A Case of Sulfasalazine-Induced Hypersensitivity Syndrome Confirmed by Enzyme-Linked Immunospot Assay

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A 24-year-old male with a history of spondyloarthropathy presented with high fever, cervical lymphadenopathy and generalized maculopapular rash. He was treated with prednisolone for chronic uveitis before being switched to sulfasalazine 3 weeks prior to admission. Laboratory findings revealed marked leukocytosis with frequent atypical lymphocytes. Sulfasalazine was discontinued and the etiology of mononucleosis syndrome explored. During admission, he developed acalculous cholecystitis and hypotension. All symptoms quickly improved following administration of systemic corticosteroids. The investigation for infectious mononucleosis yielded negative results and a diagnosis of sulfasalazine-induced hypersensitivity syndrome was confirmed using enzyme-linked immunospot assays.

Key Words: Drug hypersensitivity; enzyme-linked immunospot assay; sulfasalazine

INTRODUCTION

Drug-Induced Hypersensitivity Syndrome (DIHS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe systemic reaction typically occurring 2-6 weeks after exposure to certain drugs. DIHS is characterized by fever, skin rash, internal organ dysfunction, and hematologic abnormalities either eosinophilia or atypical lymphocytosis.¹

There is no gold standard for DIHS diagnosis other than the proposed diagnostic criteria.²³ Sulfasalazine-induced hypersensitivity syndrome is rare but well-recognized.¹ Nevertheless, when clinical presentation is not straightforward, other causes must be excluded. The available diagnostic criteria are used for the validation of suspected cases, but are not designed for early diagnosis or distinguishing drug hypersensitivity from other diseases that give similar reactions.

The enzyme-linked immunospot (ELISPOT) assay is a sensitive method capable of detecting a small number of antigen-specific cytokine-producing cells. Recently, this technique has been introduced to confirm the diagnosis of delayed-type drug hypersensitivity reactions and may be useful in patients with a remote history of drug allergy.²⁴ We report herein a case of DIHS that presented with infectious mononucleosis-like reaction, complicated by acalculous cholecystitis and hypotension. Sulfasalazine hypersensitivity was proven by interferon-gamma (IFN-γ) ELISPOT assay.

CASE REPORT

A 24-year-old Thai male presented with high fever and abdominal pain for 4 days. The patient first noticed his fever accompanied with fatigue and a bitemporal throbbing pain without organ-specific symptoms, 2 weeks prior to admission. Laboratory findings revealed marked leukocytosis with frequent atypical lymphocytes. Sulfasalazine was discontinued and the etiology of mononucleosis syndrome explored. During admission, he developed acalculous cholecystitis and hypotension. All symptoms quickly improved following administration of systemic corticosteroids. The investigation for infectious mononucleosis yielded negative results and a diagnosis of sulfasalazine-induced hypersensitivity syndrome was confirmed using enzyme-linked immunospot assays.

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pering off within 11 months. Two months later, a diagnosis of spondyloarthropathy was suspected by the rheumatologist, when Achilles tenosynovitis, plantar fasciitis, and tenderness over the sacroiliac joints developed. Sulfasalazine was then prescribed starting at 1 g/day, gradually increasing to 2 g/day for 2 weeks prior to the development of fever.

Physical examination revealed high fever (38.5°C), cervical lymphadenopathy, pharyngitis with whitish patches on soft palate and buccal mucosa. The patient had a scattered maculopapular rash over his trunk and extremities and abdominal examination revealed mild epigastrium tenderness. A complete blood count revealed marked leukocytosis with a total white blood cell count of 23,740/µL, 50% neutrophils, 16% lymphocytes, 31% monocytes, and 3% eosinophils. Atypical lymphocytes were detected in peripheral blood smears. Blood culture and anti-viral antibody profiles were investigated; sulfasalazine was promptly discontinued.

On the third day of admission, the patient developed severe abdominal pain and mild icteric sclera was noted. Liver function tests showed direct hyperbilirubinemia with total bilirubin 3.34 mg/dL and direct bilirubin 2.94 mg/dL. ASL and ALT levels were 536 and 734 U/mL, respectively, and serum alkaline phosphatase was 301 IU/mL. Upper abdominal ultrasonography revealed gallbladder wall thickening with pericholecystic fluid collection and positive sonographic Murphy’s sign. Intra-operative ceftriaxone was then administered. On the ninth day of admission, he developed hypotension (blood pressure of 70/40 mmHg) before being rescued with 1,500-mL intravenous fluid.

The diagnosis of DIHS or DRESS can be challenging. Several diseases including acute infectious mononucleosis, hematologic malignancies, and collagen vascular disorders are known to share similar clinical presentations. Management of DIHS frequently requires systemic corticosteroids and may lead to deleterious effects in immunocompromised patients. Acalculous cholecystitis has been reported in drug-induced hypersensitivity syndrome, but is uncommon. Although this patient fulfilled the diagnostic criteria for DIHS, atypical presentation of acalculous cholecystitis and the lack of peripheral blood eosinophilia deferred systemic corticosteroid administration while bacterial and disseminated viral infections were being excluded.

Despite the pathogenesis of DIHS not being fully understood, a complex interaction between drug-specific immune responses accompanied with viral reactivation is a possible mechanism. The evidence of human herpes virus 6 reactivation, supported by the elevated anti-HHV-6 IgG levels, confirms the association between the development of DIHS and human herpes virus 6 infection, as reported previously. The lymphocyte transformation test (LTT) is a useful proliferation-based assay to assess T cell responses to drugs, but the technique is time-consuming. ELISPOT assays are more sensitive in the detection of low-frequency antigen-specific T cells, and IFN-γ ELISPOT as-

![Fig. 1](http://e-aair.org) - Acalculous cholecystitis with pericholecystic fluid collection as demonstrated by abdominal computed tomography scans. G, gallbladder.

![Fig. 2](http://e-aair.org) - Sulfasalazine-specific interferon-gamma responses as demonstrated by enzyme-linked immunospot assay.
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Sulfasalazine Allergy Confirmed by ELISPOT Assay

Says are effective for the diagnosis of drug-induced maculopapular rash.12

We report a case of sulfasalazine-induced hypersensitivity syndrome complicated with acalculous cholecystitis and hypotension, the diagnosis and treatment of which was delayed due to its atypical features. Our findings suggest the potential role of IFN-γ ELISPOT assays in confirming the diagnosis of DIHS in patients in whom the diagnosis is still doubtful, or identifying the culprit drug in patients with a history of multiple drug use.

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