

Characteristics of ocular abnormalities in gout patients

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Abstract

• **AIM:** To characterize the clinical features of ocular surface in gout patients in coastal area of Shandong Province in China.

• **METHODS:** A total of 380 consecutive gout patients were examined from January 2011 to May 2011. According to the course of gout, patients were divided into group A (<5 years), B (5–10 years) and C (>10 years). Group D (control group) was consist of 50 healthy subjects. Eyelids, lateral canthus, medial canthus, palpebral conjunctiva, sclera and cornea, anterior chamber, lens, anterior vitreous were examined by slit lamp to find whether there were deposition of uric acid crystals, ocular vascular tortuosity, redness and subconjunctival hemorrhage. The ophthalmic exams of visual acuity, intraocular pressure, fundus were used to assess any gout-related eye disease.

• **RESULTS:** Uric acid crystals were found in 3 patients and the positions of the deposite were in corneal stroma, corneal epithelium and superficial stroma, and sclera respectively. The incidence was 0.79%. Dilated and tortuous blood vessels in conjunctiva and sclera surface were found in 38 (23.8%), 40 (44.0%), 58 (45.0%), 9 (18.0%) patients in groups A, B, C and D, respectively. The differences between group B and D, group C and D were statistically significant ($P < 0.01$, $P < 0.01$). Transparent vesicles with metal-like reflected light in subconjunctiva were seen in 26 (16.2%), 29 (31.9%), 41 (31.8%), 2 (4.00%) patients in groups A, B, C and D, respectively. The differences between A and D, B and D, C and D were statistically significant ($P < 0.05$, $P < 0.01$, $P < 0.01$). Subconjunctival hemorrhage was found in all groups, the difference among the four groups showed no statistically significance.

• **CONCLUSION:** Gout can cause ocular surface abnormalities, such as tophi deposition, subconjunctival transparent vesicles and hemorrhage, and vascular

changes. These features have important clinical significance in early detection of the gout and prevention of eye injury.

• **KEYWORDS:** ocular abnormalities; gout; tophi

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INTRODUCTION

Gout is one of the most common auto-inflammatory arthritis characterized by the rise of serum urate and recurrent attacks of intra-articular crystal deposition of monosodium urate (MSU), with a prevalence of approximately 8 per 1 000 persons of all ages [1,2]. Both the incidence and the prevalence of gout are increasing worldwide [3,4]. Rates of gout have approximately doubled between 1990 and 2010 [5]. Tophi can be found in the conjunctiva, cornea, iris, sclera, lens and other eye tissues, and can cause increase of intraocular pressure, inflammation of iris and ciliary, and so on [6-8]. Though ocular manifestations of gout have been reported, most of them are case reports. The clinical features of gout patients' ocular surface in coastal area, however, have not been well characterized in literatures.

SUBJECTS AND METHODS

Subjects The study was based on the data of 380 gout patients from the Gout Study Center in the Affiliated Hospital of Qingdao University Medical College from January 2011 to May 2011. All patients came from the coastal areas of Shandong Province.

According to the American Rheumatism Association Diagnostic Criteria (ACR) 1997, gout was diagnosed with any one of the following three criteria: 1) specific for synovial fluid urate crystals, 2) by chemical methods or polarized light microscopy confirmed tophus containing urate crystals, or 3) six out of the following 12 features (clinical, laboratory, X-ray findings): 1) acute arthritis attacks more than once; 2) inflammatory response in the peak within 1 day; 3) single-arthritis onset; 4) visible red joints; 5) the first metatarsophalangeal joint pain or swelling; 6) unilateral first metatarsophalangeal joint involvement; 7) unilateral tarsal joint involvement; 8) suspected tophi; 9) hyperuricemia; 10) asymmetric swelling within the joint (X-ray confirmed); 11)

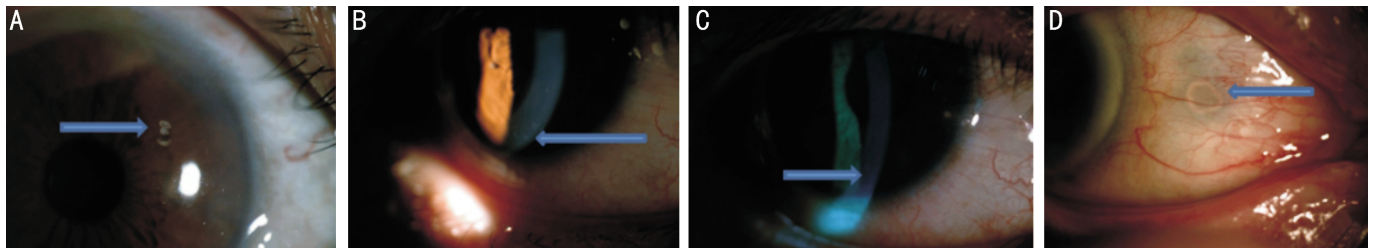


Figure 1 Three cases of uric acid crystals deposit in ocular surface A: 3 white crystals in the superficial stroma of cornea; B: A cluster of crystals in the epithelium and superficial layers of cornea; C: The fluorescein staining of these deposits; D: A chalky-white crystal in nasal superficial sclera.

no bone erosion subcutaneous bone cyst (X-ray confirmed); 12) arthritis synovial fluid attack of bacterial culture negative, except for those patients with secondary gout.

