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A Severe Multisystem Inflammatory Illness Mimicking DRESS Syndrome: Diagnostic Uncertainty and the Possible Role of Viral Infection

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Case Report

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Abstract

Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe inflammatory condition involving the skin and internal organs. Diagnosis is challenging when clinical findings overlap with other disorders and no clear trigger is identified.

Case Presentation

A 59-year-old woman presented with fever, a progressive desquamating rash, eosinophilia, acute kidney injury, and hepatic injury. Liver biopsy demonstrated eosinophil-predominant portal inflammation, raising consideration of drug-induced liver injury. Extensive medication review and infectious testing identified no convincing culprit drug or definitive infectious trigger. She recovered without immunosuppressive treatment, with normalization of liver function within two to three months and no recurrence or new thyroid or glycemic dysfunction during more than one year of follow-up.

Conclusion

This case highlights the diagnostic challenges of a severe DRESS-like multisystem inflammatory illness of uncertain etiology. Distinguishing a clinical presentation suggestive of DRESS from confirmed drug causality is essential to avoid unsupported drug allergy labeling and guide follow-up.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS), also termed drug-induced hypersensitivity syndrome (DiHS), is a potentially severe cutaneous adverse reaction characterized by fever, rash, hematologic abnormalities, and internal organ involvement, most commonly hepatitis [1, 2]. Symptoms typically develop two to eight weeks after exposure to the causative medication [1, 2]. Diagnosis can be challenging because DRESS overlaps clinically with infectious, autoimmune, and other inflammatory disorders. The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system incorporates clinical and laboratory findings to support diagnostic classification [2, 3]. No single clinical or histopathologic finding independently establishes DRESS [2–4].

Herpesvirus reactivation, particularly human herpesvirus 6 (HHV-6), has been associated with DRESS, although its role in pathogenesis remains uncertain [5]. In a scoping review of 748 patients, HHV-6 reactivation was reported in approximately 63% of those tested, usually two to four weeks after symptom onset [6]. This timing highlights the importance of appropriately timed virologic testing.

Parvovirus B19 can also cause rash and systemic symptoms that complicate the differential diagnosis. Although hepatitis is uncommon in adults, reported cases range from mild aminotransferase elevations to severe hepatic injury [7]. Parvovirus B19 serology must be interpreted in the context of testing timing, as isolated IgG positivity generally indicates previous exposure [7]. This case describes a severe DRESS-

like multisystem inflammatory illness in which neither a convincing culprit drug nor a definitive infectious trigger was identified.

Case Presentation

A 59-year-old woman with a history of severe obesity treated with sleeve gastrectomy seven years earlier, iron deficiency anemia, obstructive sleep apnea, depression, prediabetes, and intermittent asthma developed fever, chills, headache, myalgias, profound fatigue, and a progressive pruritic rash on September 27, 2025. The rash began on the trunk, spread to the extremities, and progressed to scaling and desquamation. Her temperature reached 102°F. Initial SARS CoV 2 and influenza testing was negative.

She was hospitalized from September 28 to October 7, 2025, with a sepsis-like illness characterized by tachycardia, tachypnea, leukocytosis with immature granulocytes, hypotension, and elevated lactate. An antecubital lesion raised concern for cellulitis. She received piperacillin tazobactam from September 28 to October 2, vancomycin from October 3 to October 6, and doxycycline beginning October 6 after vancomycin was discontinued because of rising creatinine. Blood cultures were negative. Her course was complicated by acute kidney and hepatic injury, hyperbilirubinemia, and jaundice. Computed tomography showed mildly enlarged mesenteric and periportal lymph nodes measuring up to 14 mm. Abdominal and renal ultrasonography were otherwise unrevealing. The rash progressed to prominent desquamation and persisted into late 2025.

Liver biopsy showed moderately active hepatitis with moderate to severe eosinophil predominant portal inflammation, moderate lobular inflammation, mild interface activity, mild interlobular duct injury, and mild ductular reaction. No significant steatosis, apoptotic hepatocyte injury, or canalicular cholestasis was identified. As per the pathologist, the differential included drug induced liver injury (DILI), autoimmune hepatitis, and viral hepatitis. Eosinophil rich inflammation favored DILI, while the absence of prominent plasma cells and marked necroinflammatory activity made autoimmune hepatitis less likely. However, the findings were nonspecific and could not establish a cause [8]. Parvovirus B19 immunohistochemical staining was negative.

Given the fever, diffuse desquamating rash, eosinophilia, hepatic injury, and acute kidney injury, DRESS was considered. Medication review identified no convincing culprit drug. Pantoprazole, fluoxetine, and famotidine had been taken for several years, while semaglutide had been initiated approximately five months before symptom onset. A single perioperative dose of cefazolin, along with fentanyl, lidocaine, propofol, tranexamic acid, acetaminophen, ondansetron, and meloxicam, had been administered approximately 100 days before symptom onset, weakening the temporal association. Piperacillin tazobactam, vancomycin, and doxycycline were started after symptoms began and could not explain the initial presentation. The patient denied initiating any over-the-counter medications, dietary or herbal supplements, or recreational drugs during the 3 months preceding symptom onset (latency period). No exposure to other recognized DRESS associated drug classes was identified.

