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CASE REPORT

Carbamazepine-Induced DRESS Complicated by HLH and VBDS: A Case Report

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Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe systemic disorder characterized by fever, rash, and multi-organ involvement, often complicated by drug-induced liver injury. Hemophagocytic lymphohistiocytosis (HLH) and vanishing bile duct syndrome (VBDS) are rare but life-threatening complications that can be triggered by antiepileptic drugs such as carbamazepine. Given the high mortality associated with these conditions, early recognition and timely intervention are crucial for improving patient outcomes.

Case: We report a unique case of an elderly woman who developed DRESS syndrome after using carbamazepine, complicated by both HLH and VBDS. The patient exhibited typical DRESS symptoms, including fever, rash, and eosinophilia, alongside signs of HLH such as hemocytopenia and elevated ferritin levels; along with persistent significant hyperbilirubinemia and coagulation abnormalities.

Results: After six months, liver function showed substantial improvement, with no signs of HLH recurrence. Additionally, our review of HLH cases induced by antiepileptic drugs highlights that the absence of eosinophilia, hemocytopenia, and elevated ferritin levels is key for early HLH identification.

Conclusion: Our findings highlight key diagnostic indicators for early HLH recognition in antiepileptic drug-induced DRESS, especially the absence of eosinophilia. This case represents the first successful management of DRESS syndrome complicated by HLH and VBDS without liver transplantation in the past decade, emphasizing the critical role of early identification and prompt, targeted treatment strategies in optimizing patient outcomes.

Keywords: drug reaction with eosinophilia and systemic symptoms, vanishing bile duct syndrome, hemophagocytic lymphohistiocytosis, immune overactivation

Introduction

Carbamazepine, a widely used anticonvulsant, is a well-known trigger of severe hypersensitivity reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.[1,2] While hepatic involvement is common in DRESS, from mild elevations in liver enzymes to severe liver dysfunction, and progressing to vanishing bile duct syndrome (VBDS) is exceedingly rare.[3,4] The most common causes include drug-induced liver injury, hematologic malignancies, autoimmune diseases, and infections. Prognosis varies based on the underlying cause and extent of bile duct loss. However, severe cases can progress to biliary cirrhosis and liver failure, requiring liver transplantation. Early identification and intervention are crucial for improving outcomes.[5,6] DRESS syndrome can also be complicated by hemophagocytic lymphohistiocytosis (HLH), a life-threatening hyperinflammatory syndrome, also a hyperinflammatory condition characterized by immune dysregulation.[7,8] Common causes of HLH include infections, such as infectious triggers, malignancies, autoimmune diseases, and genetic mutations. Some studies have suggested a potential link between DRESS and HLH, proposing that both conditions may share underlying pathophysiological mechanisms involving immune dysregulation and severe inflammation.[8] This case highlights the successful management of carbamazepine-induced DRESS syndrome complicated by HLH and VBDS. Early diagnosis and intervention facilitated effective treatment.

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Case Presentation

A 75-year-old woman presented with dark urine for more than two weeks and generalized fatigue with a poor appetite one week before admission. The day before admission, she developed a low-grade fever (37.3°C) but did not report any abdominal pain, distension, cough, sputum production, or urinary symptoms such as frequency, urgency, or discomfort. An abdominal CT scan revealed mildly enlarged retroperitoneal lymph nodes without other significant abnormalities. One month earlier, she had been prescribed carbamazepine at a dose of 0.6 mg per day, divided into three doses, for her trigeminal neuralgia. She had no significant medical history and no known history of food or medication allergies, including carbamazepine, in herself or her family members.The patient denied any history of travel or exposure to tick bites or other insect bites.

