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HISTOPATHOLOGICAL STUDY OF CUTANEOUS LESIONS IN GOUT

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Abstract

Aim*: To document the spectrum of histological changes of cutaneous lesions found in patients with gout.* ***Material and methods****: Thirteen cutaneous biopsies were studied. The biopsies were fixed in formalin solution and stained with hematoxyline and eosin.* ***Results****: A common feature in all 13 cases was the presence of deposits of basophilic material with needle-like clefts. The main histological reaction pattern was palisading granuloma. In 7 cases the deposits were subcutaneously located and in 6 cases intradermal and subcutaneously. The inflammatory infiltrate contained mainly epithelioid histiocytes and multinucleate giant cells. In 5 cases it also contained neutrophils and in one case foam cells. Secondary changes were found in 6 cases.* ***Conclusion****: When the clinical findings are atypical, cutaneous biopsy remains an important tool to establish the diagnosis of tophi, even in those cases with no possibility to exam alcohol fixed specimens under polarized light. In our study the preliminary clinical diagnosis was consistent with the histological findings in only 3 cases. The key feature that allowed the correct diagnosis was the presence of basophilic material with needle-like clefts surrounded by a palisading histiocytic infiltrate.*

key words: *tophi, gout, monosodium urate deposits.*

Background and Aims

Gout is a chronic metabolic disease caused by a disturbance of purine metabolism which is reflected by elevated serum uric acid levels: hyperuricemia [1]. Hyperuricemia is defined as a serum urate level greater than 6.8 mg/dL [2]. As a consequence of elevated serum uric acid levels, deposits of monosodium urate crystals may occur most commonly in the skin and around the joints. The cutaneous manifestations are called tophi and they represent deposits of monosodium urate within the dermis and subcutis. They usually develop after many years (around 10 years) from the onset of gout and only in rare occasions may occur without a previous acute attack of gout or history of the disease [2,3].

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The diagnosis of cutaneous lesions in gout is mainly clinical, supported by the high levels of serum uric acid and a personal medical history of gout. However, in atypical clinical cases, a cutaneous skin biopsy is necessary to confirm the diagnosis [4].

The aim of our study was to analyze the histopathological features of cutaneous lesions found in patients with gout.

Material and method

We performed a 4-year observational study in 3 hospitals from Bucharest, University Emergency Hospital, Elias University Emergency Hospital and Scarlat Longhin Hospital of Dermatology, between Jan 2008-Dec 2011. The study group comprised 254 cases of granulomatous reactions, with a predominance of foreign body reactions to endogenous bodies diagnosed by skin biopsy.

Results

From the 254 cases, 13 were foreign body reactions to monosodium urate deposits, gouty tophi. In 10 of the cases, the lesions involved the distal interphalangeal joints, elbows and Achilean tendon. In 3 cases there were finger pad lesions and in one case the lesions were disseminated, involving the periarticular sites and the soft tissues. There were a clear male predominance, with 12 male cases and only one female, confirming the data from the literature that gout affects mostly males and in a lesser percentage females, especially after menopause (our female patient was 83-year-old). In only 3 cases the pre-biopsy clinical diagnosis was of gout tophi.

We analyzed the cutaneous biopsies fixed in formalin solution and stained with hematoxylin and eosin (HE), looking for the following parameters: the presence of masses of granular basophilic material with needle-like clefts which are the clue for gouty tophi diagnosis, how deep they were located, the associated granulomatous reaction, the severity and the composition of the inflammatory infiltrate, focusing on the arrangement pattern of the histiocytes and if there were any intact yellow-brown urate crystals, secondary calcifications or ossifications. We also analyzed the changes of the epidermis. The results are summarized Table 1.

In all 13 cases we identified deposits of basophilic material with needle-like clefts surrounded by epithelioid histiocytes and foreign body cells (Figure 1).

