Title: Acute Immunoallergic hepatitis due to allopurinol use

Running head: Immunoallergic hepatitis from allopurinol

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Abstract
Acute immunoallergic hepatitis presents as acute liver injury, often accompanied by nonspecific findings of fever, rash, and abdominal pain, and is often induced by a drug ingestion. Allopurinol has been implicated in multiple cases of acute immunoallergic hepatitis. We present the case of a young East Asian male with gout who experienced acute immunoallergic hepatitis, complicated by DRESS syndrome with severe cutaneous reaction, as a result of allopurinol intake. The patient was positive for the HLA B58*01 gene, a significant risk factor for developing an allopurinol-induced liver injury. The patient's liver injury and skin reaction improved with administration of IV methylprednisolone, then a course of oral prednisone. Our case prompts clinicians to prescribe allopurinol with caution in certain high-risk populations, and it emphasizes the importance of administering corticosteroids early in such a presentation to avoid long-term liver damage.

Keywords: Drug-induced liver injury, liver function tests, liver biopsy

Introduction
Drug-induced liver injury (DILI) is one the most common causes of acute liver failure, particularly in the developed world [1]. The pattern of liver injury associated with DILI can be

either hepatocellular or cholestatic, and the symptoms and degree of liver injury can range in severity among culprit drugs and individual patients. Acute immunoallergic hepatitis is a type of DILI characterized by hepatocellular injury mediated through a hypersensitivity reaction. It is marked by a range of manifestations, including a variable degree of skin rash, fever, lymphadenopathy, facial edema, myalgias, arthralgias, eosinophilia, and atypical lymphocytosis [2,3]. Allopurinol use has been linked to multiple cases of acute immunoallergic hepatitis [2, 4-10].

Allopurinol is a xanthine oxidase inhibitor used for long-term gout management, and its metabolite, oxypurinol, is known to trigger a cytotoxic T-cell response and thought to be the cause of allopurinol-mediated hypersensitivity. [11] Chronic allopurinol therapy for gout has been associated with transient liver enzyme abnormalities in 2-6% of patients, which typically resolve spontaneously.[3] Rarely, allopurinol may induce a more severe immunoallergic hepatitis that is often linked with drug reaction with eosinophilia and systemic symptoms (DRESS). Indeed, in one study of DILI, 67% of all allopurinol-induced DILI cases were associated with DRESS. [12]

DRESS can have up to a 10% mortality rate, regardless of the culprit drug. [13] Therefore, identifying patients with this DILI-DRESS phenotype promptly upon admission, discontinuing the offending medication, and initiating steroid management are imperative to achieve good outcomes.

Case Description

A 21-year-old Vietnamese male with no significant past medical history developed a gout flare and was started on colchicine and allopurinol as an outpatient. This patient had no prior history of liver disease, no IV drug use history, and had no history of alcohol consumption. He completed a 3-day course of colchicine and his gout flare resolved, and he continued taking allopurinol 100 mg daily. After six weeks of allopurinol therapy, he noticed reddening of his skin, which worsened over the course of one week to a desquamating diffuse rash involving the face, back, arms, and hands (Fig. 1). He soon developed fevers and tachycardia as well as the acute edematous macular rash, and he presented to the emergency room for evaluation.

On admission, his mental status was intact, with no concerns for encephalopathy. His heart rate was 106 bpm on admission but improved to 98 bpm shortly after presenting to the emergency room. He was afebrile at 37.2°C and his blood pressure was 139/86. His physical exam was notable for facial edema, anterior cervical lymphadenopathy, diffuse jaundice, abdominal distention and palpable hepatosplenomegaly with no abdominal tenderness and no fluid wave, and a desquamating rash on face, back, and palms. He had no chest pain, shortness of breath, or cough, no changes in urine output, and no bloody diarrhea.

