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【 CASE REPORT 】

# Acute Liver Failure Due to Hypereosinophilic Syndrome Accompanied by Duodenal Perforation

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**Abstract:**
A 78-year-old woman presenting with severe acute liver failure was admitted to our hospital. On screening for the etiology of acute liver failure, it was diagnosed as being due to idiopathic hypereosinophilic syndrome (eosinophil count reported as 4766/μL; 33.8% of the white blood cells). Her medical history included marked eosinophilia, as observed six months prior to this admission. Corticosteroid therapy was initiated. During the clinical course, duodenal perforation occurred but was managed promptly by appropriate surgery. A liver biopsy, following the initiation of corticosteroid therapy, revealed degenerating hepatic cells with mild eosinophilic infiltration. With corticosteroid therapy, the liver function improved.

**Key words:** hypereosinophilic syndrome, acute liver failure, liver biopsy, corticosteroid therapy

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## Introduction

Hypereosinophilic syndrome (HES) was first reported by Hardy and Anderson in 1968 as a group of disorders characterized by marked eosinophilia (1). According to the criteria proposed by Chusid et al., idiopathic HES is diagnosed by the sustained elevation of a peripheral blood eosinophil count over 1,500/μL for more than 6 months with single or multiorgan involvement, when reactive or myeloid monoclonal hypereosinophilia can be excluded (2). In HES, eosinophilic infiltration involves various organs such as the skin, lungs, gastrointestinal tract, heart, and central nervous system (3). There have been several reports of liver damage associated with HES; however, severe cases leading to acute liver failure are rare (4-6).

We herein report a case of acute liver failure due to HES.

## Case Report

A 78-year-old woman presented to our hospital with a fever, malaise, and diarrhea for 10 days. She had a history of nontuberculous mycobacterial infection and bullous pemphigoid. For the treatment of these diseases, she was taking eltrombopag, clarithromycin, levofloxacin, rifampicin, carbocysteine and ambroxol. She had no history of new medication prescription in the past two years, and she did not take any herbal medicines or health foods. She had undergone splenectomy for idiopathic thrombocytopenic purpura and was asymptomatic with marked eosinophilia (2,510-5,500/μL), as reported 6 months prior to this admission. Blood tests performed three months prior to admission showed liver enzyme levels within normal limits. Her height and weight were 146.5 cm and 40.3 kg, respectively.

On admission, a physical examination revealed marked jaundice and edematous erythema on the chest, abdomen, and extremities. Blood test results on admission are shown

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**Table. Laboratory Findings on Admission.**

| | | | |
|---|---|---|---|
| White blood count | 14,100 /μL | IgG | 2,339 mg/dL |
| Eosinophil | 33.8 % | IgG4 | 112 mg/dL |
| Segmented cell | 55 % | IgE | 12,877 IU/mL |
| Lymphocyte | 6.6 % | ANA | <40-fold |
| Monocyte | 4.4 % | HAV-IgM | negative |
| Red blood count | $378\times10^4$ /μL | HBsAg | negative |
| Hemoglobin | 12.9 g/dL | Anti-HCV Ab | negative |
| Platelet count | $2.6\times10^4$ /μL | HEV-IgA | negative |
| | | EBV- IgM | negative |
| Prothrombin activity | 37 % | CMV-IgM | negative |
| Prothrombin time-INR | 1.89 | CMV antigenemia | negative |
| | | | |
| AST | 727 U/L | TSH | 2.58 μIU/mL |
| ALT | 268 U/L | Free T4 | 0.89 ng/dL |
| LDH | 491 U/L | | |
| ALP | 641 U/L | | |
| GGT | 40 U/L | | |
| ChE | 43 U/L | | |
| T-Bil | 19.5 mg/dL | | |
| D-Bil | 14.9 mg/dL | | |
| Alb | 2.0 g/dL | | |
| BUN | 14 mg/dL | | |
| CRE | 0.67 mg/dL | | |
| CRP | 3.3 mg/dL | | |

