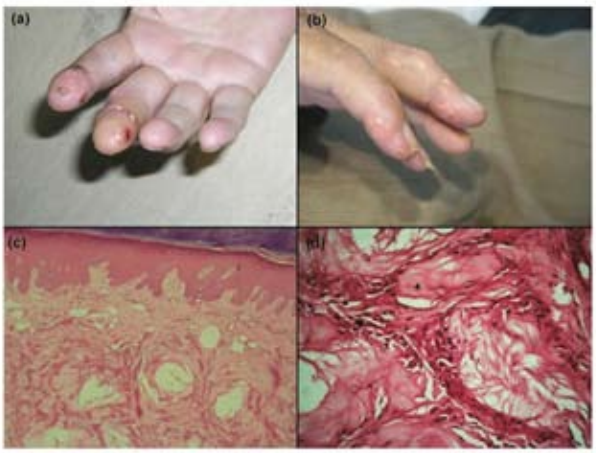

Figure 1. Erythematous nodules on the palmar (a) and dorsal aspects (b) of the fingers; (c), (d) pathological aspects: granulomatous inflammation surrounding needle-like spaces in a radial arrangement, representing crystals dissolved during processing (c: hematoxylin-eosin stain, ×20; d: hematoxylin-eosin stain, ×40).

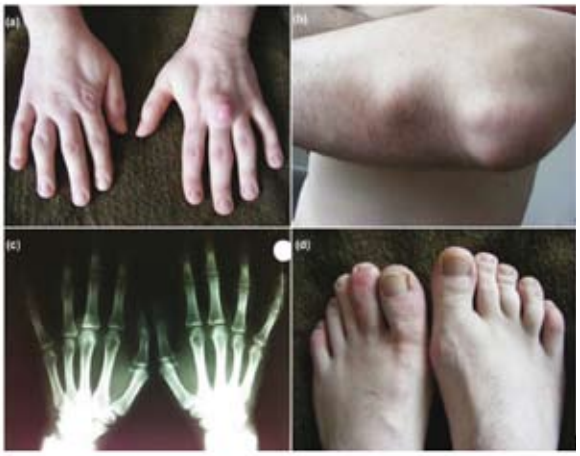

Figure 2. Multiple painful erythematous nodules 5-35 mm in diameter on the dorsal aspect of the third metacarpophalangeal joint (a) and the left elbow (b); hands X-ray revealing demineralization in both radio-carpal joints, proximal inter-phalangeal joints arthritis of left hand digits II-V (c); painful nodule on the second digit of the left foot (d).

Table 1. Clinical details of the three patients with tophaceous gout

Characteristic	Patient 1	Patient 2	Patient 3
Sex	M	M	M
Age (years)	70	33	53
Preceding history of gout	None	Cutaneous nodules for four years No arthritis/arthralgia	Cutaneous nodules for two years
Serum urate level at presentation (mg/dL)	9.8	10.5	9.7
Treatment	Allopurinol 100 mg/day NSAID	Allopurinol 100 mg/day NSAID	Allopurinol 100 mg/day NSAID
Co-existing comorbidities	None	None	Hypertension (beta blockers treatment)
Localization of the tophi	Fingers	Right hand, left ear helix, left elbow, left forearm	Ears
Follow-up (one year)	No lesions	No lesions	No lesions

patient denied smoking, alcohol consumption, other medical conditions, or any medication usage before admission.

Laboratory investigations revealed a moderate inflammatory syndrome, elevated uric acid levels, hypercholesterolemia, and hypertriglyceridemia. X-ray of the hands identified demineralization in both radio-carpal joints (predominantly on the left hand) and proximal interphalangeal joints arthritis of the left II-V digits in the hand (Figure 2, c).

The clinical picture was highly suggestive of tophaceous gout, and NSAIDs and allopurinol therapy was started, with favorable evolution of the patient (Table 1).

Case 3

A 53-year-old man presented with white-yellowish, sharply demarcated, asymptomatic nodules, 7-13 mm in diameter, firm on palpation, located on the helix and antehelix regions of both ears (Figure 3, a, b), that had been evolving for two years, with an increase of their count in the last six months.

The patient was hypertensive are was receiving treatment with beta blockers. He denied alcohol abuse.

Laboratory test revealed a moderate inflammatory syndrome, high levels of uric acid, and hepatic cytolysis.

The nodules were excised and a biopsy was performed, with the pathology report showing granulomatous inflammation surrounding needle-like spaces in a radial arrangement and negatively bi-refringent needle-like crystals by polarized microscopy.

Combining the pathology report with clinical picture and laboratory data, the diagnosis of tophaceous gout was established.

Under allopurinol treatment, the patient's evolution was favorable (Figure 3, c, d), with good general condition, no joint pain, and no new cutaneous lesions observed at one-year follow-up visit (Table 1).