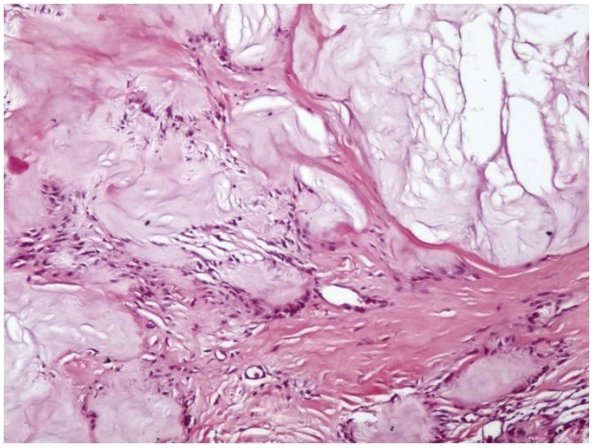

Figure 1. Masses of material with needle-like clefts representing dissolved urate crystals (HEx100).

Table 1. Histological features found in 13 cases of gout tophi.

A	B	C	D	E	F	G	H	I	J
1	large deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	++	lymphocytes	palisading and irregular pattern	–	–
2	large and small deposits	dermis and subcutis	+	epithelioid and giant multinucleate foreign body cells	++	lymphocytes and neutrophils	palisading and irregular pattern	ulceration	–
3	large deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes and few neutrophils	palisading and irregular pattern	–	calcification
4	large and small deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	palisading and irregular pattern	–	–
5	large and small deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	palisading and irregular pattern	–	–
6	large and small deposits	dermis and subcutis	+	epithelioid and giant multinucleate foreign body cells	++	lymphocytes and neutrophils	palisading and irregular pattern	atrophy	–
7	large and small deposits	dermis and subcutis	+	Epithelioid, giant multinucleate foreign body cells and foam cells	+++	lymphocytes and many netrophils	palisading pattern	ulceration	calcification ossifications
8	large and small deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	palisading pattern	–	–
9	large deposits	dermis and subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	few histiocytes in the periphery	–	fibrosis
10	large and small deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	palisading and irregular pattern	–	–

11	large and small deposits	subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	palisading pattern	–	–
12	large deposits	dermis and subcutis	+	epithelioid and giant multinucleate foreign body cells	+	lymphocytes	palisading pattern	–	
13	large deposits	dermis and subcutis	+	epithelioid and giant multinucleate foreign body cells	++	lymphocytes and neutrophils	palisading and irregular pattern	+	calcification

A - Case Number; B - Masses of pale granular basophilic material with needle-like clefts; C - Location of the deposits (dermis or/and subcutis); D - Granulomatous reaction; E - Type of histiocytes; F - Type of histiocytes; G - Type of histiocytes; H - Arrangement pattern of the histiocytes; I - Changes of the epidermis; J - Other secondary changes

The granulomatous reaction was ubiquitous. The deposits were both large and small in size. The large deposits had resulted by confluence of small ones and contained cellular septa and degenerative pseudonecrotic changes. In 6 cases the deposits were found in the dermis (Figure 2) and subcutis and in 7 cases in the subcutis (Figure 3).

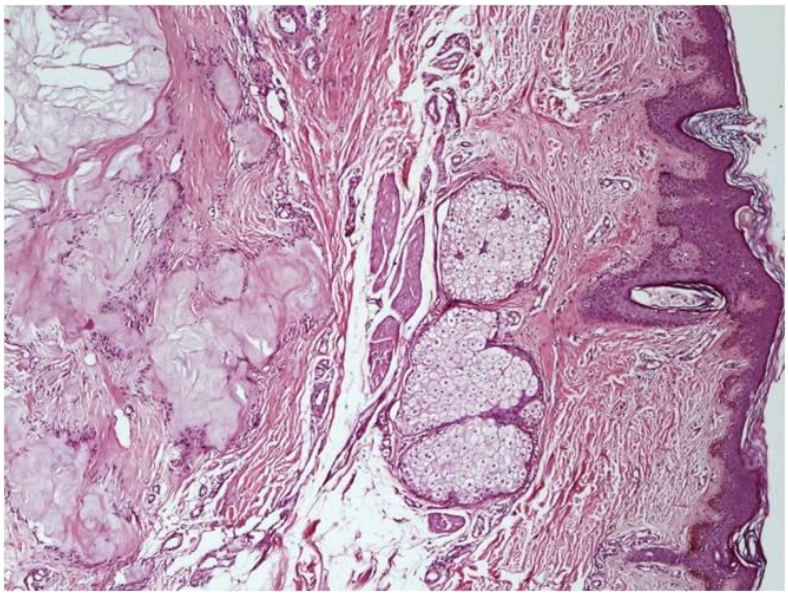

Figure 2. Deep intradermal deposits of monosodium urate (HEx40).