INR: international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, ChE: cholinesterase, T-Bil: total bilirubin, D-Bil: direct bilirubin, Alb: albumin, BUN: blood urea nitrogen, CRE: creatinine, CRP: C-reactive protein, Ig: immunoglobulin, ANA: anti-nuclear antibody, HAV: hepatitis A virus, HBsAg: hepatitis B surface antigen, anti-HCV Ab: anti-hepatitis C virus antibody, HEV: hepatitis E virus, EBV: Epstein-Barr virus, CMV: cytomegalovirus, TSH: thyroid-stimulating hormone, T4: thyroxine

in Table. The eosinophil count was 4766/μL (33.8% of the white blood cells). Liver function test results were consistent with severe liver damage: total bilirubin, 19.5 mg/dL; aspartate aminotransferase (AST), 727 U/L; alanine aminotransferase (ALT), 268 U/L. The prothrombin activity had decreased to 37% (international normalized ratio of prothrombin time, 1.89). Although her usual platelet count was about 300,000/μL, it had dropped to 26,000/μL.

Computed tomography (CT) revealed a small amount of ascites and periportal edema (Fig. 1A). The density of liver parenchyma appeared to have decreased heterogeneously. No signs of biliary obstruction were observed. Based on these findings, the patient was diagnosed with acute liver failure.

Although the AST and ALT levels as well as the prothrombin activity gradually improved, severe liver damage persisted for more than a week following admission (Fig. 2). Absence of clinical evidence to suggest viral or drug-induced liver injury supported our diagnosis of liver failure caused by HES. A bone marrow examination revealed no increase in blast cells. FIP1L1-PDGFRA fusion, PDGFRB rearrangement, and FGFR1 rearrangement, which suggest neoplastic hypereosinophilia, were not detected by fluorescence *in situ* hybridization. A G-banding analysis showed no chromosomal abnormalities. Myeloperoxidase anti-neutrophil cytoplasmic autoantibody (ANCA), a marker of ANCA-associated vasculitis, was also negative. Thus, a final diagnosis of idiopathic HES was made.

Corticosteroid therapy (prednisolone 30 mg/day, 0.7 mg/kg) was started on day 10 of admission. However, a prior liver biopsy could not be performed, considering the high risk of bleeding due to coagulopathy caused by liver failure. After starting corticosteroid therapy, the levels of AST and ALT and the eosinophil count markedly decreased, and edematous erythema also disappeared.

On day 16 of admission, the patient complained of the sudden onset of strong abdominal pain. Computed tomography revealed free air in the abdominal cavity, and duodenal perforation was diagnosed (Fig. 1B). A 1-cm perforation was found at the anterior wall of the duodenal bulbs, and omental patch repair was performed (Fig. 1C).

Following surgery there was a transient rise in the levels of AST and ALT and the eosinophil count. However, they decreased with the continuation of corticosteroid therapy. An improvement in the coagulopathy status facilitated a liver biopsy on day 24 of admission. The liver tissue showed mild eosinophilic infiltration, which is widely observed in hepatic lobules and Glisson's capsules with degenerating hepatic

