

ลักษณะทางคลินิกของผู้ป่วยโรคเกาต์เรื้อรังร่วมกับปุ่มก้อนโทฟัสที่คลินิกโรคข้อ
โรงพยาบาลหนองคาย

Clinical Characteristics of Patients with Chronic Tophaceous Gout
at the Rheumatology clinic, Nongkhai Hospital

จินตาทรา มังคะละ, พ.บ.*

JintaraMangkala, M.D*

*กลุ่มงานอายุรกรรม โรงพยาบาลหนองคาย จังหวัดหนองคาย ประเทศไทย 43000

*Division of Internal Medicine, Nongkhai Hospital, Nong Khai Province, Thailand, 43000

Corresponding Author, E-mail: jintaramangkala@gmail.com

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บทคัดย่อ

- หลักการและเหตุผล** : โรคเกาต์เป็นโรคข้ออักเสบที่พบได้บ่อยที่สุดทั่วโลก มีความชุกตั้งแต่ร้อยละ 1-6.8 และอุบัติการณ์ 0.6-2.9 ต่อ 1,000 รายต่อปีแล้วแต่การศึกษา ในขณะที่โรคเกาต์เรื้อรังร่วมกับปุ่มก้อนโทฟัสมักเป็นโรคที่เป็นมานานและการควบคุมระดับกรดยูริกไม่ดีทำให้เกิดการติดของข้อ ข้อผิดรูป และก่อให้เกิดผลกระทบต่อคุณภาพชีวิตในด้านสุขภาพ
- วัตถุประสงค์** : เพื่อประเมินลักษณะทางคลินิกของผู้ป่วยโรคเกาต์เรื้อรังร่วมกับปุ่มก้อนโทฟัสที่คลินิกโรคข้อ โรงพยาบาลหนองคาย
- วิธีการศึกษา** : นำเวชระเบียนผู้ป่วยโรคเกาต์ที่มารับการรักษาที่คลินิกโรคข้อ โรงพยาบาลหนองคาย ตั้งแต่ พ.ศ.2553-2563 มาทบทวนแบ่งผู้ป่วยเป็น 2 กลุ่มได้แก่ กลุ่มที่มีปุ่มก้อนโทฟัสและไม่มีปุ่มก้อนโทฟัส แล้วเก็บข้อมูลลักษณะทางคลินิกต่างๆ
- ผลการศึกษา** : ผู้ป่วยทั้งหมด 585 ราย เป็นผู้ป่วยที่มีปุ่มก้อนโทฟัส 126 ราย (ร้อยละ 21.5) และไม่มีปุ่มก้อนโทฟัส 459 ราย (ร้อยละ 78.5) ลักษณะทางคลินิกของผู้ป่วยโรคเกาต์เรื้อรังร่วมกับปุ่มก้อนโทฟัสได้แก่ ระยะเวลาที่เป็นโรค ≥ 5 ปี ($p=0.001$) ประวัติยาสมุนไพรรักษา ($p=0.006$) ระดับกรดยูริกก่อนรักษา ≥ 8 มก./ดล. ($p=0.001$) , ระดับฮีโมโกลบินก่อนรักษา < 12 มก./ดล. ($p=0.010$) การใช้ยา losartan ($p=0.004$) การรักษาด้วยยาลดกรดยูริกหลายชนิดร่วมกัน ($p=0.034$) และการควบคุมระดับกรดยูริกไม่ดี ($p=0.033$)
- สรุป** : จากการศึกษานี้พบว่าระยะเวลาที่เป็นโรค ≥ 5 ปี ประวัติยาสมุนไพรรักษา ระดับกรดยูริกก่อนรักษา ≥ 8 มก./ดล. ระดับฮีโมโกลบินก่อนรักษา < 12 มก./ดล. การใช้ยา losartan, การรักษาด้วยยาลดกรดยูริกหลายชนิดร่วมกัน และการควบคุมระดับกรดยูริกไม่ดีเป็นลักษณะทางคลินิกของผู้ป่วยโรคเกาต์เรื้อรังร่วมกับปุ่มก้อนโทฟัสซึ่งควรมีการติดตามการรักษาและป้องกันภาวะแทรกซ้อนต่างๆ อย่างใกล้ชิด
- คำสำคัญ** : ปัจจัยเสี่ยง ปัจจัยในการทำงาน ปุ่มก้อนโทฟัส ปุ่มก้อนโทไฟ โรคเกาต์เรื้อรัง ระดับกรดยูริกในเลือดสูง

