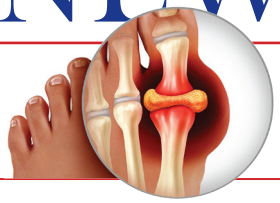
THE PATHCARE NEWS

HYPERURICAEMIA AND GOUT: IMPORTANT LESSONS TO BE LEARNT



Introduction

Gout is a common clinical disease and, furthermore, it is readily treatable and managed by the long-term use of urate lowering medication. Gout, the clinical syndrome, needs to be distinguished from hyperuricaemia which refers to the increased levels of serum urate. This newsletter is prompted by a case encountered and a seminar published in The Lancet recently, and aims to increase awareness of the importance of treatment of raised urate levels when detected.

Gouty arthritis was among the earliest diseases to be recognized as a clinical entity. It was identified by the Egyptians in 2640 BCE and podagra, the involvement of inflammation of the first metatarsophalangeal joint, was recognized by Hippocrates in the 5th century BCE. He referred to it as the "unwalkable disease".

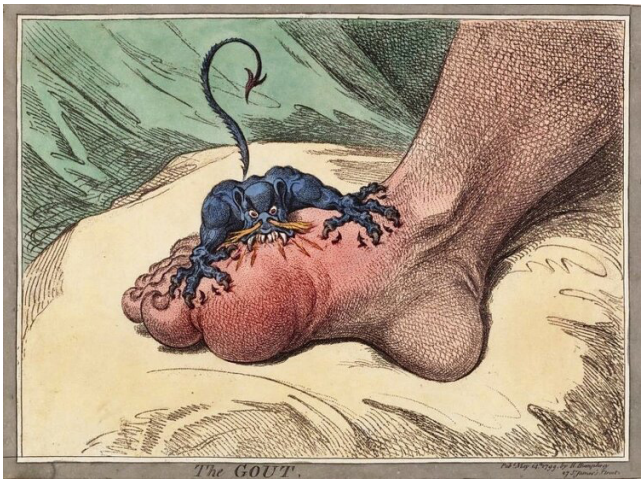


Figure 1: NYTimes.com/2013/04/27/booming/why-do-i-have-gout.html [Accessed 1/8/21.]
Figure 2: naturelife.co.za/history-of-gout-from-2640-bc-to-now/16/5/18 [Accessed 1/8/21.]

Case report:

A 66-year-old male initially presented to the orthopaedic surgeon with intermittent bilateral pain in his knees. He was not known to have had any chronic illness at the time. Clinical examination revealed bilateral tenderness predominantly over the medial compartments. There was no genu varus/valgus present and the patient had full range of motion. No signs of inflammation were present. Radiographs revealed osteoarthritis in bilateral knees; Kellgren-Lawrence grade 3. Uric acid levels were done at the time and were slightly elevated. The patient was subsequently initiated on Allopurinol for the hyperuricaemia and symptomatic treatment of the osteoarthritis.

The patient again presented two years later, reporting only a mild improvement in his knee pain. In addition, he also mentioned the development of bilateral shoulder and elbow pain. Physical examination was unremarkable. Additional blood tests were requested at this stage. The serum urate levels were still slightly elevated at 0.45 mmol/L, while his renal functions and acute phase inflammatory markers were normal (Table 1). The white blood cell count was noted to be elevated at 15.2 x10^9/L, with 64.1% lymphocyte predominance. (Table 2). Flow cytometry analysis was done on the peripheral blood sample which was in keeping with a chronic lymphocytic leukaemia (CLL) (Table 3).

Additional workup included a contrasted CT, which revealed only a mild splenomegaly. A bone marrow biopsy confirmed the diagnosis of a lymphoproliferative neoplasm best fitting chronic lymphocytic leukaemia. The oncologist is now involved in the further management of the patient. The raised urate levels are related to the increased cell turnover caused by the CLL.

Concerning issues regarding the clinical biochemistry results included the raised S-Urate level (See Table 1).

Electrolytes and Kidney Functions	
S-Na (136 - 145 mmol/L)	141
S-K (3.5- 5.1 mmol/L)	4.4
S-Cl (98 - 108 mmol/L)	105
S-TC02 (22 - 28 mmol/L)	25
Anion Gap (6 - 16 mmol/L)	11
S-Urea (2.9 - 8.2 mmol/L)	7.5
S-Creat (71 -115 umol/L)	103
Est GRF (>60mL/min)	65
S-Urate (0.21 - 0.43 mmol/L)	*0.45

Table 1

The Full Blood Count also demonstrated an absolute lymphocytosis (Table 2) which was further evaluated by flow cytometry (Table 3). Immunophenotyping diagnosed chronic lymphocytic leukaemia.