His admission labs were notable for elevated liver enzymes and hyperbilirubinemia: aspartate transaminase (AST) was 376 units/L and alanine transaminase (ALT) was 502 units/L; alkaline phosphatase was 243 units/L. Based on these values, the R factor for liver injury was 4.1, indicating a mixed pattern of liver injury, with both hepatocellular and cholestatic damage. His

total bilirubin was 3.1 mg/dL and direct bilirubin was 2.0 mg/dL. His international normalized ratio (INR) was elevated to 1.4, and platelets were normal at 251K/μL. The white blood cell count was normal at 7.9K/μL, and his absolute eosinophil count was zero. Allopurinol was stopped immediately upon admission.

Right upper quadrant ultrasound on day 1 of admission demonstrated an enlarged liver to 20 cm, with patent vasculature and no other abnormal hepatic findings. On magnetic resonance cholangiopancreatography (MRCP) conducted on day 3, the patient's liver was still enlarged, 17 cm at the mid-clavicular line, with diffuse periportal edema and enhancement suggestive of acute hepatitis. MRCP also demonstrated splenomegaly, measuring up to 16 cm in length, and marked gallbladder wall thickening and edema that completely effaced the gallbladder lumen. This finding was consistent with acalculous cholecystitis, likely secondary to adjacent hepatic inflammation.

On day 5 of admission, a transjugular liver biopsy was performed, which demonstrated a hepatitic pattern of liver injury with mixed inflammatory infiltrate and intracellular cholestasis, marked by eosinophils and acidophil bodies (Fig. 2, 3, 4). Per the pathology report, these findings were all consistent with medication-induced liver injury, most likely DRESS. Steroids had not been initiated at the time of this biopsy. Liver enzymes peaked on day 6, when his ALT and AST were both greater than 1300 units/L, total bilirubin was 18.4 mg/dL, and direct bilirubin was 14.6 mg/dL (Table 1). Also on day 6, intravenous methylprednisolone was started at a dose of 40 mg daily. After two days of IV methylprednisolone, he was transitioned to prednisone 40 mg daily.

Other notable labs over the duration of his admission included negative hepatitis serologies, negative anti-smooth muscle antibody, and negative anti-mitochondrial antibody. Given negative smooth muscle antibody, suspicion for autoimmune hepatitis was low, and no ANA or serum IgG was collected during this admission. His HLA-B*58.01 genetic test was positive. He was cleared for discharge on day 12 of admission. He was discharged on 40 mg prednisone daily, which he would take until follow-up with GI clinic.

He followed up with dermatology clinic 20 days after discharge, and his skin findings had completely resolved. He was then seen in GI clinic 35 days after discharge. At this follow-up, his liver enzymes and bilirubin levels had corrected to normal levels (Table 1). He was still taking 40 mg prednisone daily. He was prescribed a 30-day prednisone taper at this visit: 10 days of 30 mg prednisone, followed by 20 mg prednisone for the next 10 days, and 10 mg of prednisone for the final 10 days. Altogether, the total duration of steroid use was 77 days: 2 days of IV methylprednisolone and 75 days of oral prednisone. The total time required for liver enzyme recovery was 50 days (Table 1).

At his follow-up six months after his initial liver injury, he had been off all steroids for more than 3 months. His liver enzymes were still normal, and he denied any concerning symptoms. Since stopping allopurinol, the patient has had no gout flares, and he has not been on any other

medication for gout. He was never restarted on colchicine in the follow-up period, and he was not started on febuxostat as an alternative uric acid-lowering agent.

Discussion

This case represents an example of allopurinol-induced immunoallergic reaction involving fever, acute hepatitis, and DRESS. Since allopurinol was first used for treatment of gout in the late 1960s, there have been multiple documented cases of hypersensitivity reactions attributed to allopurinol in the literature, with most patients developing fever, skin rash, and liver and/or renal failure [4-6] The onset of systemic symptoms after initiation of allopurinol ranges widely in the cases reported, from 2 weeks to 3 months [7,8]. In rare cases, the sequelae of patients' allopurinol-induced hypersensitivity proved lethal – whether cardiac arrest from DRESS syndrome, to fatal liver necrosis. Thus, it is important that providers remain hypervigilant for this possible syndrome, even when patients' lab findings or symptoms do not exactly align with expectations. [9,10] Notably, the patient described in our case never had eosinophilia as one would expect in DRESS, but that may not be necessary to characterize the DILI-DRESS phenotype. In one recent study of DILI associated with DRESS, 15% of patients with DRESS did not have eosinophilia [12].