Extensive infectious testing did not establish an acute infection. Testing for hepatitis A through E, HIV, CMV, EBV, and HHV 7 was negative for acute infection. Cerebrospinal fluid PCR testing was negative for HHV 6, CMV, HSV 1/2, VZV, and other bacterial and viral pathogens. Parvovirus B19 and HHV 6 serologies obtained on December 10, 2025, showed positive IgG and negative IgM. Parvovirus B19 immunohistochemical staining of liver tissue was also negative.

The illness resolved without corticosteroids or other immunosuppressive therapy, and liver function normalized within two to three months. No recurrence occurred during more than one year of follow-up. Thyroid stimulating hormone and hemoglobin A1c remained normal, with no evidence of new thyroid or glycemic autoimmune disease.

Discussion

This case illustrates the diagnostic challenge of a severe multisystem inflammatory illness resembling DRESS without a convincing culprit drug. The absolute eosinophil count increased from 0.6 × 10^3/μL on September 28, 2025, to 1.0 × 10^3/μL on October 7 and remained elevated on October 27. Peak AST and ALT were 239 and 240 U/L, respectively, total bilirubin reached 4.2 mg/dL, and alkaline phosphatase peaked at 836 U/L. Although these findings were clinically compatible with DRESS, a definitive diagnosis could not be established in the absence of a convincing culprit drug.

Medication review did not identify an exposure with a compelling temporal relationship to symptom onset. Longstanding use of pantoprazole, fluoxetine, and famotidine, the five-month interval since semaglutide initiation, and the approximately 100-day interval since perioperative cefazolin exposure weakened causal attribution. Antibiotics administered during hospitalization followed the onset of symptoms. This uncertainty is clinically relevant because an unsupported cefazolin allergy label could unnecessarily restrict future perioperative antibiotic options [1, 2].

An unidentified infection, particularly a viral illness, remains a plausible alternative. The acute febrile onset, sepsis like presentation, and resolution without immunosuppressive therapy support this possibility. However, extensive infectious testing did not identify a definitive pathogen.

Parvovirus B19 is an uncommon but recognized cause of hepatitis in adults. Although adult infection more commonly causes mild systemic symptoms or arthropathy, reported cases include fever, rash, and hepatic injury, occasionally with severe liver dysfunction [7]. During early viremia, fever and malaise may occur, and viral DNA or capsid antigen may be detectable. As the immune response develops, viremia generally declines and rash may appear. IgM may become detectable during this period, while IgG develops during recovery and can persist long term. In this patient, delayed serologic testing revealed positive IgG and negative IgM, while liver tissue immunostaining for viral capsid protein was negative. These findings do not establish acute parvovirus B19 infection. Although an earlier infection cannot be completely excluded, the evidence is insufficient to attribute the illness to parvovirus with confidence.

HHV 6 reactivation has been associated with DRESS and often occurs after symptom onset, although its role in disease development remains uncertain [5, 6, 9]. The delayed testing in this case limited retrospective assessment of viral activity. Similarly, the eosinophil rich portal inflammation and lobular hepatitis on liver biopsy were compatible with drug related liver injury but were not specific for DRESS or another etiology [4, 8].

Autoimmune hepatitis was considered less likely because biopsy lacked prominent plasma cells and marked necroinflammatory activity. The absence of recurrence and spontaneous resolution further reduce the likelihood of a persistent autoimmune disorder, although an autoimmune mechanism cannot be definitively excluded.

Overall, the most defensible interpretation is a severe DRESS like multisystem inflammatory illness of uncertain etiology. The acute course and spontaneous recovery raise the possibility of an unidentified viral infection, but neither an infectious cause nor drug related causality was established. Continued clinical follow up remains appropriate given the potential for delayed autoimmune complications reported after DRESS.

Conclusion

This case describes a severe DRESS-like multisystem inflammatory illness characterized by fever, diffuse desquamation, eosinophilia, hepatic injury, and acute kidney injury. Despite extensive medication review and infectious testing, neither a convincing culprit drug nor a definitive infectious trigger was identified. The acute course and spontaneous recovery without immunosuppressive therapy raise the possibility of an unidentified viral infection, although this remains unconfirmed. This case highlights the challenges of distinguishing DRESS from infectious and other inflammatory mimics and the importance of cautious causal attribution when the underlying etiology remains uncertain.

Declarations

Ethics approval and consent to participate: A research determination outcome letter was obtained from the Kaiser Permanente Northern California Research Determination Office (KPNC-RDO). Consent to participate was not applicable, as this case report did not involve prospective research participation.

