

# Allopurinol-induced hypersensitivity syndrome followed by painless thyroiditis in a patient with asymptomatic hyperuricemia

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Allopurinol, an inhibitor of xanthine oxidase, is a urate-lowering drug, which has been used to prevent recurrent gout and asymptomatic hyperuricemia. It is known that allopurinol causes hypersensitivity syndrome (HS), including drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which is related to cell-mediated immunity. Allopurinol-induced hypersensitivity syndrome (AIHS) is a life-threatening adverse reaction characterized by fever, skin rashes, eosinophilia, and liver and/or renal dysfunction. Limbic encephalitis, myocarditis, and gastrointestinal disease have also been reported to occur during the course of the disease. To date, there are no available data regarding the association of painless thyroiditis with AIHS. Here, we report the first case of painless thyroiditis associated with AIHS.

A 52-year-old man was admitted to the hospital with a 4-day history of high-grade fever, itch, maculopapular rash, and malaise. He had a history of hyperuricemia, and had started taking oral allopurinol (300 mg daily) 4 weeks previously. There was no personal or family history of thyroid or hepatic diseases, or drug allergies.

Following admission, the patient had fever (temperature 40°C), with a blood pressure of 126/78 mm Hg, a pulse of 102 beats/min, and a respiration rate of 20 breaths/min. Physical examination revealed maculopapular rash involving almost 90% of the body surface. He had a grade 1 diffuse goiter. His chest sounds were normal.

The results of routine blood examinations are listed in Table I. The patient had elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine levels. His leukocyte count was normal, but his eosinophil count was increased to 1.29 (normal (N): 0.02–0.52 × 10<sup>9</sup>/l). Although his serum free triiodothyronine (fT3) and thyroxine (fT4) levels were normal, there was significant suppression of thyroid-stimulating hormone (TSH). Serology for viruses of hepatitis, human cytomegalovirus (HCMV), and Epstein-Barr virus (EBV) was negative. After consultation with a dermatologist, we considered a diagnosis of hypersensitivity syndrome induced by allopurinol. The intake of allopurinol was stopped. The human leukocyte antigen (HLA)-B locus genotyping was performed in the patient.

The patient received dexamethasone 5 mg IV every day for 5 days. Glutathione was used to maintain physiological function of cells. At 15 days after treatment, his ALT, AST and creatinine levels had decreased to 62 U/l, 48 U/l, and 88 μmol/l respectively. A repeated blood analy-

sis revealed a normal number of eosinophils. No fever was detected and the maculopapular rash on his body disappeared. Genotyping showed the presence of the HLA allele B\*5801. This result supported the diagnosis of hypersensitivity syndrome induced by allopurinol [1].

However, after 4 weeks of treatment, the patient still presented malaise. We examined his blood thyroid hormones again. Serum fT3, fT4, and TSH concentrations were measured by the chemiluminescence assays (CLIA) method using a commercial kit (Bayer, Germany).

The intra-assay and inter-assay coefficient of variation values were as follows: TSH: 2.7% and 4.7%, fT3: 3.4% and 5.5%, fT4: 2.4% and 4.2%. His serum fT3 and fT4 levels were higher than 20.00 pg/ml (N: 2.3–4.2 pg/ml) and 12.00 ng/dl (N: 0.89–1.8 ng/dl) respectively, with a TSH of 0.011  $\mu$ IU/ml (N: 0.55–4.78  $\mu$ IU/ml). The thyroid-associated antibodies and thyroid <sup>131</sup>I uptake rate were tested as well. As listed in Table II, the levels of thyroid peroxidase (TPO), antithyroglobulin (TG), and thyroid-stimulating receptor (TR) antibodies were normal. The erythrocyte sedimentation rate (ESR) level was 73 mm/h (N: 0–21 mm/h). The thyroid <sup>131</sup>I uptake rate was reduced. All these results suggested that the patient's thyroid dysfunction was not caused by thyroid autoantibodies. Thus, we considered that the thyroid dysfunction was caused by painless thyroiditis.

No therapeutic intervention was required for this patient. Follow-up was prescribed in the endocrinology clinic. Eight weeks after stopping taking allopurinol, the patient's fT3, fT4, TSH, and ESR were reduced to 3.74 pg/ml, 1.65 ng/dl, 0.013  $\mu$ IU/ml and 35 mm/h respectively. After 4 more weeks, the patient's fT3, fT4 and ESR

were further reduced to 1.64 pg/ml, 0.33 ng/dl and 14 mm/h respectively. TSH was increased to 78.155  $\mu$ IU/ml. The thyroid <sup>131</sup>I uptake rate was 15.5% (2 h), 10.7% (4 h), and 16.1% (24 h). The patient was prescribed oral levothyroxine sodium (50  $\mu$ g/daily). After 6 weeks of follow-up, thyroid function tests were re-checked in an outpatient department. The serum TSH, fT3 and fT4 were 1.993  $\mu$ IU/ml, 3.5 pg/ml, and 1.26 ng/dl respectively. Based on all these data, we diagnosed this patient as having hypothyroidism associated with painless thyroiditis due to AIHS.