Furthermore, his pathology results from his transjugular liver biopsy were all consistent with DRESS as a result of allopurinol use. Hematoxylin and eosin-stained sections demonstrated hepatic parenchyma with hepatocellular pattern of injury and scattered acidophil bodies. Also on the hematoxylin and eosin stain, extensive lobular and mixed inflammatory infiltrate and focal intracellular cholestasis were present. The pathology sections were treated with three additional special stains: trichrome stain showed no significant fibrosis, periodic acid-Schiff stain demonstrated no intracytoplasmic hyaline globules, and iron stain demonstrated patchy iron deposits in reticuloendothelial cells. Altogether, the results were consistent with medication-induced liver injury from allopurinol. In other cases of allopurinol hepatotoxicity, liver pathology sections have also demonstrated eosinophilia, intracellular cholestasis, and mixed hepatic inflammatory infiltrate [3].

This patient was also taking colchicine for the first 3 days of his treatment with allopurinol, but it is less likely that the colchicine was the causative agent in his drug-induced liver injury. The Roussel Uclaf Causality Assessment Method (RUCAM), a scoring system used to determine the likelihood that hepatic injury is due to a specific medication, was used to assess the contributions of both allopurinol and colchicine to this patient's liver injury [14]. The RUCAM grade for allopurinol was 7, and the colchicine was RUCAM grade 3. A score of 3-5 indicates a drug is a "possible" contributor to the liver injury, and a score of 6-8 indicates that a drug is a "probable" contributor to liver injury [14]. There are very few reports of colchicine-induced hepatotoxicity in the literature. Those that have been documented have had associated histopathologic findings characteristic of the mechanism of colchicine, which disrupts mitotic activity and cellular disruption [15]. In colchicine-induced liver toxicity, histologic staining would reveal enlarged nuclei, multiple mitotic figures, and cellular edema, but in allopurinol hepatotoxicity, eosinophilia, intracellular cholestasis, and/or acute granulomatous changes are noted [3,16].

The exact mechanism by which allopurinol causes DILI, DRESS, or any acute immunoallergic reaction is not fully understood, though it is suspected that a cell-mediated immune reaction (type IV hypersensitivity) to oxypurinol, the metabolite of allopurinol, is thought to be responsible [13]. It has been clearly established that allopurinol-associated DRESS with acute liver injury is closely linked with HLA-B*58.01 positivity, particularly in Asian populations [17]. Other HLA allele mutations linked with allopurinol liver toxicity include HLA-A*33.03 and HLA-C*03.02 [8]. Patients carrying the HLA-B*58.01 allele have been found to have an 80-fold increase in risk of developing severe cutaneous adverse reactions to allopurinol [7]. In one case-controlled study conducted in China, 100% of patients with allopurinol-induced hypersensitivity reactions were HLA-B*58.01 positive, compared with 15% of allopurinol-tolerant patients and 20% of healthy controls [18]. This strong correlation between HLA-B*58.01 positivity and an immunoallergic reaction to allopurinol has also been observed in other Southeast Asian populations, as well as in African-Americans [19,20].

Management of allopurinol-induced liver injury primarily involves discontinuation of allopurinol and supportive care. While the use of glucocorticoids in DRESS has not been evaluated definitively in randomized trials, consensus supports administration of steroids in DRESS with acute end-organ injury [21]. To reduce the risk of allopurinol-induced liver injury, some studies suggest that providers should consider testing, if available, for HLA-B*58.01 in patients belonging to high-risk ethnic groups before initiating gout maintenance therapy [22]. Currently, the American College of Rheumatology conditionally recommends testing for HLA-B*58.01 mutations in individuals of Southeast Asian descent and in African-Americans [23]. For those who test positive, febuxostat may be initiated instead of allopurinol as an alternative urate-lowering therapy, but it can also be associated with hypersensitivity reactions [23,24]. More investigation is warranted into alternative options for gout maintenance therapy in patients who have experienced allopurinol-induced acute immunoallergic hepatitis, or who are at high risk of having that reaction.

