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Single Case

Severe Toxic Epidermal Necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms Overlap Syndrome Treated with Benralizumab: A Case Report

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Keywords
Drug reaction with eosinophilia and systemic symptoms · Toxic epidermal necrolysis · Benralizumab · IL-5 blocker

Abstract
TEN/DRESS overlap syndrome can be difficult to diagnose, especially if it is masked by comorbidities in critically ill patients in intensive care units. The existing therapy for the two conditions is also a major challenge for the treating team. A possible alternative, especially for refractory cases, is benralizumab as an IL-5-receptor alpha-chain-specific humanized monoclonal antibody (IgG1k). We are able to show a successful treatment in this case report.

Introduction

Drug-induced cutaneous manifestations can be difficult to differentiate. In particular, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are sometimes difficult to distinguish, because of their varied initial presentation with similar skin eruptions at early stages of manifestation. However, a distinction is of particular importance here, due to different treatment procedures and drug therapies.

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TEN is a very severe bullous drug reaction that by definition affects more than 30% of the body surface area and usually the mucous membrane. The onset of symptoms occurs 4 days to 4 weeks after first administration of the culprit drug. This is followed by a maculopapular rash with blisters and reduced general condition. Mortality can be very high if not diagnosed correctly and is estimated by the Score for TEN (SCORTEN [1]).

While mucous membrane involvement is a hallmark of TEN, a striking case of eosinophilia points to DRESS. DRESS is a distinct, severe, idiosyncratic reaction to a drug characterized by a prolonged latency period. It is followed by a variety of clinical manifestations: usually fever, rash (especially with facial involvement), lymphadenopathy, eosinophilia, and a wide range of mild-to-severe systemic presentations occurring 2–6 weeks after introduction of the causative drug.

Mucosal involvement is unusual, but systemic involvement – particularly at the expense of the liver and kidneys – is nearly always present and responsible for a mortality rate of up to 10% [2–4]. Laboratory changes include high eosinophilic count, atypical lymphocytes, and possibly elevated liver enzymes and/or decreased glomerular filtration rate [2, 3].

The fact that sometimes these entities can share common features suggests overlapping syndromes [5]. Validation scores have been established by the "European Registry of severe cutaneous adverse reactions (SCARs) to Drugs and Collection of Biological Samples" (RegiSCAR) group in order to classify cases of SCARs as definite, probable, possible, or excluded [6, 7]. In this case report, we want to describe the rare case of a TEN/DRESS overlap as well as the use of benralizumab (Fasenra®), an IL-5-receptor alpha-chain-specific humanized monoclonal antibody (IgG1k) for treatment of a glucocorticoid-unresponsive eosinophilia in the context of this syndrome.

Case Report/Case Presentation

A 74-year-old male was referred to our ICU for further evaluation and subsequent treatment of a severe bullous cutaneous adverse reaction affecting 50% of the body surface area including enoral as well as ocular mucosal involvement (shown in Fig. 1a, b). After confirmation of TEN via skin biopsy, we switched the initial therapy with methylprednisolone (250 mg on day one and 125 mg on day two) to intravenous immune globulin 1 g/kg body weight per day for 3 days. As the TEN trigger, we considered allopurinol (300 mg daily), which was first taken 34 days prior to the onset of symptoms, to be the most likely agent.

Although the clinical situation quickly improved with no further bullous lesions, we observed persistent inflammation with high levels of CRP and procalcitonin. Furthermore, we observed eosinophilia exceeding 1.5 G/L on day 10 and peaking at 5.4 G/L 14 days after admission as well as more than 5% atypical lymphocytes in a blood smear. These pathological results persisted even after cessation of medication that could potentially provoke eosinophilia, i.e., daptomycin, meropenem, and aspirin. Other causes for eosinophilia could not be found. A second skin biopsy showed an acute cytotoxic reaction in accordance with the previously diagnosed TEN as well as a nonspecific cutaneous-vascular inflammation typical of regenerative processes. Differential diagnosis of autoimmune bullous diseases could be ruled out by negative serological specific antibodies.

Fulfilling RegiSCAR criteria, a diagnosis of DRESS was formally proposed. Organ involvement included sonographically confirmed lymphadenopathy, hepatopathy with elevated liver enzymes more than twice the upper limit of normal acute kidney injury, pneumopathy as well as vasoplegia and fever. An HHV-6 reactivation in serological testing was even shown, a finding required by the Japanese group's criteria for the disease [8, 9]. Finally, with

