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*Letter to the Editor*

# Probable drug-induced systemic reaction without blood eosinophilia and rash- utility of eosinophilic cationic protein for diagnosis

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Dear Editor

A 53-year-old male was admitted to our hospital from another institution due to acute dyspnea on hospital day 6. The initial diagnosis at the external hospital was bursitis prepatellaris after a bite of unknown origin 8 days prior to the initial presentation at the external hospital. His medical history included mechanical aortic valve replacement under phenprocoumon and bronchial asthma without baseline therapy. At admission to our hospital, treatment included amoxicillin/clavulanic acid, metamizole, pantoprazole, unfractionated heparin, and ibuprofen (Figure 1).

On clinical examination, blood pressure was 142/77 mmHg, heart rate was 89 beats per minute, and temperature was 37.5°C, whereas oxygen saturation was 90% in ambient air. Moreover, hyperthermia, swelling, and redness of the left knee were also observed. No cutaneous manifestation, including facial oedema, was observed in our patient. Laboratory investigations showed leucocytosis of 11.02 G/l (normal range 3.5–10) with a lymphopaenia of 0.57 G/l (1.18–3.74) and elevated C-reactive protein of 183 mg/L (<5). Aspartate transaminase (AST) was 122 U/L (<50), and alanine aminotransferase (ALT) was 159 (<50), indicating a transaminitis. Similarly, gamma-glutamyl transferase (GGT) was 526 U/L (8–61), and alkaline phosphatase (ALP) was 198 U/L (40-129). Furthermore, the R ratio was found to be 2.07, pointing to hepatitis with mixed hepatocellular and cholestatic patterns.[1] Creatinine and blood urea nitrogen concentrations were on the upper normal limits, whereas the estimated glomerular filtration rate (eGFR) was mildly decreased (Table 1). Computer tomography of the thorax demonstrated mediastinal and bihilar lymphadenopathy without intestinal alterations of the lung parenchym. Abdominal ultrasound showed normal findings with the exception of splenomegaly.

Based on the persistent knee infection, treatment with amoxicillin/clavulanic acid, metamizole, and ibuprofen was continued; knee puncture and samples taken during wound revision remained without growth. Intraoperative findings were non-irritant. Moreover, due to persistent respiratory distress, torasemide and furosemide were administrated once (Figure 1).

On hospital day 8 (2 days after admission to our hospital), the patient developed acute renal failure (Table 1) with proteinuria of 54.71 mg/mmol (normal <0.15); cholestatic parameters also worsened (Table 1). Abdominal ultrasound showed diffuse alterations of the renal parenchyma and no liver injuries. With the suspicion of acute nephropathy in the context of treatment with non-steroidal anti-inflammatory drugs or renal failure of prerenal etiology in the context of furosemide administration, the abovementioned drugs were stopped, and the patient was hydrated. Due to persistent fever (up to 38.6°C), the antibiotic therapy was also changed to cefazolin and vibramycin (Figure 1). However, clinical and laboratory findings continued to worsen (Table 1).

Persistent fever, respiratory distress, hepatitis, acute nephropathy, splenomegaly, and mediastinal and bihilar lymphadenopathy led to a wide differential diagnosis, including infections, rheumatic and haematologic diseases, and autoimmune and allergic reactions. Extensive diagnostic investigation regarding infectious diseases included hepatitis