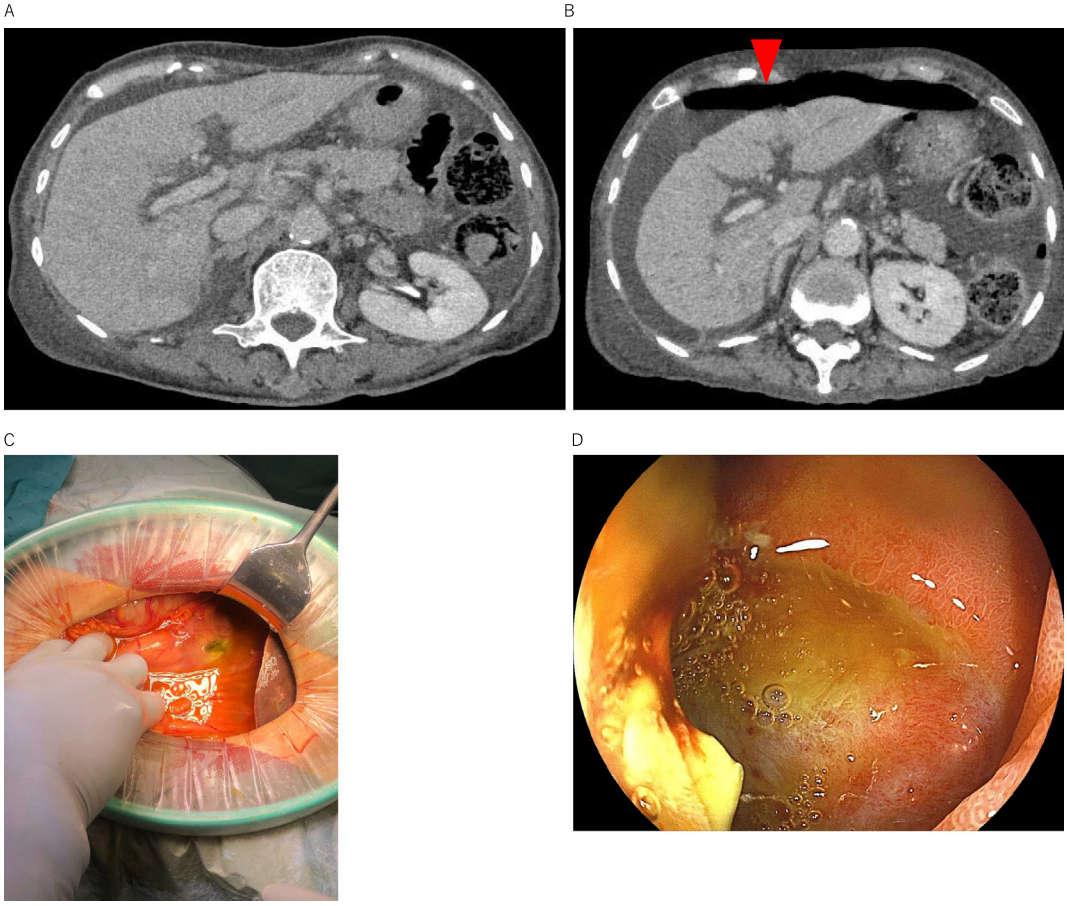


**Figure 1.** **(A) Computed tomography (CT) findings on admission. Small amounts of ascites and periportal edema can be observed, suggesting acute liver failure. The density of the liver parenchyma is seen to have decreased heterogeneously. (B) CT findings of duodenal ulcer perforation. The image shows a large amount of free air in the abdominal cavity (red arrowhead). The liver has become more atrophic than at admission. Ascites also appears to have increased. (C) Photograph of the perforated duodenal ulcer, taken during surgery. A 1-cm perforation can be seen at the duodenal bulb. (D) Endoscopic image of the perforated site in the duodenal bulb on post-operative day 7. The perforation site is seen lined with the omentum patch.**

cells (Fig. 3). Degenerating hepatic cells disappeared in some areas where eosinophils, lymphocytes, and lipofustin-laden macrophages had infiltrated. Significant infiltration of plasma cell was not seen. Consistent with the transient re-elevation of AST and ALT after surgery, edematous erythema also reappeared.

A skin biopsy of the erythema showed mild liquefaction degeneration; however, definite eosinophilic infiltration of the skin was not observed. The edematous erythema consequently disappeared with improvement in liver enzymes levels. Nineteen days after surgery, esophagogastroduodenoscopy was performed (Fig. 1D). The perforated duodenal hole was successfully repaired with an omentum patch. Several ulcers other than the perforated one were also found near the perforation area. A biopsy of the duodenal ulcers showed no definite eosinophilic infiltration.

There was no observed re-elevation of liver enzyme levels and eosinophilic count on tapering doses of corticosteroids. On day 61 of admission, the patient was discharged on prednisolone 15 mg/day. After discharge, the dose of prednisolone was tapered to 4 mg/day. At present, one year after starting treatment, the liver enzyme levels remain within normal limits, suggesting no relapse of liver damage.

## Discussion

We reported a case of acute liver failure caused by HES. Liver failure and eosinophilia improved with corticosteroid therapy. The diagnosis was made based on a clinical assessment and liver biopsy.

HES is classified into three categories: primary (neoplastic), secondary (reactive; may occur due to allergies or infections), and idiopathic (7). Based on a bone marrow examination and the clinical course, we diagnosed the present patient with idiopathic HES.