In 12 cases histiocytes were aligned in a palisade pattern at the periphery of the deposits. Epithelioid histiocytes were the main cells found and they were oval, with abundant eosinophilic cytoplasm and central nucleus. Multinucleate giant cells, although also found in all of the cases, were less numerous. In one case we found foam cells located between the granulomas. Areas of lymphocytic inflammatory infiltrate were found either at the periphery of the nodules or between the granulomas. In 5 cases the infiltrate contained neutrophils and in these cases the epidermis was ulcerated due to

transepidermal elimination of urate monosodic crystals. Other secondary changes (fibrosis, calcifications) were found in 4 cases.

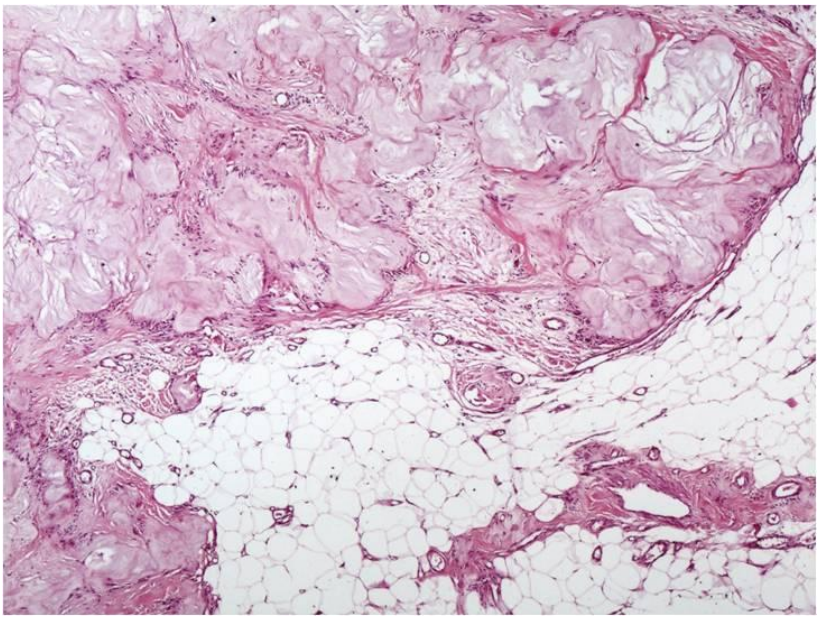

Figure 3. Subcutaneous deposits of monosodium urate (HEx40).

Discussion

Gout has been known since antiquity and historically, it has been referred to as the "king of diseases" and the "disease of kings." However, the microscopic appearance of urate crystals was first described in 1679 by the Dutch scientist Antonie van Leeuwenhoek [5], but only in 1848 the English physician Sir Alfred Baring Garrod linked gout with hyperuricemia [6,7]. The physiopathology of acute gouty arthritis was fully elucidated in 1962 [7].

Between 2 and 12% of the population in developed countries have hyperuricemia [8] and its prevalence seems to have increased over the past few decades [7]. Men are more frequently affected than the women; the male to female ration is 9:1 [7] and 20% of the patients have a family history of gout [9].

Hyperuricemia may be secondary to a high turn-over of cells (leukemia, psoriasis, etc) or to a reduced renal excretion (for example alcohol abuse during diuretic treatment with thiazides), but in most of the cases is idiopathic [8]. Hyperuricemia alone is not a clinical disease and only a small percentage of people with elevated uric acid levels develop clinical gout, the key factor being the limited solubility of monosodium urate crystals in body fluids [8]. The deposits of monosodium urate stimulate the production of interleukin-1 by macrophages [10], followed by migration and activation of neutrophils with further inflammation and tissue damage [7].