In this case the presence of transient thyrotoxicosis, and hypothyroidism in the absence of thyroid-associated antibodies suggest an etiology of painless thyroiditis. Painless thyroiditis is an autoimmune thyroiditis. Its etiology is related to autoimmune and viral infection. In the present case, as the onset of painless thyroiditis occurred after the intake of oral allopurinol and drug-induced hypersensitivity syndrome (DIHS), we speculated that the AIHS might be responsible for painless thyroiditis. There have been several reports of painless thyroiditis induced by drugs such as tamoxifen citrate, and anti-programmed cell death 1 (PD-1) monoclonal antibody [2, 3]. Kano *et al.* reported that 2 of the 145 patients with DIHS/drug reaction with eosinophilia and systemic symptoms (DRESS) developed painless thyroids after recovery from DIHS/DRESS [4]. The mechanism of the pathogenic effect of AIHS on thyroid gland function is still unknown. A few reports have focused on the role of regulatory T (Treg) cell-mediated immune response against drug antigens leading to a disorder involved in multiple organs [5]. Moreover, viral infection, such as viruses of HCMV,

**Table I.** Results of routine laboratory investigations

Test (normal value)	Result
Leukocytes (3.5–9.5 × 10 <sup>9</sup> /l)	8.46 × 10 <sup>9</sup> /l
Neutrophils (1.8–6.3 × 10 <sup>9</sup> /l)	4.97 × 10 <sup>9</sup> /l
Eosinophils (0.02–0.52 × 10 <sup>9</sup> /l)	<b>1.29 × 10<sup>9</sup>/l</b>
Procalcitonin (< 0.1 ng/ml)	0.07 ng/ml
ALT (9–50 U/l)	<b>302 U/l</b>
AST (15–40 U/l)	<b>105 U/l</b>
Creatinine (57–97 $\mu$ mol/l)	<b>125 <math>\mu</math>mol/l</b>
eGFR (> 90 ml/min)	<b>56.67 ml/min</b>
Uric acid (208–428 $\mu$ mol/l)	<b>459 <math>\mu</math>mol/l</b>
Free T3 (2.3–4.2 pg/ml)	3.60
Free T4 (0.89–1.8 ng/dl)	1.20
TSH (0.55–4.78 $\mu$ IU/ml)	<b>0.084</b>

Abnormal results are in bold.

**Table II.** Results of ESR, thyroid function and <sup>131</sup>I uptake rate

Test (normal value)	Result
Laboratory:	
ESR (0–21 mm/h)	<b>73 mm/h</b>
Free T3 (2.3–4.2 pg/ml)	<b>&gt; 20.00</b>
Free T4 (0.89–1.8 ng/dl)	<b>12.00</b>
TSH (0.55–4.78 $\mu$ IU/ml)	<b>0.011</b>
TPO antibody (0–60 U/ml)	< 28.00
TG antibody (0–60 U/ml)	52.10
TR antibody (0–1.58 U/l)	0.46
Thyroid <sup>131</sup> I uptake rate:	
2-hour (10–30%)	10.7%
4-hour (15–40%)	<b>1.8%</b>
24-hour (25–60%)	<b>0.1%</b>

Abnormal results are in bold.

human herpesvirus 6 (HHV-6) and EB [6, 7], also plays an important role in DIHS. In the patients who developed painless thyroiditis after DIHS, HCMV-DNA and EBV-DNA were not detected in their urine and whole blood. That said, further investigations are warranted to clarify the physiological mechanisms of AIHS on thyroid gland function.

The HLA-B\*58:01 allele is a risk factor for AIHS [8]. HLA-B\*58:01 is present in about 20% of certain Asian populations. HLA-B\*58:01 was found in more than 90% of patients of Han Chinese with AIHS [9]. The HLA-B\*58:01 allele had 95.20% sensitivity and 100% specificity for diagnosing allopurinol-related cutaneous adverse drug reactions (CADR) [10]. This strong association has also been reported in other studies [11, 12]. Hence, routine testing of patients with hyperuricemia for HLA-B\*58:01 could successfully reduce the occurrence of AIHS in Han Chinese populations.

In conclusion, our findings are compatible with a relationship between AIHS and painless thyroiditis. These findings also need to be confirmed by thorough retrospective analysis of patient cases with AIHS and painless thyroiditis. Clinicians who prescribe allopurinol should be aware of its potential risk for AIHS, especially in patients with the HLA-B\*58:01 allele. In addition, we would like to emphasize that careful long-term follow-up including thyroid hormone tests should be carried out in patients with DIHS/DRESS.

### Conflict of interest

The authors declare no conflict of interest.

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