ABSTRACT

- Background** : Gout is the most common inflammatory arthritis worldwide, with a prevalence ranging from 1-6.8% and an incidence of 0.6-2.9 per 1,000 cases per year, depending on the studies. Meanwhile, chronic tophaceous gout is usually a long-standing and inadequate serum urate control disease, subcutaneous tophi are the causes of joint restriction and deformity, and impact on health-related quality of life.
- Objective** : To assess clinical characteristics of patients with chronic tophaceous gout at the Rheumatology clinic, Nongkhai Hospital.
- Methods** : The medical records of gouty arthritis patients treated at the Rheumatology clinic, Nongkhai Hospital between 2010 and 2020 were reviewed. Patients were divided into the tophaceous and non-tophaceous groups. Clinical characteristics were explored.
- Results** : Of 585 patients, 126 (21.5%) and 459 (78.5%) of patients were the tophaceous and non-tophaceous groups, respectively. Clinical characteristics of patients with chronic tophaceous gout including duration of disease ≥ 5 years ($p=0.001$), a history of herbal medicine ($p=0.006$), initial uric acid ≥ 8 mg/dL ($p=0.001$), initial Hb < 12 mg/dL ($p=0.010$), losartan used ($p=0.004$), combined urate lowering therapy ($p=0.034$), and inadequate treatment ($p=0.033$).
- Conclusion** : The present study had identified duration of disease ≥ 5 years, a history of herbal medicine, initial uric acid ≥ 8 mg/dL, initial Hb < 12 mg/dL, losartan used, combined urate-lowering therapy, and inadequate treatment as clinical characteristics of patients with chronic tophaceous gout, which should be provided close monitoring and preventing complications.
- Keywords** : Risk factor, Predictor, Tophus, Tophi, Chronic gouty arthritis, Hyperuricemia

BACKGROUND

Gout is the most common inflammatory arthritis worldwide, with a prevalence ranging from less than 1-6.8% and an incidence of 0.6-2.9 per 1,000 cases per year, depending on the studies⁽¹⁾. Meanwhile, chronic tophaceous gout is usually a long-standing, misdiagnosed, and inadequate serum urate control disease⁽¹⁻⁷⁾. Pathologically, the tophus consists of chronic foreign-body granulomatous inflammatory tissue surrounding collections of monosodium urate crystals, and consequently, present as a draining

or chalk-like subcutaneous nodule which typically located in the first metatarsophalangeal joint, ears, olecranon bursa, finger pads, and Achilles' tendon^(1, 5-7). As a result, subcutaneous tophi are the causes of joint restriction and deformity, ulceration with superimposed bacterial infection, and impact on health-related quality of life⁽¹⁻⁷⁾. Recent advances in gout therapeutics including the American College of Rheumatology clinical practice guidelines 2020 have expanded urate-lowering therapy options

for patients with chronic tophaceous gout to allow faster regression of tophi and improved health-related quality of life⁽⁸⁻¹²⁾. For the above reasons, the present study was performed to assess clinical characteristics of patients with chronic tophaceous gout at the Rheumatology clinic, Nongkhai hospital. Therefore, we can apply the knowledge gained to provide close monitoring of the treatment and prevention in gouty arthritis patients who risk of developing tophi.

MATERIAL AND METHODS

This was a retrospective study of gouty arthritis patients (ICD-10 M100-109) treated at the Rheumatology clinic, Nongkhai Hospital between 2010 and 2020. The study was approved by the institutional ethics committee. Data were collected onto a medical record form including address, nationality, age, sex, body mass index, alcoholic intake, smoking, history of herbal medicine, age of onset, duration of disease, medical illness, medications, duration of treatment, blood pressure, uric acid levels, glomerular filtration rate (GFR), alanine aminotransferase (ALT), hemoglobin (Hb) before and after treatment, adequate of treatment (serum uric acid \leq 5.0 mg/dl and \leq 5.5 mg/dl in patients with or without tophi, respectively), history of drugs discontinuation and follow up. Patients were divided into the tophaceous and non-tophaceous groups. Variable factors were explored between the two groups. Statistical analysis was done by using SPSS version 23.0. Chi-square test or Fisher's exact test, unpaired sample T-test, and multiple logistic regression were used to analyze between the two groups. The *p-value* < 0.05 was considered statistically significant.