Conclusion

Allopurinol-induced drug induced liver injury can be associated with immunoallergic hepatitis in conjunction with DRESS, especially in individuals positive for the HLA-B*58.01 allele, like the patient in the case described above. In such cases of allopurinol-associated DILI with DRESS, it is imperative that allopurinol be stopped immediately, and steroids should be initiated to avoid morbid progression of the liver injury or severe cutaneous reaction.

Table 1. Trends of liver function tests and other relevant laboratory studies

Lab value (normal range)	Day 1	Day 7	Day 50
AST (10-42 units/L)	376	1355	22
ALT (17-63 units/L)	502	1528	20
Alk phos (38-126 units/L)	243	177	63
T bili (0.3-1.6 mg/dL)	3.1	18.7	1.3
D bili (0.1-0.4 mg/dL)	2.0	14.6	0.3

WBC (3.8-10.7 K/mcL)	7.9	8.6	8.9
Hemoglobin (13.2-17.7 gm/dL)	14.2	14.0	15.1
Platelets (148-362 K/mcL)	251	179	354
INR (0.9-1.0)	1.4	2.0	1.1
Creatinine (0.7-1.2 mg/dL)	0.8	0.8	0.8
Uric Acid (3.4-7.0 mg/dL)	7.8	No further trend	

Figure 1. Desquamating rash of palms on day 2 of presentation

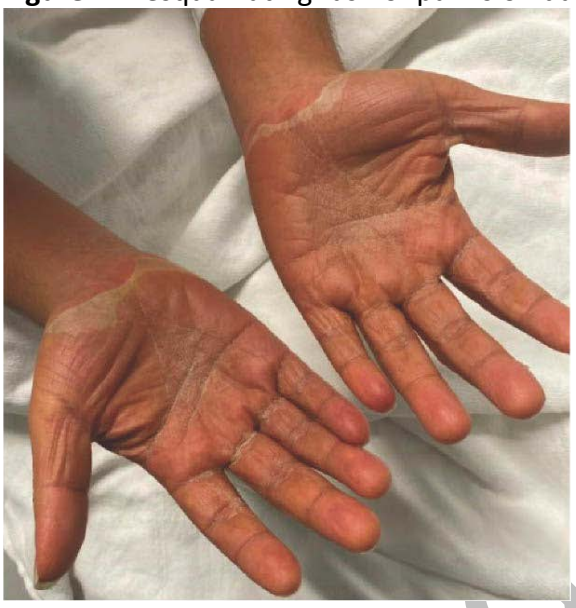


Figure 2. 100x view of hematoxylin and eosin stain of tissue from transjugular liver biopsy