On the morning of admission, the patient noticed purplish-red rashes over her body, accompanied by itching and a fever of 39.8°C. (Figure 1A and B) The patient was alert and oriented, with no signs of encephalopathy. There was no improvement in her fatigue, poor appetite, or yellow urine. Liver function tests revealed: total bilirubin at 275.5 μmol/L, direct bilirubin at 168.8 μmol/L. The abdomen is soft, with no tenderness or rebound tenderness. Given the significant increase in bilirubin levels, the patient was diagnosed with liver insufficiency and admitted to the gastroenterology department. After admission, the patient's rash rapidly progressed, accompanied by facial and eyelid edema, recurrent fever, and oliguria. (Figure 1C and D) By the third day, bilirubin levels had increased to 362 μmol/L, hemoglobin and platelet counts had gradually decreased, atypical lymphocytes had risen to 20%, and serum creatinine had increased to 285 μmol/L. Ultrasound examination revealed multiple enlarged lymph nodes and splenomegaly. Given the patient's delayed rash, systemic lymphadenopathy with splenomegaly, recurrent fever with temperatures exceeding 38°C, acute liver and kidney dysfunction, and significant increase in atypical lymphocytes, along with the history of carbamazepine use in the past month, DRESS was diagnosed according to the RegiSCAR scoring system[9](Supplementary Table 1). It is noteworthy that the patient's eosinophil count and percentage did not significantly increase. We conducted next generation sequencing(NGS) of blood and other tests, which did not provide evidence of bacterial or viral infection. We initiated treatment with intravenous methylprednisolone. Given the significant elevation in bilirubin, we also performed plasmapheresis to reduce bilirubin levels and decrease inflammatory mediators and immune complexes in the blood. Post-treatment, the patient's rash and acute renal insufficiency significantly improved, with notable resolution of rash and edema by the third day of treatment.(Figure 1E and F).

During this period, the patient's hemoglobin and platelets continued to decline, with platelets dropping to 26×10^9/L. Bilirubin levels exceeded 600 μmol/L, and fibrinogen levels decreased significantly (Supplementary Table 2). The current

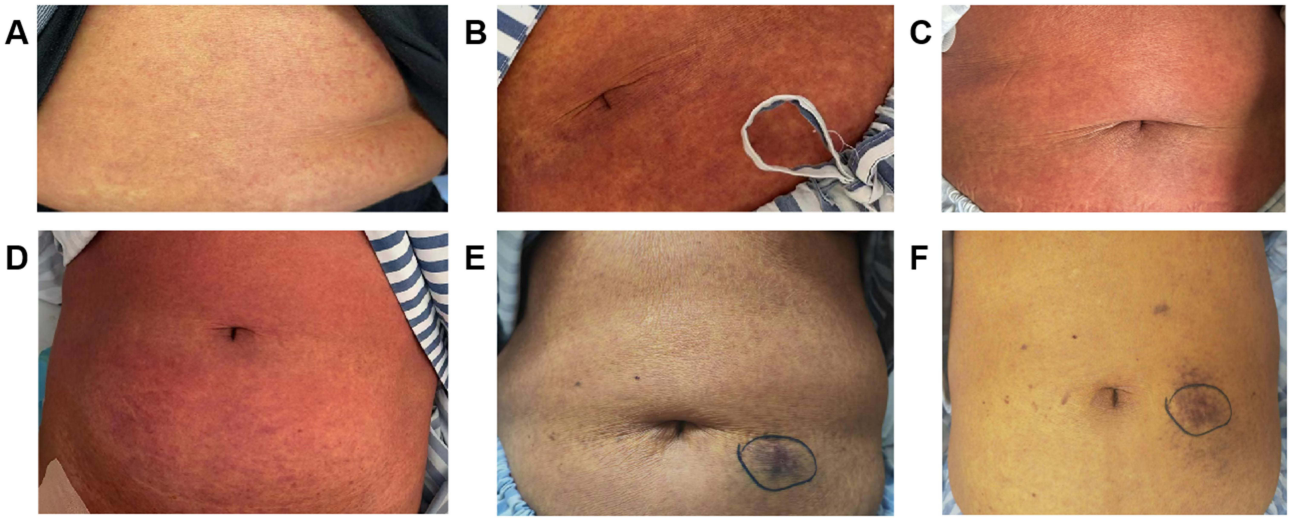

Figure 1 Clinical presentation of skin rash in a patient with DRESS syndrome before and after treatment. (**A–F**) illustrate the progression of the abdominal rash on days 1, 2, 4, 5, 8, and 10 after admission. By the second day, the rash had become widespread, accompanied by facial edema. Hormone therapy was initiated on the fourth day. By the eighth day, the rash had largely subsided.

