

## Drug-Induced Hypersensitivity Syndrome Combined with Hemophagocytic Lymphohistiocytosis related to Piperacillin-Tazobactam: A Case Report

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Drug-induced hypersensitivity syndrome (DIHS) ,also known as drug response with eosinophilia and systemic symptoms (DRESS), which is characterized by fever, rash, elevated eosinophils, various internal organ impairment, and lymph node enlargement [1]. Hemophagocytic lymphohistiocytosis (HLH) is a rare, highly lethal disease that can be distinguished as primary or secondary HLH depending on whether the disease is caused by inherited or acquired abnormalities in immune regulation [2]. In recent years, several investigators have found that DIHS and HLH have similar clinical manifestations and laboratory findings, suggesting that both diseases can not only co-exist but also may be share a common immune mechanism [3,4]. However, no cases of DIHS combined with HLH caused by piperacillin-tazobactam have been reported so far. We performed a report of a patient confirmed as DIHS combined with HLH related to piperacillin-tazobactam in our center. Informed consents were obtained from the patient and his family for the writing and publication of this article.

A 43-year-old male was admitted to the hospital in January 2022 due to right chest pain with shortness of breath after activity for more than half a month. He had no previous underlying disease. Chest CT showed right pleural effusion with right lower lung atelectasis (Supplementary Figure 1A), and the patient was treated empirically with piperacillin-tazobactam combined with levofloxacin after admission. Levofloxacin was discontinued on day 3 as relevant tests showed no basis for atypical pathogenic infections. On Day 12, the patient began to develop intermittent fever, with a progressive temperature that reached a maximum of 40.1 °C on Day 15 (Supplementary Figure 2), accompanied by a red rash mainly distributed over the trunk of the body (Figure 1A).

A follow-up chest CT showed no progression of intrapulmonary lesions (Supplementary Figure 1B), and next-generation sequencing (NGS) of the tracheoscopic lavage fluid indicated *Streptococcus pneumoniae* and *Streptococcus pseudopneumoniae*. A delayed allergic reaction to piperacillin-tazobactam was considered, and it was discontinued and replaced with imipenem combined with linezolid. The patient later developed coagulation abnormalities, with a markedly prolonged TT up to 160 sec, accompanied by a decrease in fibrinogen and a marked bleeding tendency. A large hematoma appeared after blood collection from the right femoral artery (Figure 1B), along with elevated liver enzymes and blood creatinine. Imipenem and linezolid were stopped on Day 17, and then the patient's eosinophil count gradually increased to  $2.10 \times 10^9/L$  and the leukocyte count increased to

25.01\*10<sup>9</sup>/L (Supplementary Figure 2). In addition, we found that the patient's triglycerides were significantly elevated (3.81 mmol/L).

Combined with the patient's clinical manifestations and laboratory findings, DIHS was considered, with a RegiSCAR score of 7(Supplementary Table 1) [5]. Considering that the patient had severe coagulation disorders and significantly elevated triglycerides, we further performed tests such as ferritin, bone marrow aspiration biopsy, sCD25, and NK-cell activity. The results showed that the patient's ferritin was as high as 3260mg/ml, and the bone marrow aspiration results suggest phagocytosis with reduced NK cell activity, all the results supporting the diagnosis of HLH according to HLH- 2004 diagnostic criteria (Supplementary Table 2) [6]. Then we applied intravenous human immunoglobulin (pH4) to the patient (20g/d for 5 days)), systemic corticosteroid therapy (intravenous methylprednisolone sodium succinate 1mg/kg/d for 7 days, then slowly reduce the amount), and rational transfusion of plasma according to the patient's coagulation results. On Day 24, the patient's fever stopped, the generalized rash slowly subsided, and the relevant indices gradually returned to normal. One month after discharge, the patient's all laboratory parameters returned to normal and the pulmonary lesions were gradually absorbed compared to before. To further clarify the allergenic drugs, we performed a drug lymphocyte stimulation test (DLST) with piperacillin-tazobactam and levofloxacin 9 months after the patient was discharged from the hospital, and the results showed

marked lymphocyte proliferation by piperacillin-tazobactam

(stimulation index (S.I.) was 628%), while levofloxacin was negative (S.I. was 116%)

In addition to skin rash and fever, the patient mainly showed severe hepatic impairment, with transaminase levels more than 3 times the high limit of normal, as well as renal impairment. This multisystem impairment caused by DIHS is another important feature to differentiate from common drug allergies. Coagulation abnormality was the most severe manifestation in this patient, who had a significant tendency to bleed. The results of the patient's ferritin, triglycerides, bone marrow aspiration and biopsy allowed us to confirm the patient's diagnosis of HLH.

DIHS presents with elevated CD4 / CD8 T cells, and untreated cases may eventually lead to increased proliferation and activity of macrophages as inflammatory cytokines remain elevated. This may be one of the mechanisms by which HLH occurs in DIHS [7]. Rosemary et al reported a case with rash, fever, eosinophilia, and liver function impairment after 3 weeks of minocycline application, which was clearly diagnosed as DIHS according to the RegiSCAR criteria. However, the patient had both splenomegaly and elevated ferritin, and he also developed hypertriglyceridemia after the application of glucocorticoids, so the patient had four diagnostic criteria for HLH. Fortunately, the patient had a decrease in ferritin soon after the application of glucocorticoids, which led the researchers to quickly rule out the diagnosis of HLH, as HLH often requires immunosuppressants and biological agents before the symptoms and indicators are improved [8].

Ammar et al. reported a case of a 45-year-old male diagnosed with DIHS after the application of sulfasalazine. This patient had concomitant HHV-6 reactivation and HLH, who was eventually died due to gastrointestinal bleeding [9]. Jason et al retrospectively analyzed the case data of 23 patients with DIHS combined with HLH, and the results showed that the mortality rate among these patients was significantly higher than that of patients diagnosed with DIHS alone, reaching 24% [10]. In addition, a large proportion of DIHS patients did not have a differential diagnosis of HLH, resulting in a missed diagnosis in most patients.

Therefore, it is recommended that screening related to HLH (such as coagulation function, triglycerides, ferritin, spleen ultrasound) be routinely performed in patients with DIHS to achieve the goal of early diagnosis, early treatment, and reduced morbidity and mortality. To our knowledge, this is the first reported case of DIHS combined with HLH caused by piperacillin-tazobactam.

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### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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**Figure 1.** Rash on the right upper limb (A) and hematoma at the femoral artery puncture (B).