Potential conflicts of interest : none

Ethics approval : Ethics approval was attained from The Research Ethics Committee (REC) at Nongkhai Hospital (No. 2/2565)

RESULTS

There was a total of 616 gouty arthritis patients at the Rheumatology clinic, Nongkhai Hospital between July 2010 and December 2020. 31 cases could not be collected completely. A total of 585 eligible patients were enrolled, 513 were males (87.7%) with mean age (standard deviation) of 62.9 (12.1) years. Females had onset of gout at 62.0 (10.3) years, while males were 53.0 (12.7) years. Patients often have co-morbidity diseases, including hyperlipidemia, chronic kidney disease, obesity, hypertension, diabetes mellitus type 2, and fatty liver. 23.8 % and 21.0% of patients had a history of alcohol abuse and herbal medicine used, respectively. The median duration of disease and treatment were 8.72 (6.9) and 4.4 (2.6) years, respectively (Table 1). Up to 74.4% of patients were diagnosed by clinical and uric acid levels > 7.0 mg/dl. Mean uric acid levels before and after treatment was 9.3 (1.5), 3.5 (1.2) mg/dl, respectively. Mean GFR before and after treatment was 65.5 (25.5), 66.9 (25.2) ml/min, respectively. Mean ALT before and after treatment was 29.0 (0.7), 30.2 (1.1) units per liter, respectively. Mean systolic blood pressure (SBP) before and after treatment was 127.5 (14.1), 127.4 (13.5) mm Hg, respectively. Mean diastolic blood pressure (DBP) before and after treatment was 76.8 (9.4), 76.1 (8.8) mm Hg, respectively. Patients received aspirin 18.8%, diuretics 5.3%, losartan 22.9%, and fenofibrate 0.7%. They lose follow-up of 0.2 (0.02) times

per year, with a mean gouty attack of 0.2 (0.02) times per year. Of 45.8% of patients were treated with allopurinol plus benzbromarone, 39.0% of allopurinol, and 9.4% of benzbromarone. Allopurinol and benzbromarone allergies were 2.7% and 0.7%, respectively. Urate-lowering therapy (ULT) was discontinued by the physicians and the patients 1.5% and 20.2%, respectively. There were 94.0% and 90.3% of patients achieved target uric acid levels at 1 year and throughout treatment. 126 (21.5%) and 459 (78.5%) of patients are the tophaceous and

non-tophaceous groups, respectively. Clinical characteristics of patients with chronic tophaceous gout including duration of disease ≥ 5 years ($p=0.001$), a history of herbal medicine ($p=0.006$), initial uric acid ≥ 8 mg/dL ($p=0.001$), initial Hb < 12 mg/dL ($p=0.010$), losartan used ($p=0.004$), combined urate-lowering therapy ($p=0.034$), and inadequate treatment ($p=0.033$). (Table 2, 3).

TABLE 1 Comparison between the tophaceous and non-tophaceous groups categorized by baseline characteristic of patients

Characteristics	Tophaceous =126	Non-tophaceous = 459	Crude OR	p
	N (%)	N (%)		
Address: Others	80 (13.7%)	329 (56.2%)	1.455	0.076
Nationality: Foreigners	121 (20.7%)	448 (76.6%)	1.683	0.356
Sex: Male	115 (19.7%)	398 (68.0%)	1.603	0.168
Age < 60 years	82 (14.0%)	293 (50.1%)	1.056	0.796
Age of onset ≤ 30 years	8 (1.4%)	14 (2.4%)	2.155	0.109
Duration of disease ≥ 5 years	112 (19.1%)	295 (50.4%)	4.447	0.001*
Alcoholic intake	26 (4.4%)	113 (19.3%)	0.796	0.352
Smoking	6 (1.0%)	27 (4.6%)	0.800	0.629
Herbal medicine used	41 (7.0%)	82 (14.0%)	2.218	0.001*
BMI ≥ 25.0 kg/m ²	42 (7.2%)	200 (34.2%)	0.648	0.039*
Before treatment				
• Uric acid ≥ 8 mg/dl	116 (19.8%)	343 (58.6%)	3.923	0.001*
• GFR < 60 ml/min	63 (10.8%)	114 (31.5%)	1.495	0.046*
• ALT > 40 units/L	25 (4.3%)	98 (16.8%)	0.912	0.713
• Hb < 12 mg/dL	62 (10.6%)	157 (26.8%)	1.863	0.002*
Medical illness				
• DLP	97 (16.6%)	394 (67.4%)	0.552	0.017*
• CKD	98 (16.8%)	313 (53.5%)	1.633	0.037*
• HT	73 (12.5%)	269 (46.0%)	0.973	0.893
• IFG/DM	77 (13.2%)	301 (51.5%)	0.825	0.353
• Fatty liver	11 (1.9%)	68 (11.6%)	0.550	0.077
• Renal stones	19 (3.2%)	54 (9.2%)	1.332	0.319
• CVA	5 (0.9%)	35 (6.0%)	0.501	0.150
• IHD	8 (1.4%)	25 (4.3%)	1.177	0.697