corticosteroid dose was maintained, and human immunoglobulin was added to reduce circulating immune complexes. Further investigations ruled out infections, connective tissue disorders, and malignancies. Due to significantly elevated ferritin levels, decreased NK cell activity, and increased CD25 expression, the patient was diagnosed with hemophagocytic lymphohistiocytosis (HLH) based on the HLH-2004 diagnostic criteria[10,11] (Supplementary Table 3). Subsequent PET/CT scans and a bone marrow biopsy ruled out tumor-related conditions, suggesting an immune-related etiology for the HLH. Bone marrow biopsy revealed hyperactive marrow; however, hemophagocytic activity was not observed.

Therefore, we adjusted the hormone dosage and administered dexamethasone intravenously once daily. The patient's blood parameters gradually improved. However, bilirubin levels remained persistently elevated above 600 μmol/L, and plasma exchange did not provide improvement. We conducted further assessments, including tests for viral hepatitis, autoimmune hepatitis, thyroid function, and ceruloplasmin, as well as an MRCP scan. The patient denied any history of hyperlipidemia or alcohol consumption. With a Roussel Uclaf Causality Assessment Method score of 10,[12] carbamazepine was deemed highly likely to have caused drug-induced liver injury. (Figure 2).

We initiated treatment with ursodeoxycholic acid (UDCA) for cholestatic therapy, alongside hormone therapy for HLH. After one month of continuous oral treatment, the patient's bilirubin levels gradually decreased, and coagulation function improved. A liver biopsy was performed to identify the underlying cause. The biopsy revealed multiple bile duct deletions in the portal area, only two CK19-positive small bile ducts were detected in a whole liver biopsy specimen, indicating a rare case of VBDS. (Figure 3A) And the immunofluorescence-stained HHV-6 in the patient's liver biopsy tissue was negative. (Figure 3B) Consequently, we continued long-term oral administration of ursodeoxycholic acid. After six months of follow-up, the patient's bilirubin levels slowly decreased to 70 μmol/L (Figure 3C and 3D).

Methods

To further investigate, a liver biopsy was performed, using multiple immunofluorescence stained to assess bile duct and cholestasis-related damage, and to check for viral reactivation Epstein-Barr virus (EBV)(123771-1-AP, proteintech, America) and Human Herpesvirus 6(HHV-6)(ab128404, Abcam, England) following steroid therapy. Informed consent was obtained from the patient for publication of this case report and accompanying images.

Tyramide Signal Amplification

Paraffin-embedded tissue sections were baked at 62°C for 1 hour, then deparaffinized in xylene and rehydrated through graded ethanol solutions. To block endogenous peroxidase, sections were treated with hydrogen peroxide and then subjected to antigen retrieval in Tris-EDTA buffer. Sections were blocked with 5% BSA and incubated overnight with the first primary antibody at 4°C. After equilibration, sections were washed, incubated with a secondary antibody, and subjected to tyramide signal amplification (TSA). This process was repeated for additional primary antibodies, using TSA-Cy3 and TSA-Cy5 for

