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Case Report

A Rare Case of Gitelman Syndrome Revealed by Chronic Tophaceous Gout

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Abstract: Background: The most common complications of non-treated chronic hyperuricemia are tophaceous gout and kidney impairment with metabolic acidosis. Metabolic alkalosis and hypomagnesemia are unusual during gout. We report the case of a woman with chronic tophaceous gout that revealed Gitelman syndrome. Case report: A 40-year-old woman was complaining of chronic joint pain and swelling for 7 years, complicated by the occurrence of tophi, in a context of impaired general condition. The diagnosis of chronic tophaceous gout was made based on physical examination and elevated serum uric acid level and radiological features. The discovery of Gitelman syndrome was made based on hydro-electrolytic disorders and arterial gasometry, revealing hypokalemia, hypochloremia, hypomagnesemia, and metabolic alkalosis. The patient was admitted and stabilized in an intensive care unit, and then she has been referred to us. Tophaceous gout was treated with a xanthine oxydase inhibitor (allopurinol) and the ionic disorders were corrected with potassium and magnesium supplementation. Conclusion: Gitelman syndrome is a rare inherited tubulopathy characterized by renal loss of sodium and potassium associated with hypomagnesemia and metabolic alkalosis. It can also expose, in the long term, the development of calcium pyrophosphate deposition disease, as a consequence of low magnesium levels. However, the association of gout and Gitelman syndrome is rare but possible given that this syndrome simulates thiazide diuretics intake, and that may be the main mechanism of the occurrence of gout in this case.

Keywords: Severe Gout, Tophus, Gitelman Syndrome

1. Introduction

Gout is a microcrystalline disease due to tissue and intra-articular deposition of monosodium urate crystals following chronic hyperuricemia [1]. Hyperuricemia may be primary or secondary, by purine hypercatabolism or renal hyposecretion. The association of gout with Gitelman syndrome is rare, but possible, given that Gitelman syndrome simulates thiazide diuretics intake, and therefore can induce reabsorption of urate and uric acid [2]. Gitelman syndrome is an autosomal recessive inherited disorder due to mutations in the gene encoding the Na-Cl thiazide co-transporter. It is characterized by renal loss of sodium, and potassium, and magnesium. The diagnosis is generally made made by excluding the other causes of ionic loss.

We report a rare case of chronic tophaceous gout associated with Gitelman syndrome.

2. Case Report

A 40-year-old woman was admitted for joints pain and swelling for 7 years, complicated by the occurrence of hard swelling, firstly in the lower limb (large toes, knees, ankles) then ascending towards the other joints and skin too. There was no family history of gout. She had been taking 20 mg/d of prednisone orally as self-medication for the past year. Physical examination found a lethargic confused patient, with mild signs of dehydration. Large and small joints were tender. Multiple

tophi were found on hands, feet, elbows, and knees. Some were on the skin too, ulcerated. Laboratory finding showed severe ionic disorders (low natremia: 121 mmol/l, low potassium level: 1.6 mmol/l, low magnesemia: 12 mg/l, and hyperuricemia 124 mg/l). Renal function was normal (GFR: 98.62 ml/min). Arterial blood gas was performed, and it showed metabolic alkalosis. Urine test found normal chloride level, hypocalciuria, and low uric acid level (Ca < 20 mg/l, uric acid: 75 mg/24 h). Radiological examination of both hands and feet showed soft-tissue swelling with minor destructions with no evidence of chondrocalcinosis. The gout was treated with allopurinol gradually increased to 300 mg/d in combination with colchicine at 1 mg/d and a gradual decrease of corticosteroids. As for Gitelman syndrome, treatment was based on intravenous then oral magnesium and potassium supplementation. After a one month follow-up, joints pain and mobility were improved with a considerable decrease in the level of serum uric acid (60.1 mg/l) and normalization of blood electrolytes.