TABLE 1 Comparison between the tophaceous and non-tophaceous groups categorized by baseline characteristic of patients (continued)

Characteristics	Tophaceous =126 N (%)	Non-tophaceous = 459 N (%)	Crude OR	p
Medications				
• Aspirin	26 (4.4)%	84 (14.4)%	1.161	0.553
• Diuretics	3 (0.5)%	28 (4.8)%	0.375	0.099
• Non-prescribed losartan	89 (15.2)%	362 (61.9)%	0.645	0.051
• Non-prescribed fenofibrate	125 (21.4)%	456 (77.9)%	0.822	1.000
Singled ULT	55 (9.4)%	240 (41.0)%	1.404	0.086
Inadequate treatment	20 (3.4)%	36 (6.2)%	2.217	0.007*
Loss follow up	61 (10.4)%	200 (34.2)%	1.215	0.333
Duration of treatment ≥ 5 yrs	49 (8.4)%	193 (33.0)%	0.877	0.524
Gout flares	67 (11.5)%	155 (26.5)%	2.227	0.001*
Drugs discontinuation	33 (5.6)%	94 (16.2)%	1.378	0.168

* $p < 0.05$ (statistically significant)

TABLE 2 Compare means between the tophaceous and non-tophaceous groups categorized by baseline characteristic of patients

Characteristics	Tophaceous N = 126	Non-tophaceous N = 459	95% CI		p
			Lower	Upper	
BMI (kg/m ²)	23.756	24.955	-2.003061	-0.395650	0.004*
Age of onset (yrs)	49.484	55.473	-8.3847	-3.5926	0.001*
Duration of disease (yrs)	13.16	7.50	4.161	7.163	0.001*
Initial SBP (mmHg)	128.97	127.06	-1.138	4.961	0.218
Initial DBP (mmHg)	77.36	76.70	-1.238	2.553	0.495
Initial uric acid (mg/dL)	10.099	9.062	0.7275	1.3462	0.001*
Initial GFR (ml/min)	64.545	65.768	-6.4418	3.9969	0.645
Initial Hb (mg/dL)	11.967	12.712	-1.1956	-0.2930	0.001*
Initial ALT (units/L)	26.19	29.79	-7.039	-0.162	0.040*
Duration of treatment (yrs)	4.47	4.40	-0.453	0.592	0.793
Gout flares (times/yr)	0.316	0.183	0.0383	0.2282	0.006*
Loss follow up (times/yr)	0.249	0.213	-0.0404	0.1127	0.353

* $p < 0.05$ (statistically significant)

TABLE 3 Comparison between the tophaceous and non-tophaceous groups categorized by baseline characteristic of patients

Characteristics	Tophaceous N = 126	Non-tophaceous N = 459	Adjusted OR	95% CI		p
				Lower	Upper	
Address: Others	80 (13.7)%	329 (56.2)%	1.591	0.983	2.574	0.059
Sex: Male	115 (19.7)%	398 (68.0)%	1.592	0.711	3.565	0.258
BMI \geq 25.0 kg/m ²	42 (7.2)%	200 (34.2)%	0.861	0.515	1.440	0.568
Age of onset \leq 30 yrs	8 (1.4)%	14 (2.4)%	2.450	0.823	7.290	0.107
Duration of disease \geq 5 yrs	112 (19.1)%	295 (50.4)%	5.207	2.726	9.947	0.001*
DLP	97 (16.6)%	394 (67.4)%	0.583	0.313	1.088	0.090
CKD	98 (16.8)%	313 (53.5)%	1.230	0.695	2.174	0.477
CVA	5 (0.9)%	35 (6.0)%	0.615	0.208	1.818	0.379
Fatty liver	11 (1.9)%	68 (11.6)%	0.585	0.269	1.274	0.177
Herbal medicine used	41 (7.0)%	82 (14.0)%	2.076	1.229	3.505	0.006*
Initial uric acid \geq 8 mg/dl	116 (19.8)%	343 (58.6)%	3.623	1.750	7.502	0.001*
Initial GFR $<$ 60 ml/min	63 (10.8)%	114 (31.5)%	1.094	0.640	1.871	0.742
Initial Hb $<$ 12 mg/dL	62 (10.6)%	157 (26.8)%	1.898	1.165	3.093	0.010*
Singled ULT	71 (12.1)%	219 (37.4)%	0.592	0.365	0.962	0.034*
Diuretics	3 (0.5)%	28 (4.8)%	0.338	0.091	1.249	0.104
Non-prescribed losartan	89 (15.2)%	362 (61.9)%	0.465	0.275	0.787	0.004*
Drugs discontinuation	33 (5.6)%	94 (16.2)%	0.868	0.505	1.495	0.610
Gout flares	67 (11.5)%	155 (26.5)%	1.551	0.977	2.460	0.062
Inadequate treatment	20 (3.4)%	36 (6.2)%	2.198	1.065	4.537	0.033*