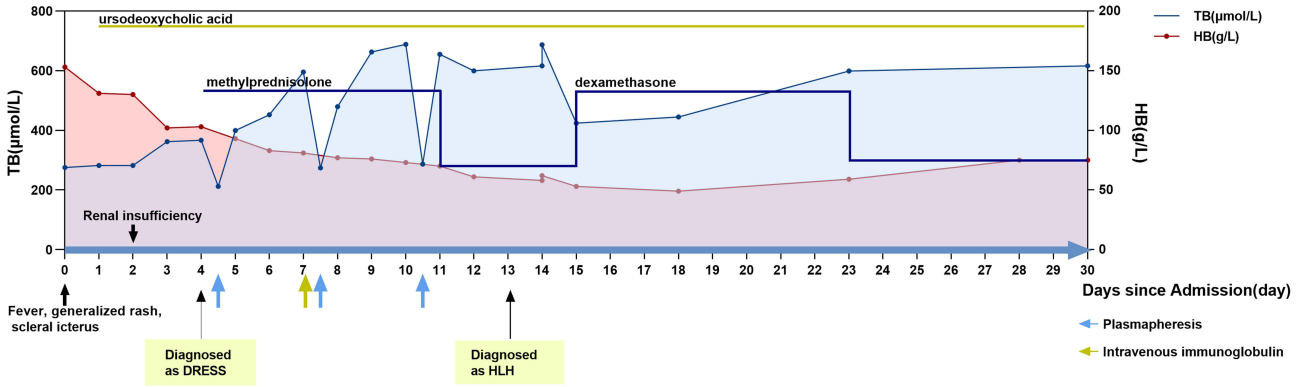

Figure 2 Timeline of the patient's diagnosis, treatment, and key biomarker changes. This figure depicts the changes in hemoglobin and bilirubin levels during the early stages of the disease. As the disease progressed, the patient underwent plasma exchange, received human immunoglobulin, and hormone therapy, with hormone dosages adjusted according to the patient's condition.

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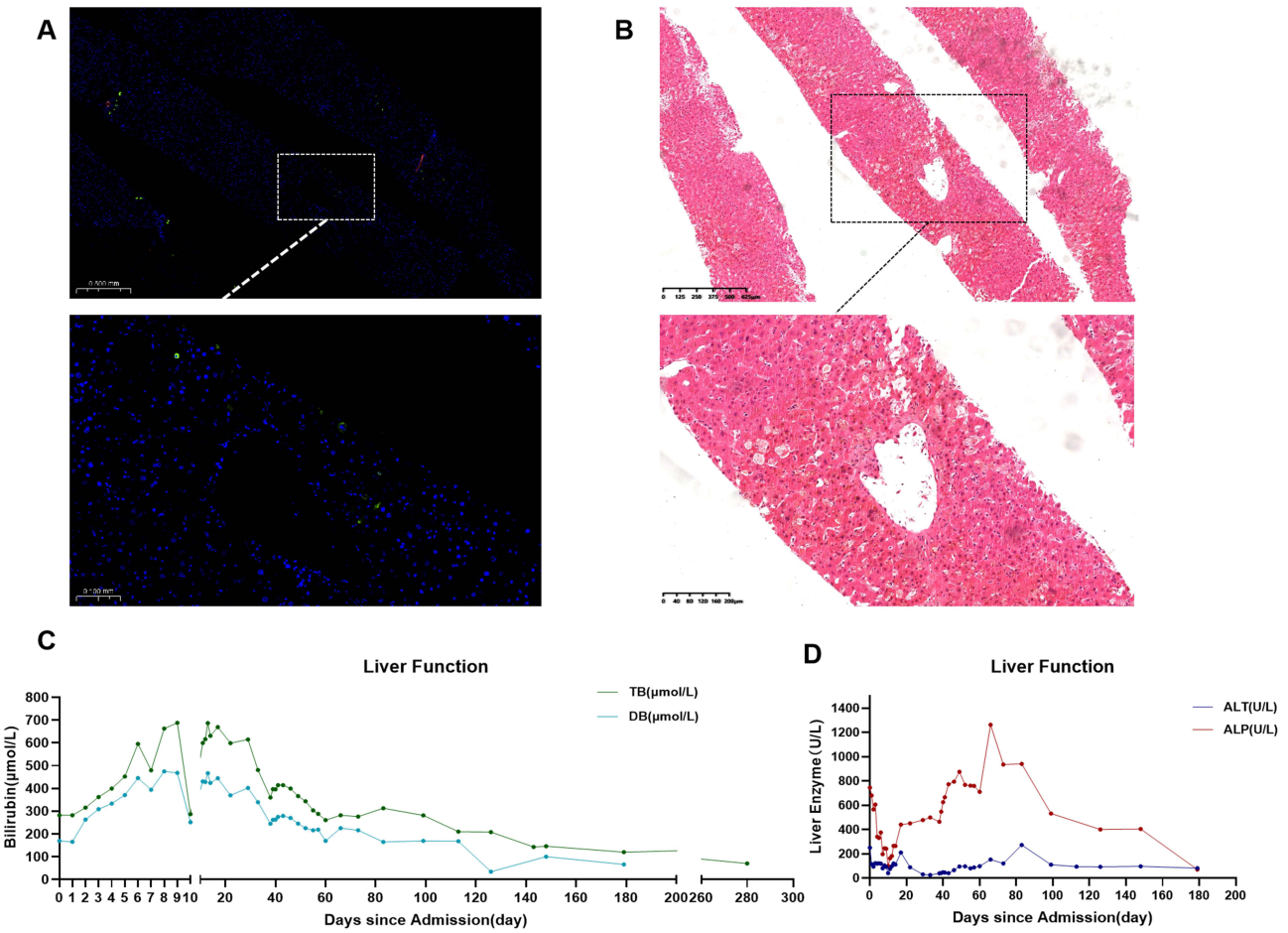

