

# 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 spondyloarthritis 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.<sup>1</sup>

There is no gold standard for DIHS diagnosis other than the proposed diagnostic criteria.<sup>2,3</sup> Sulfasalazine-induced hypersensitivity syndrome is rare but well-recognized.<sup>4</sup> 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.<sup>5</sup> 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- $\gamma$ ) 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 when attending an outpatient clinic. Viral infection was the presumptive diagnosis. His low-grade fever remained for several weeks until 4 days prior to admission, when high fever and a progressive maculopapular rash developed. He also experienced epigastric pain, which brought him to our hospital again seeking medical attention.

The patient was diagnosed with bilateral chronic uveitis 2 years ago, when topical steroids had been prescribed. Low-dose oral prednisolone (15 mg/day) was subsequently added before ta-

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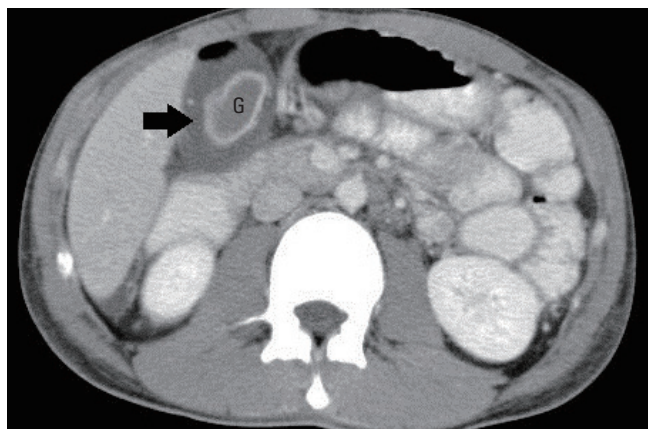
• There are no financial or other issues that might lead to conflict of interest.

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/ $\mu$ L, 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. Intravenous 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. Abdominal computed tomography scans showed a collapsed gallbladder with a moderate amount of pericholecystic fluid, but no gallstones could be demonstrated (Fig. 1); hepatosplenomegaly and minimal ascites were also noticed. Dexamethasone (5 mg) was administered every 12 h intravenously for six doses, resulting in cessation of the fever and abdominal pain, after the third dose.

The viral studies yielded negative results for IgM and IgG



**Fig. 1.** Acalculous cholecystitis with pericholecystic fluid collection as demonstrated by abdominal computed tomography scans. G, gallbladder.

against Epstein-Barr virus, cytomegalovirus, and Dengue virus. Blood culture results showed no bacterial growth. Anti-HIV and anti-human herpes virus 6 (HHV-6) IgM antibodies were also negative, but anti-HHV-6 IgG was positive (17.05 units with a cut-off value of 11 units). Two days after the initiation of steroids, the numbers of IFN- $\gamma$ -releasing cells in the peripheral blood were measured by ELISPOT assay (Mabtech, Stockholm, Sweden) upon stimulation with four drugs as described previously.<sup>6</sup> Significant numbers of IFN- $\gamma$ -secreting cells were demonstrated (1,048 spots forming cells/ $10^6$  PBMCs) upon incubation with 100  $\mu$ g/mL sulfasalazine, but not with other drugs administered concurrently (ceftriaxone), previously (amoxicillin), or never (ceftazidime) (Fig. 2). Dexamethasone was then replaced with prednisolone 1 mg/kg/day before being tapered off over 3 weeks. His liver function tests returned to normal levels in 1 month; no complications were noted after 2 years of follow-up. His symptoms are now well controlled with NSAIDs and methotrexate.

## DISCUSSION

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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup> The lymphocyte transformation test (LTT) is a useful proliferation-based assay to assess T cell responses to drugs, but the technique is time-consuming.<sup>11</sup> ELISPOT assays are more sensitive in the detection of low-frequency antigen-specific T cells, and IFN- $\gamma$  ELISPOT as-



**Fig. 2.** Sulfasalazine-specific interferon-gamma responses as demonstrated by enzyme-linked immunospot assay.

says are effective for the diagnosis of drug-induced maculopapular rash.<sup>12</sup>

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- $\gamma$  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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### REFERENCES

1. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am* 2009;29:481-501.
2. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.
3. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007; 156:1083-4.
4. Kunisaki Y, Goto H, Kitagawa K, Nagano M. Salazosulfapyridine induced hypersensitivity syndrome associated with reactivation of human herpes virus 6. *Intern Med* 2003;42:203-7.
5. Beeler A, Engler O, Gerber BO, Pichler WJ. Long-lasting reactivity and high frequency of drug-specific T cells after severe systemic drug hypersensitivity reactions. *J Allergy Clin Immunol* 2006;117: 455-62.
6. Tanvarasethee B, Buranapraditkun S, Klaewsongkram J. The potential of using enzyme-linked immunospot to diagnose cephalosporin-induced maculopapular exanthems. *Acta Derm Venereol* 2013;93:66-9.
7. Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Saf* 1999;21:489-501.
8. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. The DRESS syndrome: a literature review. *Am J Med* 2011; 124:588-97.
9. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* 2006;55:1-8.
10. Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, Belaich S, Crickx B. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001;137:301-4.
11. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy* 2004;59:809-20.
12. Rozieres A, Hennino A, Rodet K, Gutowski MC, Gunera-Saad N, Berard F, Cozon G, Bienvenu J, Nicolas JF. Detection and quantification of drug-specific T cells in penicillin allergy. *Allergy* 2009;64: 534-42.