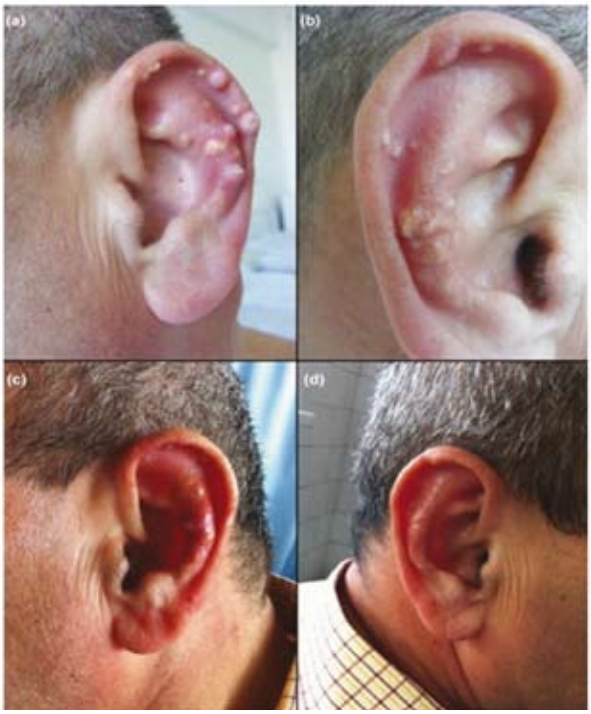

Figure 3. Multiple white-yellowish nodules, 7-13 mm in diameter, sharply demarcated, asymptomatic, firm to palpation, located on the helix and antehelix regions of the left ear (a) and right ear (b); favorable evolution under allopurinol treatment on left ear (c) and right ear (d).

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DISCUSSION

Gout develops as a consequence of purine metabolism abnormalities in which urate crystals precipitate from body fluids and form tissular deposits, including cutaneous ones – tophi (3). Elevated plasma levels of uric acid represent a risk factor for the development of gout, but tophaceous gout without previous recurrent flares of gouty arthritis is associated with lower levels of serum uric acid (6). Hyperuricemia can be primary (due to a genetic enzymatic defect of the purine metabolism) or secondary, with multiple causes: renal excretion impairment, drug-induced, alcohol abuse, excessive dietary intake of purines, and increased turnover of nucleic acids (myeloproliferative or lymphoproliferative disorders, hemolytic anemia). The most frequently incriminated drugs in the development of hyperuricemia are diuretics, cyclosporine and salicylates (1).

In general, tophi develop after an average of ten years after the onset of gout and usually in patients with previous uncontrolled gout (4). However, in unusual cases they can represent the first manifestation of the disease. Calcium pyrophosphate dehydrate crystal deposits in pseudogout (chondrocalcinosis), xanthomas, and rheumatoid nodules can be confused with gouty tophi, but histopathologic examination helps to confirm the diagnosis of gout.

Tophaceous gout is currently considered uncommon, and its presentation should elicit an investigation for various causes of hyperuricemia (9), (10). Purine enzyme defects are rare both in young and elderly patients. Genetic testing was not performed in our patients; secondary causes of hyperuricemia were taken into account. Renal failure, acidosis, and increased nucleotide turn-over were excluded by laboratory tests, and alcohol abuse or potential gout-precipitating medication administration was denied by all three patients. Therefore, it was necessary to investigate other rare conditions involving hyperuricemia, like hypothyroidism, hyperthyroidism, and hypoparathyroidism, which was achieved by testing for serum calcium levels and TSH – found to be within normal limits. Accordingly, it was concluded that excessive dietary purines were the cause of tophaceous gout development in our patients.

Chronic tophaceous gout, if not managed properly, is associated with important functional and quality of life impairment (11), eventually leading to significant erosive bone disease and notable joint damage (12), which may prove to be significantly debilitating.

The cases presented in this paper present some unique aspects. Firstly, all patients presented immediately with tophaceous gout as the first manifestation of the disease, without any prior history of recurrent gouty arthritis, given that tophi develop in the last stage of poorly controlled gout (3). Secondly, all patients were men and, although gout is more frequently encountered in male patients, tophaceous gout is found more frequently among female patients (4). Furthermore, although it is well-known that tophaceous gout without previous gouty flares is encountered especially commonly in the elderly population (6), two of the patients we presented were of 33 and 53 years old. Lastly, one of the patients presented with multiple ulcerated tophi, ulceration being quite uncommon in such lesions (13).

CONCLUSION

Although it is the rule of the natural progression of gout for the cutaneous tissue to be affected after the joints have been previously affected, in clinical practice patients might present with skin involvement in the shape of tophi as the first sign of this disease. Furthermore, even if, patients with gout are started on the appropriate treatment and therefore they do no develop tophi in the modern era of medicine, in daily practice, medical doctors may encounter cases of tophaceous gout as a result of either a longstanding unknown and uncontrolled gout or as a first clinical manifestation. Therefore, this clinical article highlights the necessity of dermatologists being aware of this uncommon first manifestation of gout in establishing an early diagnosis and proper management of such cases, leading to a decrease in the significant debilitating potential of this disease.

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