A total of 380 gout patients underwent a detailed eye examination by an experienced ophthalmologist. These patients were divided into group A, B and C according to the course of disease. Group D (control group) had 50 healthy subjects whose ages were between 20 and 76. Group A (<5 years) had 160 patients with ages range from 18 to 72 years old; group B (5-10 years) had 91 patients with ages between 22 and 77 years old; group C (>10 years) had 129 patients with ages range from 38 to 81 years old. Patients in group D had no hypertension, diabetes, gout and other systemic diseases.

Methods Visual acuity, intraocular pressure and fundus were checked routinely. Eyelids, lateral canthus, medial canthus, eyelid conjunctiva, sclera and cornea, anterior chamber, lens, anterior vitreous were examined by slit lamp to find whether there were deposition of uric acid crystals, ocular vascular tortuousness, redness or subconjunctival hemorrhage. Topcon's SL-DT Camera was used to make pictures.

Statistical Analysis SPSS 17.0 statistical software package was used to analyze these data. Results were compared by the Chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Uric acid crystal deposit in ocular surface In 380 cases, uric acid crystal deposit in ocular surface was found in three patients, the incidence was 0.79%. Two deposits were in the cornea. Patients whose deposits were in the cortex of cornea had a 20-year history of gout. Both eyes revealed a mild hyperemia in conjunctiva and superficial of sclera, some of the blood vessels were tortuous and thickened. Three white crystals with irregular shape were found in the right eye, each measuring about 0.3mm×0.5mm in the superficial stroma of cornea, separated from the other transparent cornea by a clear high density ring-like zone (Figure 1A). There was no clinical sign of inflammation in or around the crystals. Laboratory analysis revealed remarkable increase of uric acid (558 μ mol/L, normal range, 150-420) when the crystals were found for the first time. Tophus were found in the roots of the left index finger.

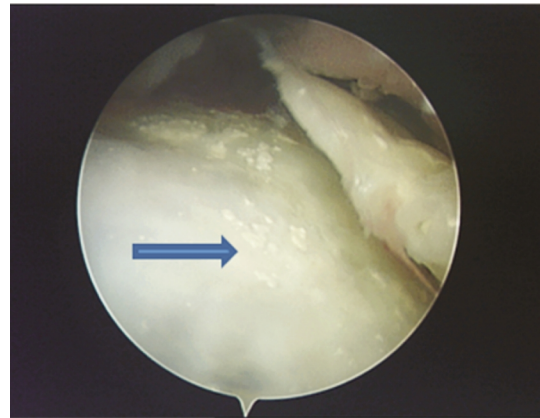


Figure 2 Tophi deposits were found in the left popliteal fossa articular capsule.

Other patients whose deposits were in the epithelium and superficial stroma of cornea had a 3-year history of gout. The right eye near the bottom margin of the cornea revealed a cluster of irregular, flake-like crystals in the epithelium and superficial layers of cornea, which was slightly higher than in corneal surface (Figure 1B). The fluorescein staining of the deposits was negative (Figure 1C). No clinical sign of inflammation in or around the deposits was found. Laboratory analysis revealed significant increase of uric acid (627 μ mol/L). Tophi deposits were found in the left popliteal fossa articular capsule (Figure 2).

Uric acid crystal deposit was found in sclera of the third patient with 12-year history of gout. His right eye revealed a chalky-white crystal with irregular shape, measuring about 3mm×4mm in size in the nasal superficial sclera, separated from the other sclera by a clear high density ring-like zone (Figure 1D). No clinical sign of inflammation in or around the crystals was found. The blood vessels of bulbar conjunctiva thickened and were slightly tortuous. More tophi deposits were seen in both ears and feet. Laboratory analysis revealed increased uric acid (462 μ mol/L).