Clinical manifestations found in gout are tophi, recurrent attacks of acute arthritis and renal disease involving glomerular, tubular and interstitial tissues and blood vessels, and uric acid nephrolithiasis [2].

Tophi are present in less than 10% of patients with gout and their prevalence has decreased as the diagnosis and treatment of

this disease have improved [7]. Tophi are firm, skin-colored to white-yellow or red papules and nodules or a fusiform swelling with a smooth or multilobulated contour [7]. The surface may be ulcerated, draining a thick chalky material which contains monosodium urate crystals. Generally, tophi can occur at any location or tissue of the body, with a predilection for the distal interphalangeal joints, olecranon bursa, dorsal aspect of the proximal interphalangeal joints, metacarpophalangeal joints, the dorsal toes and the helix of the ear. However, they may be found in unusual locations, such as eyes, nose, larynx, breast and heart valves [3]. In some patients, gout panniculitis can develop, which presents with nodular lesions on the legs that ulcerate and drain a crystal-containing fluid [11]. There are few cases reported in literature of disseminated cutaneous gout.

Monosodium urate crystals can contribute to bone lesions by reducing osteoblastic activity and are associated with enhanced osteoclast activity in the vicinity of tophi. Mild trauma triggers monosodium urate crystal release from tophi, resulting in cell activation and production of cytokines and proteases. This could enhance bone erosion leading ultimately to bone fragility and fracture [12].

The histopathological features in gout are masses of pale granular basophilic material with needle-like clefts in radial arrangement represented by dissolved urate crystals during the processing of the specimen [4]. The epidermis may be preserved or ulcerated. Occasionally, secondary calcifications and ossifications can occur. However, the clue to histopathologic diagnosis of gout in sections of tissue stained with hematoxylin and eosin are the needle-like spaces found in a homogenous basophilic material [4].

If the specimen is fixed in absolute alcohol, which best preserves the urate crystals, the histological features found in gout are pretty characteristic and could be identified by polarized light microscopy.

In sections of tissue HE stained, the urate crystals are dissolved during the processing of the specimen and they look like needle spaces in a homogenous basophilic material [4]. These masses act as foreign bodies, attracting histiocytes which tend to become aligned in a palisade pattern around them. In some cases the deposits of urate seem to be as inert as those of calcium and no granulomatous reaction is seen around them [4]. In those specimens fixed in formalin only rarely few intact yellow-brown urate crystals can be seen [4].

When the sections are stained with 20% silver nitrate solution (von Kossa stain), the crystals appear black and the surrounding tissue yellow [7].

We performed the differential diagnosis of gouty tophi with other types of foreign body reactions: rheumatoid nodules, triamcinolone injected into the dermis or subcutaneous fat, *calcinosis cutis*, pseudogout, xanthomas, silica granuloma and *chondrodermatitis nodularis helicis*. We used the following additional stains in order to eliminate these histological entities: PAS (periodic acid Schiff), von Kossa, Van Gieson elastic, Gömöry, Congo Red. Polarized light microscopy exam was not useful as the specimens were placed in formalin solution 10% which dissolved the crystals.

The rheumatoid nodules may have similar clinical presentations, but the biopsy shows

important deposits of fibrin of various sizes in the deep reticular dermis and/or subcutaneous fat surrounded by histiocytes aligned in a palisade [4]. In old lesions the fibrin is replaced by crowded and thick collagen bundles.

In foreign body reactions to triamcinolone the histological exam shows a pale basophilic material, devoid of needle-like clefts and with a foamy appearance [4].

In *calcinosis cutis*, the calcium compounds are extensively basophilic in sections of tissue stained with hematoxilin and eosin and stain black with von Kossa silver stain (Figure 4).