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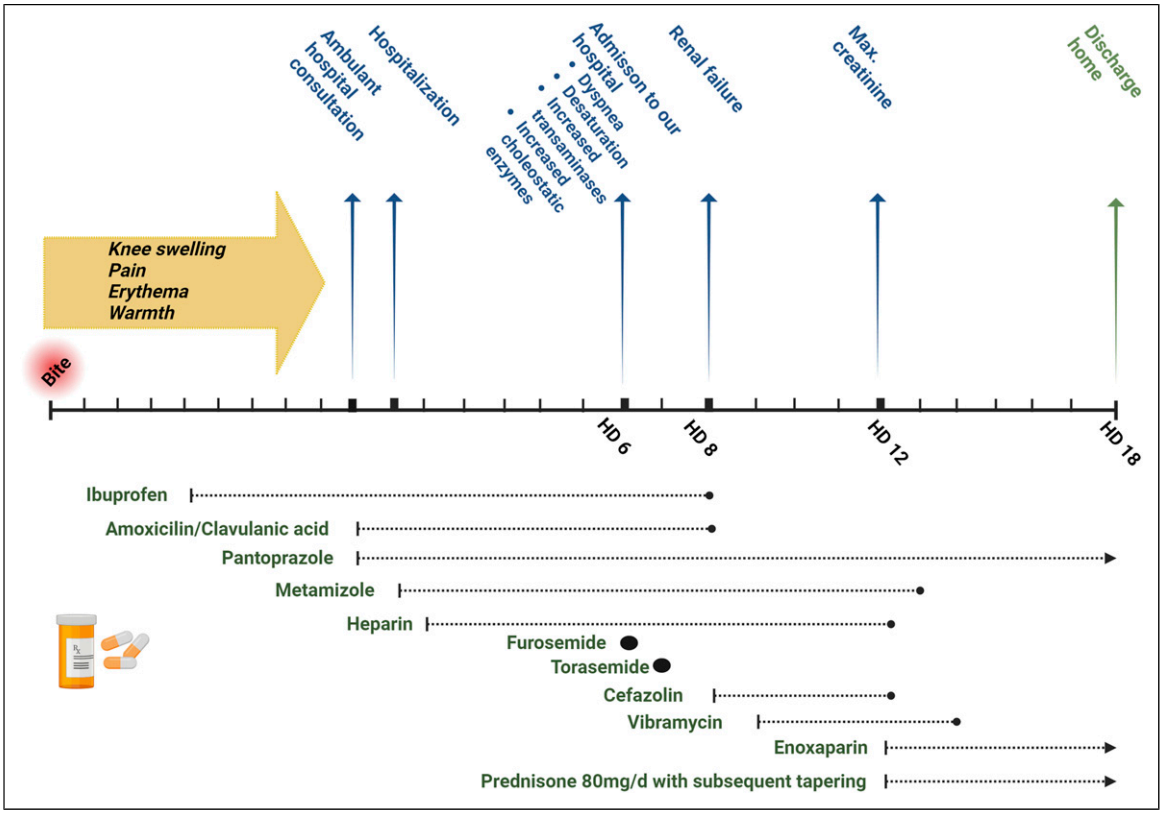


**Figure 1.** Timeline of the patient's clinical course, including clinical events and medication H.D.: Hospital day.

**Table 1.** Laboratory data.

| | Reference values | 6 H.D. | 8 H.D. | 9 H.D. | 10 H.D. | 12 H.D. | 13 H.D. | 14 H.D. | 15 H.D. | 17 H.D. |
|---|---|---|---|---|---|---|---|---|---|---|
| Leucocytes (G/l) | 3.5–10.0 | 11.0 | 7.9 | | | 7.3 | | 10.0 | | 13.0 |
| Eosinophils (G/l) | 0.04–0.54 | 0.40 | 0.35 | | | 0.42 | | 0.15 | | 0.05 |
| Creatinine (umol/l) | 59–104 | 104 | **116** | **145** | **159** | **199** | **207** | **186** | **168** | **131** |
| eGFR (ml/min/1.73 $m^2$) | | **70** | **61** | **47** | **42** | **32** | **30** | **34** | **39** | **53** |
| BUN (mmol/l) | 2.76–8.07 | **8.3** | | **12.5** | | **17.1** | **19.4** | **18.6** | **14.4** | |
| AST (U/l) | <50 | **122** | **84** | **106** | **94** | **89** | | 42 | 47 | 40 |
| ALT (U/l) | <50 | **159** | **153** | **170** | **125** | **73** | | **70** | **67** | **72** |
| GGT (U/l) | 8–61 | **526** | **673** | **794** | **875** | **985** | | **883** | **789** | **693** |
| ALP (U/l) | 40–129 | **198** | **240** | **253** | **266** | **277** | | **243** | **207** | **171** |
| Total bilirubin (umol/l) | <21 | 6.2 | 9.2 | | 13.3 | 6.7 | | 7.2 | | 7.9 |
| CRP (mg/l) | <5 | **183** | **243** | **174** | **141** | **61** | **52** | **34** | **18** | **8** |

ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate transaminase; BUN: blood urea nitrogen; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; H.D.: hospital day. Bold text indicates pathological values.

A, B, C, and E, *Brucella*, *Coxiella burnetii*, leptospirosis, toxoplasmosis, tularemia, and cytomegalovirus (CMV) screening (all negative). The autoimmune panel includes antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), antibodies to double-stranded (anti-ds)-DNA, anti-glomerular basement membrane (anti-GBM), and proteinelectrophoresis proved negative. Blood polymerase chain reaction (PCR) for herpes viruses, including herpes simplex (HSV)-1 and −2, CMV, Ebstein-Barr virus, and human herpes virus (HHV)-6 and −7 was also negative. Because the patient's pathology mimicked a Drug Reaction with Eosinophilia and Systemic Symptoms but with the absence of blood eosinophilia and skin rash, the blood eosinophil cationic protein (ECP) was determined and found elevated (88 µg/L, normal <13.4). ECP is the best studied protein of the large secondary eosinophilic granules and

has been proposed as a marker of eosinophilic disease and T helper lymphocyte 2 (Th2)-associated inflammatory processes, including allergic asthma and allergic rhinitis. It could be quantified in a variety of biological fluids, including serum.[2] A recent study, which assessed the ECP levels in eight patients with DRESS, described ECP elevations in all of them, but in contrast to our case, all patients had a rash. Moreover, all but one patient with elevated ECP values had blood eosinophilia.[3] Considering the multiorgan involvement, the persistent fever, the lymphadenopathy, and the elevated ECP, a drug hypersensitivity reaction resembling DRESS without, however, the presence of blood eosinophilia and cutaneous lesions was suspected. Indeed, based on the Severe Cutaneous Adverse Reaction (RegiSCAR) scoring system, the case was categorized with a score of five as "probable" for DRESS despite the absence of blood eosinophilia and rash. The RegiSCAR criteria rely on clinical findings such as fever, lymphadenopathy, presence and extension of skin rash, and laboratory observations, for example, presence and severity of blood eosinophilia, presence of atypical lymphocytes, and parameters indicating organ involvement, and employ a scoring system to enable the classification into four categories: "negative case," "possible case," "probable case," and "definitive case" of DRESS.[4] Moreover, alternative differential diagnoses should be excluded.[4]

Antibiotic and anti-inflammatory treatment were replaced by high-dose steroid therapy (prednisone 80 mg/day), resulting in an overall clinical and laboratory improvement (Table 1). Skin tests, conducted approximately 12 weeks after the initial episode, examined various medications including beta-lactams and ibuprofen. A weak delayed sensitization to pantoprazole was shown. A lymphocyte transformation test revealed a release of interleukin (IL)-5 and IL-13 only in the highest concentration of amoxicillin/clavulanic acid (500 μg/ml) and a release of all cytokines (IL-5, IL-13, interferon-γ, granzyme b, granulysine) only in the highest concentration of metamizole; for pantoprazole there was no clearly positive result (Table 2). In case of DRESS, these results were atypically weak.[5] Given that the lymphocyte transformation test is a dependable in vitro technique for verifying the responsible drug in cases of drug eruptions[6] and that metamizole is not described as a typical trigger for DRESS[4,7,8], we assume that most likely amoxicillin/clavulanic acid was the primary sensitization. Moreover, the findings were improved despite the continuation of pantoprazole. Nevertheless, true co-sensitization may have also developed. It should be noted, however, that the sensitivity of lymphocyte transformation test is limited, ranging around 60%–70% for beta-lactam allergy. Despite this limitation, it still surpasses the sensitivity of other tests used in drug hypersensitivity diagnosis.[5]