Hepatic involvement in HES has been reported previously with a frequency of 30-32% (4, 5). Several reports have described cases of chronic hepatitis. However, acute liver failure due to HES is rare. Aoyama et al. reported a 46-year-old man who was diagnosed with severe acute hepatitis caused

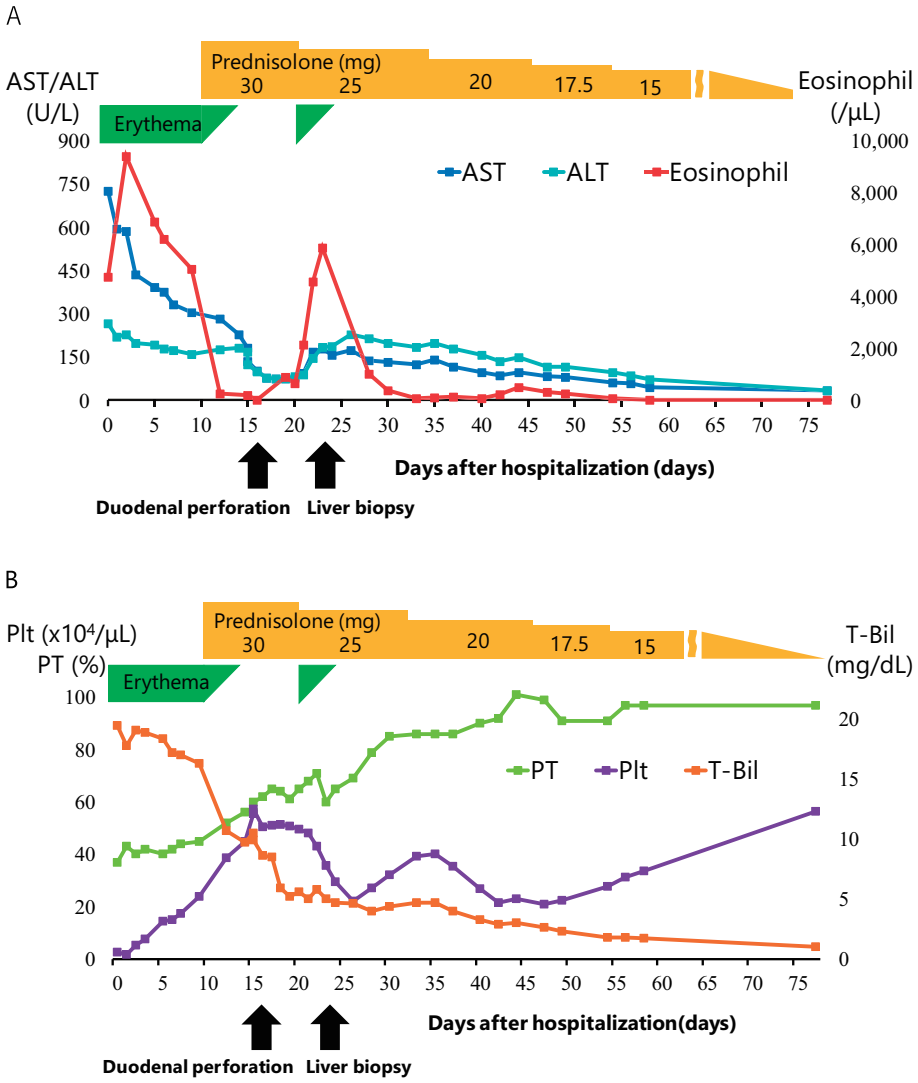


**Figure 2.** **The clinical course. The level of aspartate aminotransferase (AST) and eosinophil count gradually decreased after admission and then decreased even further on the initiation of prednisolone 30 mg/day on day 10 of admission. On day 16 of admission, duodenal ulcer perforation was diagnosed. Following the surgery for perforation, the level of AST and eosinophil count transiently increased and then decreased again with continuation of corticosteroid therapy. A liver biopsy was performed on day 24 of admission. The AST level and eosinophil count showed no marked change, regardless of the reduction in the corticosteroid dose.**