Tortuous vessels in the conjunctiva and sclera surface

We found many patients of gout had seriously tortuous vessels in the conjunctiva and sclera surface (Table 1). Some of the tortuous blood vessels were spiral (Figure 3A). It was observed that most of the cases were asymptomatic. The tortuous vessels in the conjunctiva and sclera surface of the

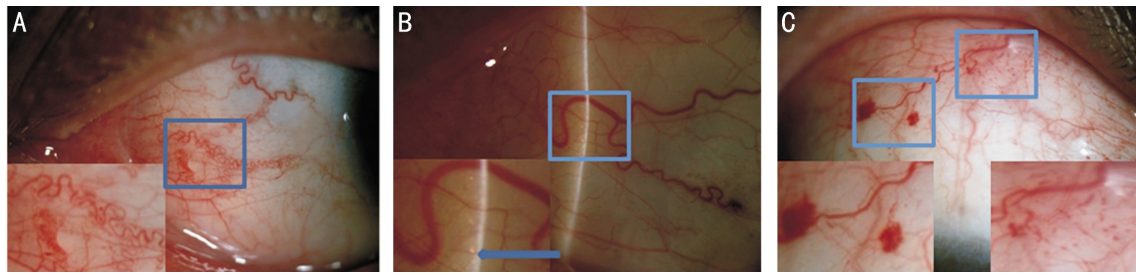


Figure 3 A: Tortuous blood vessels were found in the conjunctiva and sclera surface; B: Transparent vesicles with metal-like reflective in subconjunctival were found around the tortuous vessels; C: Subconjunctival hemorrhage.

gout patient are not unique. There were 12 patients in group D who also had tortuous blood vessels though no patients had spiral vessels. The percentage of patient with tortuous vessels was significantly increased in the conjunctiva and sclera surface in group B and C compared with those in the group D ($P < 0.01$, Table 1). While the difference between group A and D was not statistically significant.

Transparent vesicles with metal-like reflective in subconjunctiva Many patients involved in gout were found to have transparent vesicles with metal-like reflection in subconjunctiva (Table 2). Most of the vesicles were found around the tortuous vessels (Figure 3B). Transparent vesicles were found also in group with low incidence. An increased percentage (>4 times) of transparent vesicles was seen in group A than that in D group. The percentage of transparent vesicles in group B was similar to that in C group and nearly two times more than that in group A (Table 2).

Subconjunctival hemorrhage There were 12 (7.50%), 9 (9.90%), 11 (8.50%) patients with subconjunctival hemorrhage in group A, B and C, respectively (Figure 3C). These hemorrhage was multifocal, spot and little patchy, not like the ordinary large areas of subconjunctival hemorrhage. Group D had no subconjunctival hemorrhage (Table 3). The subconjunctival hemorrhage was asymptomatic. All patients' visual acuity and intraocular pressure was normal. Tobramycin and dexamethasone eye drops were instilled 4 times a day for two weeks. The hemorrhage had no change after 2 weeks and was still not absorbed after 3 months.

DISCUSSION

In recent years, a large number of epidemiological studies show that the incidence of gout is increasing. The prevalence of gout reached at least 1% of population in Western countries [8]. The incidence of gout reached 1.14% in China, especially in some coastal cities [10]. Gout has become a serious disease which threatens human health. But few attentions have been paid to the ocular complication caused by gout. In this study, we screened a total of 380 gout patients and found that unusual ocular complications caused by gout are far beyond people's imagination.

Tophi are nodules caused by chronic inflammation and the

Table 1 Tortuous vascular in the conjunctiva and sclera

Groups	Cases	%	χ^2_a	P
A(n=160)	38	23.8	0.725	>0.05
B(n=91)	40	44.0	9.59	<0.01
C(n=129)	58	45.0	11.2	<0.01
D(n=50)	9	18.0		
χ^2		17.4		
P		<0.01		

χ^2_a vs group D.

Table 2 Transparent vesicles with metal-like reflection

Groups	Cases	%	χ^2_a	P
A(n=160)	26	16.2	4.95	<0.05
B(n=91)	29	31.9	14.6	<0.01
C(n=129)	41	31.8	15.2	<0.01
D(n=50)	2	4.0		
χ^2		11.9		
P		<0.01		

χ^2_a vs group D.

Table 3 Subconjunctival hemorrhage

Groups	Cases	%	χ^2_a	P
A(n=160)	12	7.50	2.71	>0.05
B(n=91)	9	9.90	3.76	>0.05
C(n=129)	11	8.50	3.18	>0.05
D(n=50)	0			
χ^2		0.433		
P		>0.05		

χ^2_a vs group D.