3. Discussion

Severe gout is defined as the presence of more than 4 tophi or the existence of at least one unstable, complicated or severe tophus [3]. In the absence of adequate treatment, the progression of hyperuricemia may lead to chronic tophaceous arthropathy and gout nephropathy. These complications can occur after 3 to 42 years with an average of 11 years [4]. In our patient, the diagnosis was made clinically, in addition to laboratory findings that showed a very high serum uric acid level. Many risk factors for gout development have been identified, including genetic factors, dietary factors, alcohol consumption, the presence of metabolic syndrome, chronic kidney failure, or taking certain drugs such as thiazide diuretics (Table 1) [5]. Our patient had no obvious risk factors. However, a genetic origin cannot be eliminated. It may be explained by a tubulopathy such as Gitelman syndrome, given the severity of gout, the young age of the patient and the absence of other secondary risk factors, and the hypo-uraturia. In addition, the presence of severe hydro-electrolytic disorders without a real cause of loss supported this diagnosis. Gitelman syndrome is an autosomal recessive inherited disorder secondary in more than 80% of cases to mutations in the SLC12A3 gene encoding the Na-Cl thiazide co-transporter, it usually occurs in children and young adults. It is characterized by renal loss of sodium and potassium associated with hypomagnesemia without hypercalciuria nor defective urine concentration [6]. Gitelman syndrome is a very mild form of Bartter syndrome, which usually occurs before birth [7]. Hypokalaemia or hypomagnesemia is often fortuitously discovered during a blood test [8]. Nevertheless, neuromuscular signs or extracellular dehydration signs may be found. On the electrolyte panel, hypomagnesemia and hypokalemia are marked, calciuria is low, and there is no nephrocalcinosis nor renal insufficiency [9]. Some abnormalities can be visible on the electrocardiogram due to hypokalemia but the only real life-threatening complication is ventricular fibrillation [10]. Genetic diagnosis isn't performed oftenly to confirm Gitelman syndrome, because it requires expertise, given the large number of mutated genes involved. Its interest lies mainly in the Bartter syndrome [9]. Several differential diagnoses must be eliminated before Gitelman syndrome is retained, such as the acquired causes of renal or digestive potassium loss due to some medications or vomiting, especially in the presence of alkalosis, or finally due to autoimmune tubulopathy [11-13]. Beside cardiac involvement, Gitelman syndrome exposes, in the long term, the development of calcium pyrophosphate deposition disease, as a consequence of low magnesium level. However, cases of gout and Gitelman syndrome association were reported only twice in the literature [14, 15]. Unfortunately, there is no curative treatment for Gitelman syndrome. A generally rich diet with potassium and magnesium supplements is what is prescribed for these patients. Other treatments have been studied, but their potential side effects limit their use, such as renin-angiotensin system antagonists, potassium-sparing diuretics, and aldosterone antagonists. Gitelman syndrome manifestations in our patient were essentially signs related to extracellular dehydration, and hydro-electrolyte disorders in blood tests. On the electrocardiogram, negative T-waves and a u-wave on some leads were found. The diagnosis of Gitelman syndrome was made after excluding the other causes of ionic loss. The correction of ionic disorders was started in an intensive care unit and then continued orally. Concerning tophaceous gout, the main objective of the treatment is to reduce and then eliminate sodium urate crystals by normalizing uricemia, a target value of less than 50 mg/l is often recommended by Rheumatology societies according to the "treat to target" approach [16, 17]. In our patient, a xanthine oxidase inhibitor: allopurinol in combination with colchicine has been introduced. Moreover, therapeutic education was performed to increase the awareness of the severity of ionic disorders induced by Gitelman syndrome, and the importance of a convenient diet and regular treatment to normalize serum uric acid level and thus dissolve tophi.

Table 1. *Main etiologies of gout.*

Primary gout	Secondary gout
Hyperproduction: 1. Enzymopathic gout: 2. HGPRT deficiency (Lesch-Nyhan disease) 3. Activity of PRPP synthetase 4. Glycogenesis type I (Von Gierke's disease)	Hyperproduction: 1. Myelo and lymphoproliferative disorders 2. Extended psoriasis, obesity 3. Alcohol, fructose
Hyposecretion 1. Family uratic nephropathy: Uromodulin mutation (autosomal dominant type 2 cystic medullary nephropathy) 2. Urinary uric acid excretion failure involving multiple transporters (90% of primary gouts)	Hyposecretion: 1. Chronic renal failure 2. Alcoholism, prolonged fasting, boneless diet 3. Hyperparathyroidism, hypothyroidism, diabetes insipidus 4. Iatrogenic: long-term diuretics, ciclosporin, laxatives, low-dose salycilic acid, pyrazinamide, ethambutol.. etc

HGPRT: hypoxanthine-guanine phosphoribosyl transferase. PRPP synthetase: phosphoribosylpyrophosphate synthetase

4. Conclusion

Gitelman syndrome is a rare inherited autosomal recessive salt-losing tubulopathy characterized by severe ionic loss and metabolic alkalosis. The relationship between this syndrome and occurance of hyperuricemia is not clearly established. The most likely mechanism may be the similarity with chronic thiazide diuretics intake, which usually increases the risk of developing gout [9]. To our knowledge, this case represents the 3rd in the literature justifying the need to conduct studies to prove this theory.

Conflicts of Interest

All the authors do not have any possible conflicts of interest.

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