Figure 3 Liver histopathology and changes in liver function during the clinical course of this patient with DRESS syndrome. (**A** and **B**) show HE staining of the liver biopsy, revealing areas of missing bile ducts. (**C** and **D**) display multiple immunofluorescence staining for CK7 and CK19 in the corresponding areas of the liver biopsy. No CK19-positive small bile ducts were detected; only CK7-positive cholestatic liver cells were observed. Figure E illustrates the fluctuation of bilirubin levels during treatment. (**C** and **D**) show the changes in liver function during treatment.

subsequent antibodies. Finally, sections were mounted with an antifade medium containing DAPI. All slices were scanned utilising the PerkinElmer Vectra (Vectra 3.0.5, PerkinElmer, Massachusetts, USA). (Supplementary).

Discussion

This case report describes a patient who developed a severe hypersensitivity reaction to carbamazepine, presenting as DRESS syndrome. The condition further complicated into HLH and VBDS. DRESS, HLH, and VBDS are all rare but severe drug reactions with high mortality rates and the potential for multi-organ damage. This case is particularly unusual because the patient developed HLH and VBDS in addition to DRESS syndrome. To our knowledge, this is the first reported case of carbamazepine-induced HLH and VBDS, highlighting the complex interplay between drug-induced hypersensitivity and immune system dysregulation.[13–18] This reactivation leads to excessive immune activation, resulting in the characteristic hyperinflammatory response of HLH.[19] Early detection of HLH is crucial for improving patient outcomes, as timely intervention can mitigate the risk of multi-organ failure and mortality. In this case, the prompt recognition of HLH allowed for the initiation of immunosuppressive therapies, effectively controlling the hyperinflammatory state and preventing further progression. Delayed diagnosis often results in irreversible organ damage and a poorer prognosis. This case, along with similar reported instances, underscores the need for heightened clinical awareness of atypical HLH presentations in the context of severe drug reactions such as DRESS syndrome.