Haematology: FBC	
HB & Red Cell Indices	
B-HB (13.5 - 17.5 g/dL)	15.3
B-RBC (4.5 - 5.9 10^12/L)	5.5
B-HCT (41 - 53 %)	46.4
B-MCV (80 - 100 fL)	85
B-MCH (26 -34 pg)	28
B-MCHC (31 - 37 g/dL)	33
B-RBW (11 - 16 %)	13
B-Mentzer Index (> 13)	15
Platelets	
B-MPV (8.8 - 12.5 fL)	9.8
B-Plt (150 - 450 10^9/L)	185
White Cells	
B-WBC (4 - 10 10^9/L)	*15.2
B-Neutrophils (40 - 80 %)	*13.9
B-Neut abs (2 - 7 10^9/L)	4.7
B-Imm Gran (0 - 5 %)	0.3
B-Imm Gran abs (0 - 0.5 10^9/L)	0.05
B-Lymphocytes (20 - 40 %)	*64.1
B-Lymph abs (1 - 3 10^9/L)	*9.7
B-Monocytes (2 - 10 %)	2.8
B-Mono abs (0.2 - 1 10^9/L)	0.4
B-Eosinophils (0 - 6 %)	1.4
B-Eos abs (0.02 - 0.5 10^9/L)	0.21
B-Basophils (0 - 2 %)	0.5
B-Bas abs (0.02 -0.1 10^9/L)	0.08
B-Erythoblasts (0 - 1 %)	0.3
B-Erythoblasts abs (0 - 0.5 10^9/L)	0.05

Table 2

Flowcytometry

Interpretation

Plasma cells comprise 0.03% of nucleated cells and show cytoplasmic Kappa:Lambda ration of 2.50.
B-Lymphocytes comprise 47.34% of nucleated cells and show a Kappa:Lambda ratio of 112.58.
Clonal, mature B-Lymphocytes show Kappa light restriction with dual expression of CD5/CD19, dim CD20, bright CD23, CD24 and CD200.
T-Lymphocytes comprise 10.74% of nucleated cells and show a CD4:CD8 ratio of 0.97.
Natural killer cells comprise 3.81% of nucleated cells.
Myeloblasts comprise 0.08% of nucleated cells.

Conclusion

Features are in keeping with involvement by a lymphoproliferative neoplasm. The phenotype is classical of Chronic Lyphocytic Leukaemia.

Table 3

Clinical Presentation

The patient will present with a pain described as stabbing, gnawing, burning or throbbing. Classically this feature has a short time from onset to reach a peak intensity usually in less than 12 hours. There are varying degrees of erythema, swelling and warmth associated with the joint involved. The flare is usually self-limiting over a period of 7 – 14 days and the patient is pain-free until another flare occurs. This pattern of involvement usually aids in the recognition of the gout flare as the lower limbs (foot, ankle and knee) are predominantly affected. The upper limb is usually involved in poorly controlled long-standing hyperuricaemia.

Gout flares are usually monoarticular but oligo- and polyarticular incidents do occur, particularly in poorly controlled cases as well as hospitalisation where severe systemic symptoms (fever, chills and even delirium) may be found.

With longstanding exposure to raised urate levels the asymptomatic periods decrease and each flare can last longer and even merge. Adequate S-urate control is critical in preventing this condition.

Pathophysiology

Four stages are required to progress from hyperuricaemia to the clinical condition of gout. These are:

1. Raised S-urate.
2. Deposition of monosodium urate crystals.
3. Acute inflammatory response to the deposited crystals.
4. Advanced disease with tophi.

Some patients may present, without having had previous gout flares, advanced disease characterised by tophi.

Risk factors

The following factors are associated with an increased risk for incident gout:

1. Metabolic syndrome.
2. Chronic kidney disease.
3. Medication, such as diuretics and cyclosporin.
4. Purine-rich foods such as red meat and seafood.
5. Alcohol, especially purine-rich beer and sugar-sweetened drinks.
6. Increased cell turnover as found in malignancies.

Primary prevention of gout should be the management of asymptomatic hyperuricaemia.

Outcomes and treatment of this disease have been suboptimal worldwide. Many patients do not receive regular urate-lowering treatment and in contrast to rheumatic arthritis the mortality gap for gout has not improved over the last 20 years. Gout is associated with an increased risk of death – cardiovascular disease is the major cause of this.

Summary

1. The underlying cause of gout is well documented and effective treatment is available, but despite this fact no progress has been made in the management of this condition over the last 20 years.
2. Dietary management as a cornerstone for management is uncertain and needs further research.
3. Also controversial is the direct role that gout plays in the pathogenesis of hypertension, cardiovascular disease and chronic renal disease.
4. Clinical outcomes for gout patients have made major advancement in a nurse-led treat-to-target in a clinical trial in the UK. This involved education, S-urate testing and dose titration of urate-lowering therapy. High adherence and uptake was reached in this study. High quality gout care can lead to major improvements in patient outcomes.

Conclusion

Gout is a chronic and common easily treatable condition. Despite the freely available inexpensive and effective therapies available, there are low rates of urate-lowering therapy initiation and persistence. We need increased awareness and a multidisciplinary approach to initiate treatment and persistence of treatment of this common disease, and a rethink of strategies is needed to ensure major improvements in patients' quality of life and outcomes. We urgently need to take do a reevaluation of our management of hyperuricaemic patients.

Further reading:

Dalbeth, N, Gosling, AL, Gaffo, A & Abhishek, A. 2021. Gout. The Lancet. https://doi.org/10.1016/S0140-6736(21)00569-9 [Accessed 2 April 2021].

Dubreuil, M. et al. 2013. Increased Risk of Recurrent Gout Attacks with Hospitalization. *The American Journal of Medicine*. 126: 1138-1141.

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