Drug-induced hypersensitivity syndrome (DiHS) — widely known as DRESS — is a severe, idiosyncratic, delayed, T-cell-mediated drug reaction, commonly associated with heterogeneous combinations of widespread rash, facial oedema, lymphadenopathy, organ involvement, and haematological abnormalities, frequently blood eosinophilia, and atypical lymphocytes.[7] The nomenclature of this fascinating and challenging syndrome has changed several times over the years, reflecting the incomplete understanding of its pathophysiology and clinical presentation.[9] The term Drug Rash with Eosinophilia and Systemic Symptoms was first proposed by Bocquet et al. to limit the ambiguity of the denomination of hypersensitivity syndromes and to distinguish severe drug reactions accompanied by blood eosinophilia from others without eosinophilia.[10] Shortly after, due to the diversity of cutaneous lesions, the word "rash" was replaced by the word "reaction".[11] Moreover, due to the wide recognition of the syndrome and the improved understanding of its pathophysiology, the term DRESS has been further questioned due to the non-universal presence of blood eosinophilia. As such, the lowercase "e" is often used.[7] Conventional descriptions of DRESS syndrome emphasize two primary characteristics: the delayed onset after initiating the causative drug and a slow recovery process, which can lead to a therapeutic dilemma if medication needs to be used, with a propensity for relapse, distinguishing it from other forms of delayed-type drug hypersensitivity reactions. Typically, DRESS syndrome is reported to appear 2–8 weeks after beginning the culprit drug, and the Japanese Severe Cutaneous Adverse Reaction (J-SCAR) scoring system stipulates that the rash must develop more than 3 weeks after drug initiation to qualify as DiHS/DRESS. However, in 2019, a retrospective study examined cases of rapid-onset DRESS, which occurs within 15 days of initial drug intake. The drugs most frequently associated with rapid-onset DRESS were primarily antibiotics and iodinated contrast media. Rapid-onset DRESS cases described in this study were less likely to exhibit lymphadenopathy in retrospective comparisons to typical-onset DRESS cases but were otherwise similar in presentation.[7,8] Moreover, by re-exposition to the causative drug, symptoms can emerge within hours to days.[7] In addition, in about 2% of cases, no exposure to a pharmaceutical agent is reported.[4] Furthermore, despite skin manifestations occurring in 73%–100% of patients with DRESS, cases without skin involvement are also reported.[4,6-8] Haematologic abnormalities are commonly noticed, with blood eosinophilia appearing in more than 95% of cases and atypical lymphocytes occurring in approximately 65%–80%.[4,8]

**Table 2.** Immunological response to various concentrations of amoxicillin/clavulanic acid, metamizole, and pantoprazole.

| Substances | Reference values | IL-5 | IL-13 | IFN-γ | GzB | GL |
|---|---|---|---|---|---|---|
| Amoxicillin/Clavulanic acid | | | | | | |
| 125 μg/mL | Negative | 1.00 | 1.00 | 1.00 | 1.00 | 0.59 |
| 250 μg/mL | Negative | 1.00 | 1.00 | 1.00 | 1.00 | 0.95 |
| 500 μg/mL | Negative | **10.40** | **11.26** | 1.00 | 1.00 | 1.93 |
| Metamizole | | | | | | |
| 1 μg/mL | Negative | 1.00 | 1.00 | 1.00 | 1.00 | 0.88 |
| 10 μg/mL | Negative | 1.11 | 1.35 | 1.00 | 1.00 | 1.11 |
| 50 μg/mL | Negative | **42.23** | **34.87** | **7.93** | **8.05** | **4.69** |
| Pantoprazole | | | | | | |
| 0.5 μg/mL | Negative | 1.00 | 1.00 | 1.00 | 1.00 | 1.13 |
| 2 μg/mL | Negative | 1.00 | **5.82** | **2.15** | 1.00 | 0.80 |
| 10 μg/mL | Negative | 1.00 | 1.00 | 1.00 | 1.00 | 0.88 |
| Control | | | | | | |
| Pokeweed mitogen | Positive | **46.20** | **662.32** | **4000.00** | **4784.69** | **1368.36** |
| Tetanus toxoid | Positive | **341.30** | **293.49** | **589.02** | **4784.69** | **251.66** |