* $p < 0.05$ (statistically significant)

DISCUSSION

A total of 585 eligible patients were enrolled. Of 126 (21.5%) and 459 (78.5%) of patients were the tophaceous and non-tophaceous groups, respectively. Most patients had co-morbidity diseases including hyperlipidemia, chronic kidney disease, obesity, hypertension, diabetes mellitus type 2, fatty liver, which were the same as previous studies^(13, 14). Patients were given a mean dose of allopurinol 495.85 mg/case, benzbromarone 96.83 mg/case, febuxostat 78.75 mg/case, consistent with previous studies suggesting that the physicians should gradually increase the dose of allopurinol

(dose escalation)⁽¹⁵⁻¹⁹⁾, use of allopurinol at doses greater than 300 mg^(20, 21), or consider concomitant prescribe allopurinol with benzbromarone in patients unresponsive to a single drug⁽²²⁻²⁴⁾, to achieve targeted uric acid levels. In several studies, febuxostat has been effective in reducing uric acid levels to the target with fewer side effects compared to allopurinol^(21, 25-27), but only 32 patients were enrolled in this study (because it had been used in the hospital in the last 2-3 years).

Furthermore, there were 94.0% and 90.3% of patients achieved target uric acid

levels at 1 year and throughout treatment. The patients had a mean gout flare of 0.2 (0.02) times per year throughout treatment, which was better than other studies^(28,29). This might be because all of the patients were treated by a rheumatologist causing no variety of treatment. It was also found that when comparing the levels of glomerular filtration rate and serum uric acid levels of patients before and after treatment, there was a statistically significant ($p=0.018$ and $p=0.001$, respectively). In addition, the trends in before and after treatment of diastolic blood pressure were different ($p=0.090$), concordant to other studies that adequate treatment of gouty arthritis can reduce the risk of cardiovascular disease and chronic renal disease^(4,30).

Duration of disease ≥ 5 years ($p=0.001$, adjusted OR 5.207) was one of the most important characteristics of patients with chronic tophaceous gout resulting in collections of monosodium urate crystals and chronic granulomatous inflammatory tissue which is consistent with previous studies^(1-7,31-33). Second, a history of herbal medicine used (7% and 14% in the tophaceous and non-tophaceous group, respectively) ($p=0.006$, adjusted OR 2.076) might be explained by obscured inflammation and gout flares resulting in delayed treatment which was not mentioned in previous studies. Third, initial uric acid ≥ 8 mg/dL ($p=0.001$, adjusted OR 3.623) correlates with long-standing disease, the annual incidence of gout flares, complications especially chronic kidney disease, and inadequate treatment, which was similar to previous studies^(1-7,31,33). Fourth, initial Hb < 12 mg/dL ($p=0.010$, adjusted OR 1.898) might probably be

caused by anemia of chronic disease or iron deficiency anemia (due to a long-standing disease, and chronic blood loss from NSAIDs and steroids used to relieve gout flares) which were not mentioned in previous studies. Fifth, non-prescribed losartan ($p=0.004$, adjusted OR 0.465) which was a protective factor of subcutaneous tophi which was not mentioned in previous studies, maybe due to in the current study, patients received losartan only 22.9%. Seventh, single urate-lowering therapy ($p=0.034$, adjusted OR 0.592) which is different from previous studies⁽³⁴⁾, maybe since this study is a retrospective study and all patients were treated at the Rheumatology clinic, most of them received combined urate-lowering therapy (49.6%). Finally, inadequate treatment ($p=0.033$, adjusted OR 5.207) which was the same as the previous study^(1-7,31,33,34), caused the accumulation of monosodium urate crystals present as subcutaneous tophi. The present study had some limitations due to there being some missing and incomplete data, patients were entered from only one single center, the observational nature and lack of a control group in our study do not allow causal inferences.

CONCLUSION

The present study had identified duration of disease ≥ 5 years, a history of herbal medicine, initial uric acid ≥ 8 mg/dL, initial Hb < 12 mg/dL, losartan used, combined urate-lowering therapy, and inadequate treatment as clinical characteristics of patients with chronic tophaceous gout, which should be provided close monitoring and preventing complications.

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