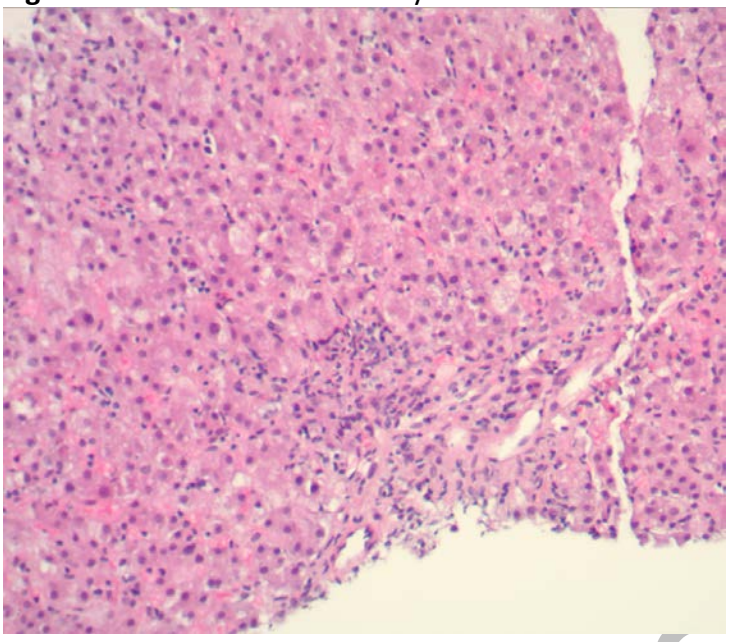


Figure 3. 400x view of H+E stain, with black arrow indicating acidophilic body

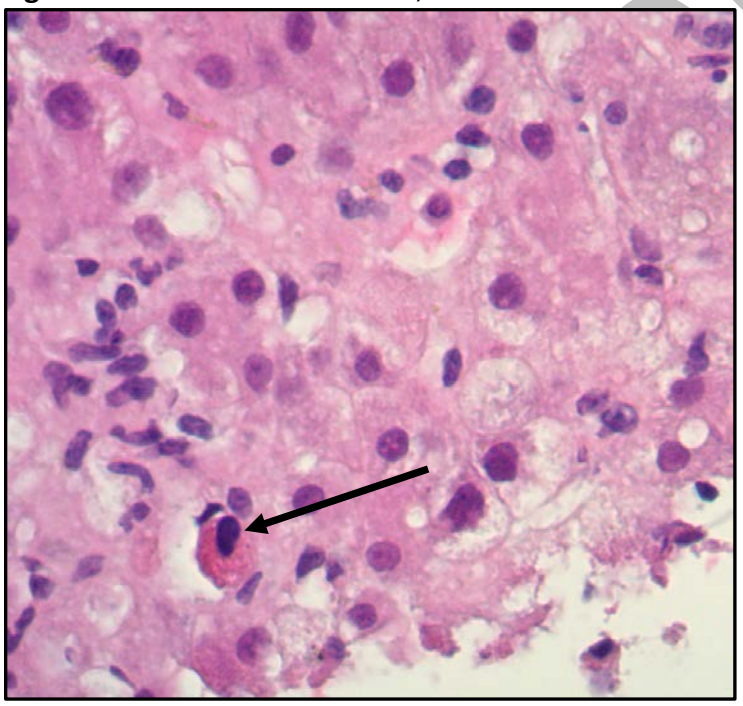
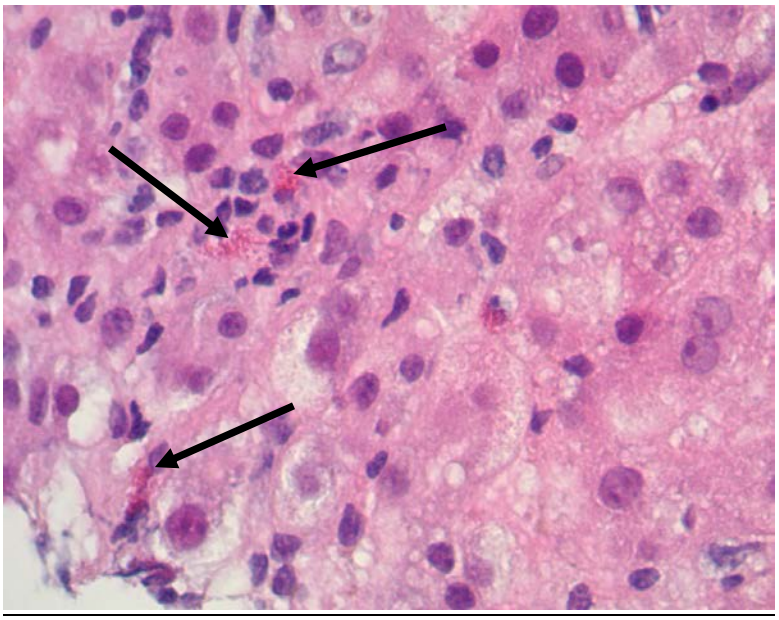


Figure 4. 400x view of H+E stain, with black arrow indicating eosinophils



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