GL: granulysine; GzB: granzyme b; IFN: interferon; IL: interleukin. Bold text indicates pathological values.

Although DRESS syndrome can affect almost every internal organ, including the kidneys, lungs, intestines, pancreas, thyroid, heart, and brain, the liver is the organ most commonly affected with rates ranging from 51% to 87%.[12,13] Liver involvement primarily presents as hepatocellular injury, with occasional concurrent cholestasis, and rarely leads to fulminant hepatitis, commonly of the cholestatic type, and death.[14,15] The occurrence of renal involvement in DRESS syndrome varies across different sources, with reported rates ranging from 5% to 65%. However, in the majority of retrospective studies, it typically falls within the range of 15% to 35%.[16] In DRESS syndrome, renal injury is marked by abnormal serum urea and creatinine levels, reduced creatinine clearance and GFR, and the occurrence of proteinuria, haematuria, and eosinophiluria.[17] Moreover, a recent systematic review highlights that oliguria is observed in 18% of DRESS cases, while anuria has an incidence of 6%.[16] While most cases of kidney disorder are mild and resolve upon discontinuation of the causative drug, severe interstitial nephritis can potentially develop resulting in kidney failure. An elevated risk of renal failure is observed in patients with pre-existing renal comorbidities and older individuals.[4,17] Interestingly, previous research indicates a higher prevalence of renal dysfunction among patients with liver dysfunction, and conversely, individuals with liver dysfunction are more prone to experiencing renal dysfunction.[18]

The incidence of pulmonary involvement in patients with DRESS is not clear, with percentages ranging between 5% and 73.3% in different studies.[12,19-21] Indications of pulmonary involvement may suggest a more severe clinical course and elevated mortality rates. Within DRESS syndrome, pulmonary manifestations demonstrate diversity, including nonspecific interstitial pneumonitis, pleural effusion, pneumonia, pulmonary nodules, and, in severe cases, acute respiratory distress syndrome (ARDS). Symptoms like dyspnea, pleurisy, and cough are commonly observed in individuals experiencing pulmonary manifestations.[22] Despite not being commonly categorized as a pulmonary finding, mediastinal lymphadenopathy presents as an additional manifestation that can occur even when peripheral lymphadenopathy is absent.[23]

DRESS can pose a considerable challenge, especially in its early stages, due to its nonspecific individual symptoms and its overlapping clinical features with infections, lymphoproliferative disorders as for example angioimmunoblastic T-cell lymphoma, and autoimmune diseases.[24-26] Individuals afflicted with DRESS remain susceptible to relapses and potential complications for weeks and, in some instances, months, often during the gradual tapering of steroid treatment following the acute episode. Notably, there have been documented cases of unexplained cross-reactivity to multiple drugs with differing chemical structures, even those administered subsequent to the onset of DRESS. Moreover, individuals who have experienced DRESS are at risk of developing enduring autoimmune sequelae. These sequelae can manifest after a prolonged, symptom-free interval following the complete resolution of the acute phase of DRESS or as a continuation of organ involvement that initially emerged during the acute phase. Remarkably, the time gap between the resolution of the acute phase and the emergence of autoimmune sequelae can extend up to 4 years.[24]