DRESS syndrome is a severe and potentially life-threatening condition characterized by a constellation of symptoms including fever, rash, lymphadenopathy, and multi-organ involvement. This syndrome typically manifests 2 to 6 weeks

after the initiation of the causative drug, making early recognition critical for effective management.[1,3,8,20] Despite the well-established association of DRESS with various drugs, recent studies have highlighted a concerning overlap with HLH, a hyperinflammatory syndrome that can further complicate the clinical picture. In DRESS syndrome, viral reactivation including of HHV-6, Epstein-Barr virus (EBV), and CMV has been widely recognized as a trigger for HLH. Viral reactivation can lead to excessive immune activation, resulting in persistent inflammation, cytokine storm, and hemophagocytosis, ultimately causing secondary HLH. Studies have shown that HHV-6 reactivation is one of the most common triggers in DRESS-associated HLH. However, in this case, immunofluorescence staining for HHV-6 in the patient's liver tissue was negative, the severe immune dysregulation induced by carbamazepine-triggered DRESS syndrome itself may have played a predominant role in the development of HLH. This underscores the heterogeneity of mechanisms underlying HLH in DRESS syndrome, where viral reactivation is a critical but not universal factor. The overlap between DRESS and HLH, though not widely reported, is an emerging concern, particularly in the context of anti-epileptic drugs (AEDs). The similarities and correlations in the mechanisms of DRESS syndrome and HLH can lead to the occurrence of DRESS overlapping with HLH, or to drugs directly inducing HLH.[21] DRESS often involves significant immune activation, as evidenced by T-cell proliferation and a cytokine storm, including cytokines such as IFN-γ, TNF-α, and IL-2. These mechanisms are also critical in the pathophysiology of HLH.[8] Additionally, AEDs can directly affect humoral and cellular immunity by altering the expression and synthesis of various molecules, primarily cytokines. For example, carbamazepine can increase the levels of cytokines like IL-1, IL-2, and IL-6.[22] AEDs may also induce hypogammaglobulinemia, particularly affecting IgG4 and IgM, which could partly explain the association between B-cell and T-cell immunosuppression and viral reactivation.[23,24] The association between DRESS syndrome and HLH involves significant immune system activation and dysregulation. HLH induced by AEDs is extremely rare.[7]

The challenge in clinical practice arises when a patient presents with DRESS and fails to respond to initial treatment, subsequently developing HLH. The diagnosis of HLH in such cases is often delayed, typically taking around 2 weeks to establish, during which time the patient's condition may deteriorate significantly.[19] This delay underscores the importance of considering HLH early in the differential diagnosis, particularly in patients with a lack of response to treatment for DRESS. In the case presented, the patient exhibited symptoms of fever, dark urine, and rash upon hospital admission, yet no increase in eosinophils was observed throughout the treatment course. This clinical observation is particularly noteworthy, as it aligns with findings from a review of reported cases of HLH induced by AEDs over the past decade. The review revealed that patients initially diagnosed with HLH often presented with symptoms that closely mimic those of DRESS, such as fever, rash, and liver dysfunction. However, a key distinguishing feature was the persistent decline in blood cell counts, a significant rise in ferritin levels, and the absence of eosinophilia. These findings suggest that clinicians should maintain a high index of suspicion for HLH in patients with suspected DRESS syndrome, especially when eosinophil levels do not rise as expected, and there is evidence of hemocytopenia and elevated ferritin levels.[21,25–34] Early identification and treatment are crucial to improving outcomes in this complex and overlapping clinical scenario, and Table 1 provides a summary of the distinguishing features between DRESS syndrome and HLH in the context of AEDs use (Table 1).

In terms of treatment, the standard management of DRESS syndrome typically involves systemic corticosteroids.[35] In severe cases, intravenous immunoglobulin (IVIG) or other immunosuppressants may be required. The treatment of HLH, however, is more complex and often requires high doses of corticosteroids combined with immunosuppressants such as cyclosporine or etoposide, with possibly a longer treatment duration.[11] A treatment algorithm proposed by the French group led by Descamps et al suggests that in cases where severe complications like HLH occur in patients with drug hypersensitivity, continuous use of systemic corticosteroids and IVIG is recommended.[36] In the present case, the patient's HLH improved after adjusting the hormone dosage.We reviewed the treatment and prognosis of anticonvulsant drug-induced HLH cases reported in the past 10 years and found that most cases have a good prognosis with early diagnosis and treatment (Table 2).