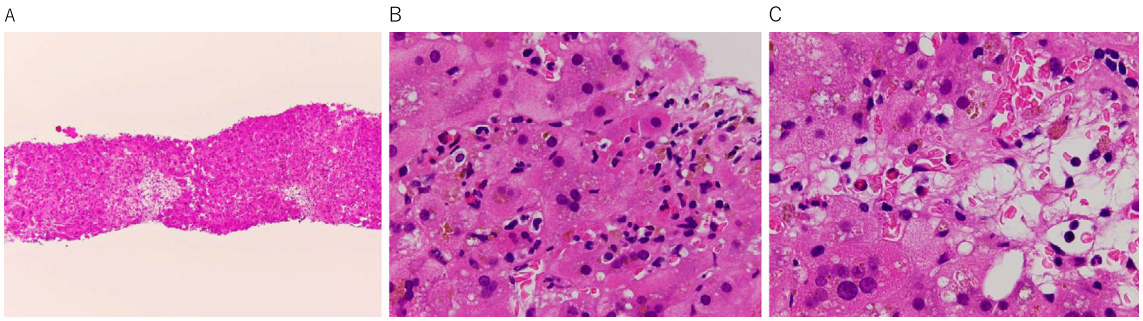


**Figure 3.** **Pathological findings of the liver biopsy. (A): A liver tissue obtained with a needle biopsy demonstrated two focal lesions in the lobular area with dilated sinusoids. (B): Many eosinophils infiltrated the hepatic sinusoid of the lobules with degenerating hepatic cells and bile thrombi. (C): The focal lesions showed the disappearance of degenerating hepatic cells. Note that the lesions showed infiltrating eosinophils and lymphocytes as well as lipofustin-laden macrophages.**

by HES (8). Acute liver failure was severe, and the patient underwent plasma exchange. The patient was treated with corticosteroid. Hepatitis recurred twice on reducing the corticosteroid dosage. Finally, he was treated with a combination of corticosteroid and azathioprine. In contrast, our patient was able to be treated with corticosteroid monotherapy and reported no relapse of liver damage, even after reducing the dose of corticosteroid. In their case, serum immunoglobulin G4 (IgG4) levels were elevated. They reported that the level of IgG4 was associated with the eosinophil count and the clinical condition. However, in our case, elevation of the IgG4 level was not observed.

Previous reports have described acute (8) and chronic (9, 10) liver injury associated with HES. However, it is difficult to distinguish between purely acute, acute on chronic, and chronic liver injury when patients do not undergo blood tests before the diagnosis of liver injury. In our case, the patient underwent regular blood tests in our hospital for idiopathic thrombocytopenic purpura and nontuberculous mycobacterial infection, and elevation of liver enzymes was never observed before this episode. Thus, the liver injury was able to be diagnosed as acute, not chronic or acute on chronic. For this reason, the present case is noteworthy.

HES presents with various manifestations. Ogbogu et al. reported that, in a study of 188 patients, the most common presenting manifestation of HES was dermatologic (37%), followed by pulmonary (25%) and gastrointestinal (14%) (3). In the present case, the patient presented mainly with dermatologic and gastrointestinal symptoms. She initially presented with diarrhea and edematous erythema in the skin and was later diagnosed with duodenal perforation. These manifestations were possibly associated with HES, although they could not be pathologically confirmed.

Eosinophilic gastritis, enterocolitis, and colitis were previously reported as symptoms of gastrointestinal tract involvement of HES (5). Inayat and Hurairah reported a 20-year-old man with gastrointestinal and hepatic involvement in HES (11). The patient had a seven-month history of progressively worsening jaundice. On CT, the colon showed loss of a normal mucosal pattern. Colonoscopy showed mild inflammatory changes, mucosal edema, patchy erythema, and loss of vascularity, consistent with mildly active chronic colitis. Gastrointestinal and hepatic involvement were simultaneously observed, similar to the present case. Khallaayoune et al. reported a patient with HES who presented with bullous pemphigoid-like rash (12). In our case, although the patient had a history of bullous pemphigoid, the skin rash that appeared at the time of the diagnosis of HES was considered to be different from bullous pemphigoid, based on the findings of the skin biopsy.

**The authors state that they have no Conflict of Interest (COI).**

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