Consent to publish: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials: Not Applicable.

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Author Contributions: EN drafted the manuscript. RV, the treating physician, contributed to the clinical management of the patient, provided clinical expertise, and reviewed the manuscript. CC provided supervision and critically reviewed the manuscript. All authors discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

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Figures



Figure 1

Images of patient’s hand presentation.

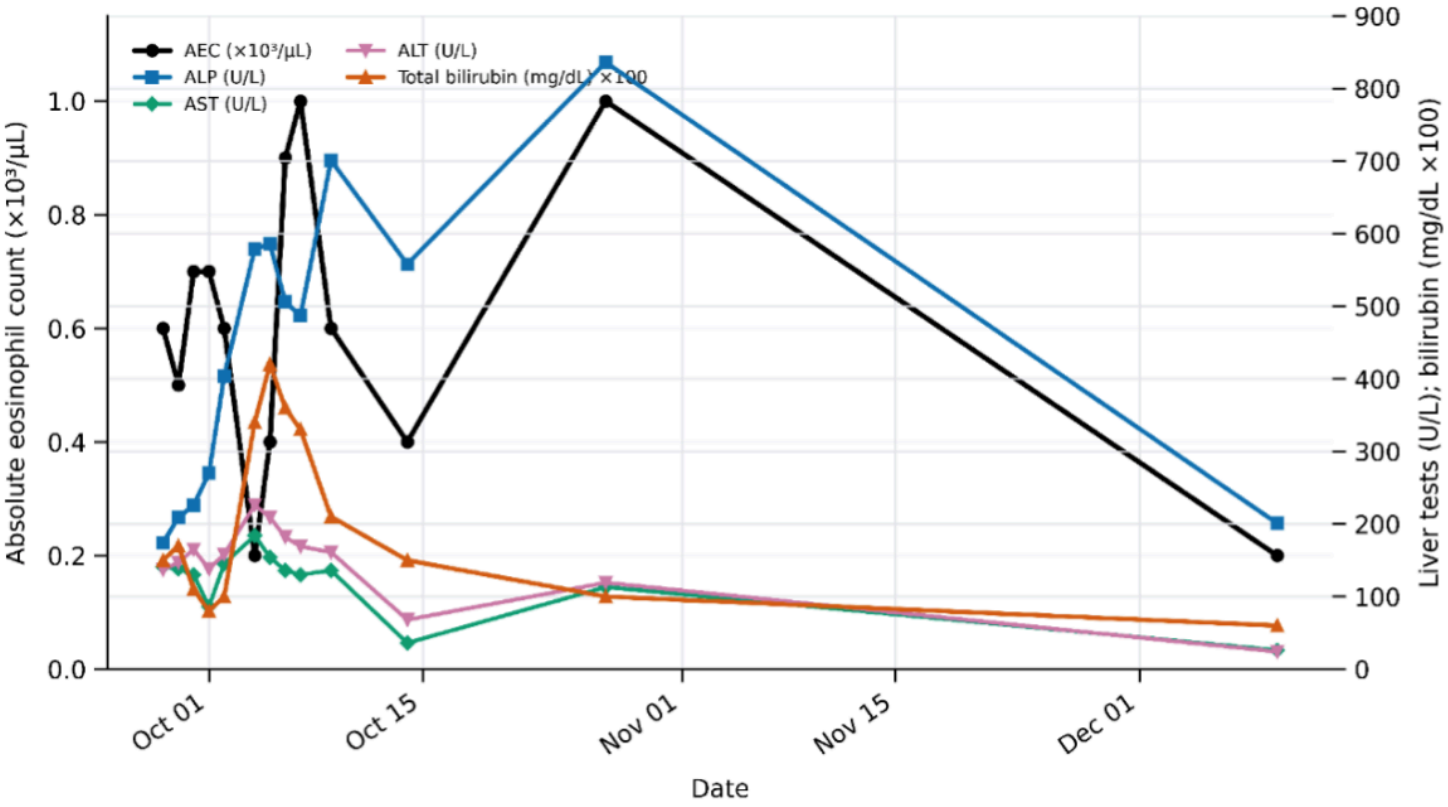


Figure 2

Temporal relationship between eosinophilia and liver biochemical abnormalities

Figure legend. Serial absolute eosinophil count (AEC), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin during illness and recovery. Total bilirubin is plotted as mg/dL multiplied by 100 on the right axis. Bilirubin peaked at 4.2 mg/dL on October 5, 2025. AST and ALT peaked at 239 U/L and 240 U/L on October 3. AEC reached 1.0 × 10³/μL on October 7 and October 27, while ALP peaked at 836 U/L on October 27. By December 10, AEC, ALP, AST, ALT, and bilirubin had decreased to 0.2 × 10³/μL, 201 U/L, 26 U/L, 24 U/L, and 0.6 mg/dL, respectively.

Supplementary Files

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- HighlightsandAbbreviations.docx