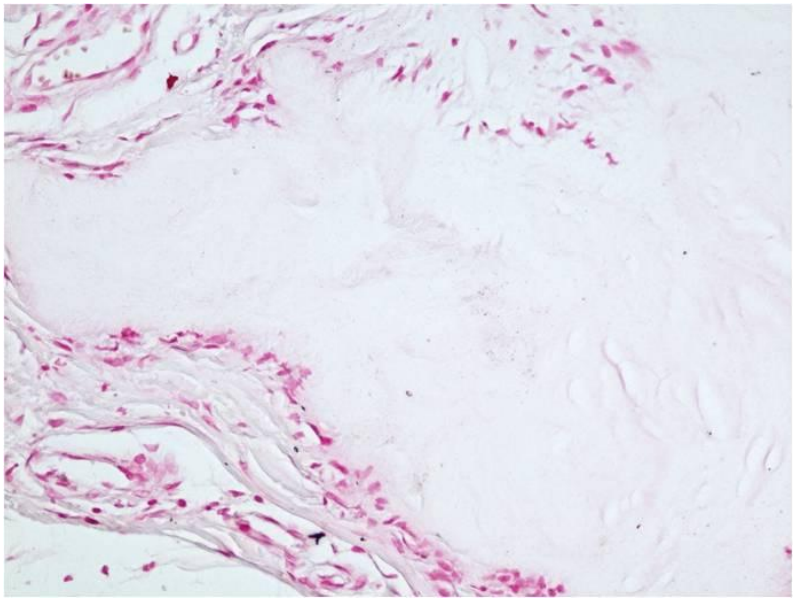

Figure 4. Negative von Kossa stain to exclude the diagnosis of calcinosis cutis (x200).

Pseudogout is a form of arthritis due to deposits of calcium pyrophosphate dihydrate crystals within the large joints, especially the knees. The histological exam shows shorter and often romboid crystals with a weakly positive birefringence [7].

Silica granuloma is an uncommon condition and it represents a chronic reaction to silica crystals, which were traumatically introduced into the dermis. Histological exam shows an epitheloid granuloma that may resemble sarcoidosis; however, polarized light will show birefringent foreign material. To confirm this diagnosis there are two useful analyses, scanning electron microscopy and energy dispersive X-ray microanalysis which are not widely used.

Chondrodermatitis nodularis chronica helicis is a common, benign, painful condition of the helix or antihelix of the ear. It often affects middle-aged or older men. The exact cause of this disease is unknown, although it is believed that it is caused by prolonged and excessive pressure. In most cases, the diagnosis is a clinical one because of typical history of a painful lesion on the ear and the appearance of a small tender papule that may be ulcerated. Sometimes the diagnosis is made on skin biopsy which shows a zone of eosinophilic fibrinoid material overlying the affected area of cartilage. Frequently, superficial epidermal ulceration occurs.

Conclusions

Most frequently the diagnosis of gout tophi is based on clinical findings correlated with high levels of serum uric acid and a personal medical history of gout. In atypical cases and without recent lab tests, skin biopsy may help establishing the correct diagnosis. Monosodium urate crystals can be easily identified under polarized light only if the biopsies are submitted in alcohol fixative. However, the clinical diagnosis is not always made because tophi may be the initial findings of gout or because they may have atypical features mimicking other entities as discussed above. In our study, in 10 out of 13 cases the clinical diagnosis of gout was not suspected and the skin biopsies were submitted in formalin fixative.

The main histological pattern, found in 12 out of 13 cases, was palisading granuloma surrounding masses of basophilic material. These masses were located in the dermis or/and in the subcutis. They were usually large in size and were associated with epithelioid histiocytes in the periphery and a small number of foreign body multinucleate giant cells. Lymphocytic inflammatory infiltrate was sparse. The infiltrate in ulcerated lesions contained neutrophils. We may conclude that the histological findings were pretty characteristic and they allowed us to establish the diagnosis using HE stained sections and several other additional stains. However, if classical findings are sparse or masked by reactive changes, the diagnosis is more difficult and it could be necessary to repeat the biopsy using the correct fixative and exam under polarized light.

Correct diagnosis is essential as tophi could be the first symptom of systemic hypeuricemia and the clinician should be accurately alert in order to initiate the appropriate treatment.

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