Hepatic involvement is common in DRESS syndrome, with reported incidence rates ranging from 51% to 84% among affected patients.[1,3,37] Less common gastrointestinal manifestations of DRESS syndrome include acute pancreatitis, colitis, esophagitis, and autoimmune enteropathy, which can present with abdominal pain, diarrhea, dysphagia, and weight loss. A systematic review found pancreatic involvement in 56.9% of cases, colitis in 41.2%, and esophageal involvement in 7.8%, while gastric involvement and autoimmune enteropathy are rare but clinically significant.[38,39] Besides, DRESS syndrome frequently involves the kidneys. Approximately 13% to 35% of patients with DRESS

Table 1 Characteristics of Published Cases Antiepileptic Drug-Induced HLH

Ref.	Ignaszewski et al[25]	Hancock et al[26]	Suleman et al[27]	Koning et al[28]	Kaur et al[29]	Kırık et al[31]	Zhou et al[32]	Lakhoua et al[33]	Swanson et al[34]	Mandato et al[21]
Fever	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Skin and mucosa		Y	Y		Y	Y	Y	Y	Y	Y
Hemocytopenia	Y	Y	Y		Y		Y	Y	Y	
Splenauxe		Y				Y		Y		Y
Lymphadenopathy						Y				Y
Other systems are involved	Y	Y	Y	Y			Y	Y	Y	Y
TG>3mmol/L/FG<1.5g/L	Y		Y		Y	Y	Y	Y		Y
Ferritin>500ng/mL	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Haemophagy is found	Y	Y	Y	Y	Y	Y	Y		Y	
The number or activity of NK cells decreased			Y						Y	Y
CD25 elevation		Y	Y	Y						
Eosinophils are elevated									Y	
Atypical lymphocytes were found										

Abbreviation: Y, Patients have related symptoms or test positive.

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Table 2 Treatment Protocols and Prognosis of Antiepileptic Drug-Induced HLH Cases Reported in the Last 10 years

Ref.	Medicine	Patient no.	Age/Gender	Treatment	DRESS	Skin and Mucosa	Prognosis	Liver Function
Ignaszewski et al[25]	Lamotrigine	1	26/male	Etoposide and dexamethasone	N	Not described	Improve	Not described
Hancock et al[26]	Lamotrigine	1	47/male	Etoposide and dexamethasone	N	Diffuse rash	Improve	Not described
Suleman et al[27]	Lamotrigine	1	31/male	Etoposide and dexamethasone	N	Morbilliform rash covering the chest and back, extending into the neck and face	Improve	Hepatocellular damage
Koning et al[28]	Lamotrigine	1	43/male	Supportive care	N	Not described	Improve	Hepatocellular damage
Kaur et al[29]	Carbamazepine	1	4/female	Oral prednisolone	N	Flushed skin and petechial rashes over the face	Improve	Not described
Kırık et al[31]	Oxcarbazepine	1	3/male	Intravenous immunoglobulin	N	Rash and widespread edema	Improve	Hepatocellular damage
Zhou et al[32]	Lamotrigine	1	45/female	Etoposide and dexamethasone	N	Maculopapular rash on the trunk and bilateral lower extremities	Improve	Hepatocellular damage
Lakhoua et al[33]	Phenobarbital	1	24/female	Steroids	N	Maculopapular eruption on the whole body	Improve	Mixed injury
Swanson et al[34]	Phenytoin, lamotrigine, levetiracetam, and phenobarbital	1	21/female	Chemotherapeutic treatment	Y	Cutaneous rash	Died	Not described
Mandato et al[21]	Palproate	1	11/male	Prednisone	Y	Generalized rash	Improve	Hepatocellular damage

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; N, DRESS not complicated by HLH; Y, DRESS complicated by HLH.