proliferation of fibrous tissue swelling because sodium urate crystals deposit in the tissue. According to the physical and chemical theory, the higher the uric acid and supersaturation are, the easier the crystals precipitated. The uric acid concentration is very high in some gout patients, but sometimes is not so high. It shows that the incidence of uric acid crystals is not only associated with uric acid concentration, but also with other factors. The process of uric acid crystals' dissolution and deposition is involved in

multi factors and could result in the physical and chemical equilibrium state finally. The occurrence of crystallization can be comprehended that the balance transfer to the crystal orientation in the condition of one or more factors changed. In the eye, precipitation of urate crystal has been described in eyelids, tarsal plates, conjunctiva, cornea, sclera, tendons of extraocular muscles, orbit, and lens [11-18]. It was reported that tophi can be deposited in the iris or in the anterior chamber, causing anterior uveitis or glaucoma [19]. In addition to the above factors, eye tophi deposition is also associated with a variety of special ocular surface structure. Ocular structures may be a poorer solvent for monosodium urate than plasma; with hyperuricemia, the urates become supersaturated particularly with lower temperatures. With prolonged hyperuricemia, crystals and microtophi develop in the conjunctiva. Inorganic crystals, including monosodium urate, can stimulate the formation of specific antibodies, which is able to rapidly accelerate the formation of new crystals [20].

We examined eyes of 380 gout patients and discovered 3 patients with uric acid crystals in their ocular surface. These patients' characteristics including medical history, eye examination, the shape and the location of deposits and without inflammation in ocular surface, were highly consistent with those tophi that previously reported in literature. So we highly suspected these deposits as tophi, especially the patients with uric acid crystal deposits in the sclera, whose eyes had been ophthalmological examined 8 years ago and no crystal deposits were found in sclera surface at that time. We inferred that with the prolonged hyperuricemia, urate crystals and microtophi developed in the sclera. The patient also had many trophi in both ears, finger roots, feet and kidney. These multiple tophi were not only due to the physical and chemical factors, hyperuricemia, but also to the hereditary susceptibility. The shape of the deposits that located in the cortex of cornea was very similar to which located in the sclera. All of them were irregularly shaped, chalky-white crystalline substances, rounded by a clear high density ring-like zone. Therefore we proposed that these deposits were associated with gout. The deposits had no direct relationship with the course of gout, because there was one patient with deposit in ocular surface in groups A, B, C respectively. Although most patients with tophi have had gout for many years, the presence of a tophus may be the initial sign of the disease [16]. Serum uric acid levels, ocular local special organizational structure, hereditary susceptibility, flow velocity, temperature and other factors may control the situation.

Ferry *et al* [6] reported that the most common abnormality was bilateral ocular redness caused by hyperemia of the

conjunctival and episcleral vessels. When evaluating a patient who is troubled by bilateral chronic conjunctival redness, the clinician should consider gout in the differential diagnosis. Bakhritdinova [21] reported a Morphometry of the bulbar conjunctiva vessels in 50 patients with gout was carried out by television capillaroscope with videorecording. The findings indicated that microcirculatory disorders start with dilatation of the venules, in which arterioles and capillaries are involved. This results in alteration of the arteriovenular coefficient and of the blood flow velocity in the capillaries. Hence, the metabolic form of gout may be regarded as the initial stage of disease. These reports are similar to our clinical observations. Thirty eight patients in group A were found with ocular surface changes in blood vessels, including tortuosity, spiral, thick, conjunctival congestion. These changes in group A confirmed the vascular changes in early stage. Moreover, the incidences of ocular vascular changes in group B and C increased compared to that in group A. The differences were statistically significant. In addition, the presence of objective signs and the course of gout were correlated.

There were 12, 9, 11 patients respectively in group A, B and C had unexplained asymptomatic subconjunctival hemorrhage that was not like the ordinary subconjunctival hemorrhage. The differences among the three groups were not statistically significant (Table 3). Our findings suggested that the hemorrhage has no relationship with the duration of gout. As we all know that most ordinary subconjunctival hemorrhage would be absorbed in 2 to 3 weeks. But the subconjunctival hemorrhage in gout patients had no change after 2 weeks with Tobramycin and dexamethasone eye drops instilled topically and was not absorbed after 3 months. This is another important point that can make a distinction between subconjunctival hemorrhage in gout patients and that in other patients. Twenty six, 29, 41, 2 patients in A, B, C, D groups respectively were found to have transparent vesicles with metal-like reflection in subconjunctival. The differences among group A, B, C were statistically significant. This is a strong point to indicate that these vesicles increased with the course of gout.

Though confirmed urate crystals in the eyes were reported rarely in the past 40 years, the occurrence of ocular abnormality caused by gout is far beyond people's imagination. One reason is that the majority of gout patients' ocular abnormalities are asymptomatic. The other reason is not only patients but also ophthalmologists are short of the knowledge of ocular abnormality caused by gout. Ophthalmologists should take gout into account when they discover a deposit, serious ocular vascular changes, metal-like transparent vesicles and multifocal, spot and little

patchy subconjunctival hemorrhage for the first time. Further screening of a large sample will be summed up more ocular abnormalities in patients with gout and help to diagnose in the early stage of gout.

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