Although DRESS is a challenging diagnosis and there is currently no diagnostic tool available to provide a definitive confirmation, our case underscores the importance of

recognizing and documenting potential atypical presentations of DRESS or unknown DRESS mimics at this time, sharing similar pathophysiology with DRESS. The absence of eosinophilia, skin rash and, facial oedema, in this case, challenges traditional diagnostic criteria for the syndrome. Healthcare providers should maintain a high index of DRESS suspicion, particularly in patients with relevant drug exposure, even in the absence of these classical features. Moreover, this atypical presentation highlights the complexity of DRESS syndrome diagnosis. Clinicians must be aware that DRESS syndrome can manifest with diverse clinical features, and diagnosis should rely on a comprehensive assessment that considers clinical history, laboratory findings, and diagnostic tests. Timely recognition and management remain crucial in improving patient outcomes. Given the high mortality of DRESS syndrome (approximately 10%)[24] and the rarity of such suspected atypical cases, further research is needed to elucidate the underlying mechanisms behind clinically atypical DRESS presentations. Investigating potential genetic factors, drug-specific variations, and immune responses may provide valuable insights into the syndrome's pathophysiology. Certain biomarkers observed during the acute stage of DRESS/DiHS have been identified in studies to provide diagnostic and prognostic insights in addition to these clinical features. Elevated levels of serum thymus and activation-regulated chemokine/CCL17 (TARC/CCL17), soluble ST2, and sOX40 were noted.[27] Certainly, previous research suggests that serum TARC levels may correlate with the initial presentation of DRESS and its disease activity over time, suggesting their potential value as indicators for early diagnosis and disease monitoring.[28] Indeed. TARC or CCL17 is primarily produced by dendritic cells (DCs), Langerhans cells, and keratinocytes.[29] Its primary receptor, CC chemokine receptor type 4 (CCR4), is predominantly found in Th2-type T cells.[29,30] TARC/CCL17 levels are notably elevated in the serum[28,31] of patients with DRESS Syndrome (DiHS), elevations which analogically correlate with blood eosinophil count[32] and disease activity and potentially represent a predictive marker for HHV-6 reactivation.[28,31] Exploring the use of TARC in diagnosing atypical DRESS cases could provide a valuable tool for physicians and warrants further investigation. Another example is serum soluble OX40, which has been found to be elevated in patients with DRESS during the acute stage, coinciding with high serum soluble OX40 expression on CD4 + T cells. Serum soluble OX40 levels were significantly positively correlated with disease severity and with serum levels of TARC, IL-5, and IL-10.[27,33] Moreover, innate lymphoid cells 2 (ILC2s), according to mounting evidence, play a significant role in generating CD4 + Th2 mediated cytokines, including IL-5 and IL-13. These cytokines are recognized for their ability to increase the recruitment of eosinophils from the bloodstream to the airways and skin.[34] Furthermore, recent research indicates that patients with DRESS during the acute phase show an increased presence of ILC2s expressing receptor ST2 in both the skin and the bloodstream. Additionally, these patients display elevated serum levels of soluble receptor ST2, suggesting the involvement of the IL-33/ST2 pathway and ILC2s in the pathogenesis of DRESS/DiHS, highlighting the necessity for further investigations to corroborate this correlation.[27,35]

In conclusion, this rare case of suspected DRESS syndrome with fever, lymphadenopathy, and organ involvement but without blood eosinophilia, facial oedema, and skin rash underscores the need for vigilance in diagnosing and managing atypical presentations of the syndrome. By expanding our understanding of the clinical spectrum of DRESS syndrome, patients' management and health outcomes can be improved. As indicated by our case, determination of ECP in the absence of blood eosinophilia and skin rash might be helpful. Further research is required for its investigation.

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Figure 1 created with BioRender.com

## Author's contributions

The study was designed by MZ. MZ and UMW were involved in the diagnosis and management. MZ, EL and UMW searched the articles. MZ drafted the manuscript. EL and AE revised the manuscript. All authors read and approved the final manuscript.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical statement

### *Ethical approval*

The project did not meet the definition of human subject research. Ethical approval was not required for this case report in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of his medical case and any accompanying images.

### *Informed consent*

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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## Data availability statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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