syndrome experience renal involvement, presenting as acute kidney injury.[40] In some cases, the kidney may be the only affected internal organ, accounting for approximately 21% of cases.[41] The estimated mortality rate of DRESS syndrome is around 10%, primarily due to liver failure.[42] Recently, attention has been focused on drug-induced liver injury associated with DRESS. Hepatic involvement in DRESS can manifest as various types of liver injury, including hepatocellular damage, cholestatic injury, and mixed injury. Cholestatic injury in DRESS syndrome is relatively rare, accounting for about 12% of cases.[43] It is characterized by elevated bilirubin and alkaline phosphatase levels and often leads to a poorer prognosis due to the potential for long-term liver dysfunction and chronic liver disease. Cholestatic injury can be further classified into conditions such as cholangitis, pericholangitis, and VBDS.[44] VBDS is a severe cholestatic liver disease characterized by the progressive disappearance of intrahepatic bile ducts, leading to severe cholestasis and liver dysfunction. Patients with VBDS may experience prolonged liver insufficiency, and in some cases, liver transplantation may be necessary[45]. The treatment of VBDS typically involves discontinuing the offending drug and providing supportive care. Common treatment regimens include the use of ursodeoxycholic acid, plasma exchange, and liver support therapy. A case report has described the use of long-term immunosuppression.[46] There have been anecdotal reports of success in treating drug-induced VBDS unresponsive to UDCA alone by using plasmapheresis and methylprednisolone.[47,48] It can be observed that the treatment plan for severe VBDS is similar to that for DRESS syndrome and HLH, as both conditions require the suppression of the severe inflammatory response associated with the disease. In this case, the patient initially underwent plasma exchange. However, the effect was limited, as liver function markers rapidly rose again due to severe cholestasis shortly after plasma exchange. Subsequent treatments included corticosteroid therapy and IVIG. Following a period of maintenance with low-dose corticosteroids and long-term UDCA therapy, the patient's bilirubin levels gradually decreased to 70 μmol/L.

HLH associated hepatitis typically presents with significant hepatomegaly, markedly elevated ALT and AST levels, and rapid deterioration of liver function. Cholestasis is relatively rare in HLH patients but can significantly worsen liver dysfunction and prognosis when it occurs. Literature on the combination of HLH and VBDS is extremely limited, with only a few case reports available. In the past 10 years, we found only four case reports, all of which had poor outcomes: two patients were waiting for liver transplantation, and two patients died.[14,15,17,49] This highlights the severe and complex nature of this combination. This case provides experience for the treatment of severe DRESS and further induced HLH and VBDS. Unlike most DRESS cases, this patient did not exhibit significant eosinophilia. While eosinophilia is considered a hallmark of DRESS, cases complicated by HLH may exhibit immune dysregulation that prevents a marked increase in eosinophil counts. This atypical presentation underscores the need for clinicians to consider DRESS even in the absence of eosinophilia, and vigilance is required for potential progression to HLH. Additionally, this case highlights the intersection of HLH and VBDS management. The standard treatment for HLH primarily involves immunosuppressive therapy, including corticosteroids and intravenous immunoglobulin. While this approach provided some benefit during the acute phase of VBDS, long-term management required sustained therapy with UDCA and close monitoring. The patient ultimately showed gradual improvement with prolonged UDCA and low-dose corticosteroids treatment.

Conclusion

Our study highlights the importance of closely monitoring key indicators in DRESS patients, particularly when eosinophilia is not significantly elevated, as this may indicate early-stage HLH rather than a typical DRESS presentation. Additionally, we summarize the key diagnostic features of AEDs-induced HLH, providing important clinical references for the early identification and differential diagnosis of DRESS syndrome. Notably, this case represents the successful management of drug-induced HLH complicated by VBDS without the need for liver transplantation in recent decade, offering valuable insights for the treatment of similar cases. These findings further underscore the critical role of early recognition and precise intervention in improving the short-term prognosis of patients with severe immune-mediated complications and provide further guidance for the long-term management of drug-induced VBDS.

Consent for Publication

The patient has provided written informed consent for the publication of data concerning the case presentation included in this article.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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