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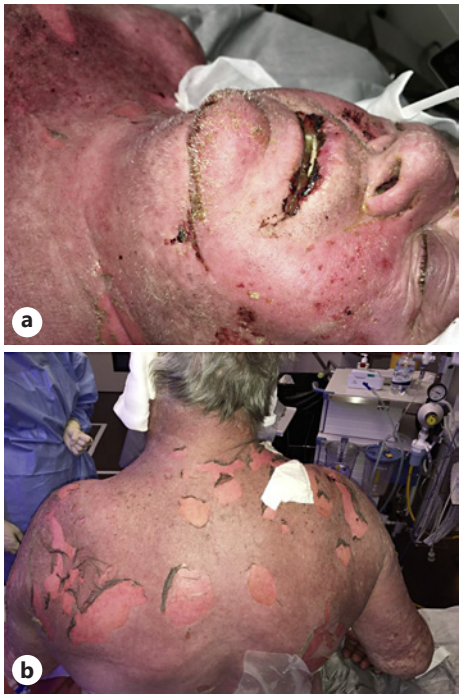

Fig. 1. a, **b** skin findings at the time of admission to ICU.

a RegiSCAR-Score for diagnosing DRESS of 7 points, a definite case was diagnosed [10]. Details are shown in Table 1.

Considering the confirmed TEN diagnosis on the basis of skin biopsy as well as clinical presentation and the fulfilled criteria for DRESS, we confirmed a case of TEN/DRESS overlap syndrome [5]. The skin findings at that time are shown in Figure 2.

Administration of methylprednisolone initially showed a favorable effect. However, the blood eosinophilia and systemic inflammation showed a quick rebound with dose reduction of methylprednisolone. Due to the lack of improvement on steroids, we administered benralizumab 9 days after starting the steroid treatment [11]. Subsequently, a rapid clinical recovery in the sense of regression of systemic symptoms and eosinophilic levels in the blood could be observed, and methylprednisolone could be tapered quickly without a rebound at the time of transfer to the normal ward (shown in Fig. 3). After delayed weaning of respiratory support and 6-week rehabilitation, the patient could be discharged home without further support.

Discussion

True cases of TEN/DRESS overlap syndrome are rare and difficult to diagnose. Other comorbidities or infections may also obstruct a correct diagnosis. The RegiSCAR group established validation scores, using clinical/biological/histological parameters in order to retrospectively classify cases as a "definite," "probable," "possible," or "excluded" diagnosis of acute generalized exanthematous pustulosis, DRESS, or SJS/TEN [6, 7]. A true overlap is then defined as a case where a patient can be classified as "probable" or "definite" for 2 SCARs at the same time [5].

In the case presented here, the mucosal involvement and the histopathological examination were consistent with the diagnosis of TEN. At the same time, the patient fulfilled the criteria for a "definite" DRESS through eosinophilia, the presence of atypical lymphocytes, organ involvement, and positive viral serology for HHV-6.

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Table 1. Patient details

General information	
Sex	Male
Age, years	75
Ethnicity	Caucasian (Central Europe)
Pre-existing conditions	Diabetes mellitus type 2, coronary and valvular cardiopathy, arterial hypertension, dyslipidemia, adipositas G III, chronic nephropathy G IV (KDIGO)
TEN characteristics	
SCORTEN	4/7 (age >40 years, >10% BSA, BUN >10 mmol/L, bicarbonate <20 mmol/L)
Skin eruption (50% body surface area)	Maculopapular exanthema
Skin histopathology suggestive of TEN	Yes, subepidermal bullae with inflammatory infiltrate containing eosinophils
DRESS characteristics	
RegiSCAR DRESS score	7
Detailed DRESS features	
Skin eruption	Maculopapular exanthema
Skin histopathology suggestive of DRESS	No
Fever	Yes
Lymphadenopathy	Yes
Peak eosinophilia	5.4 × 10E9/L
Atypical lymphocytes	>5%
Organ involvement, lab values at the time of diagnosis	
Kidney	Yes, cvvHD
Liver	Yes, AST 99 U/L; ALT 213 U/L
Lung	Yes, ARDS
Heart/muscle	Yes, myoglobin 1,630 µg/L
Pancreas	None
Other	None
Viral serology at DRESS diagnosis	HHV6: positive EBV, CMV, HSV1/2: negative
Previous history of drug allergies	None
First-line DRESS treatment	Intravenous methylprednisolone

ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; DRESS, drug rash with eosinophilia and systemic symptoms; SCORTEN, Score for TEN.
Normal ranges of laboratory test values: myoglobin: 28–72 mg/L; AST and ALT: <50 U/L.

The most likely culprit drug was allopurinol. This drug has repeatedly been described as being involved in a large proportion of cutaneous drug reactions and more specifically in TEN and DRESS [6, 12].

Subsequent treatment according to our guidelines for TEN was carried out alongside topical therapies with intravenous immune globulin, which initially showed improvement. With eosinophilia and involvement of the liver, lungs, and kidneys – as in our patient – we diagnosed a TEN/DRESS overlap syndrome.

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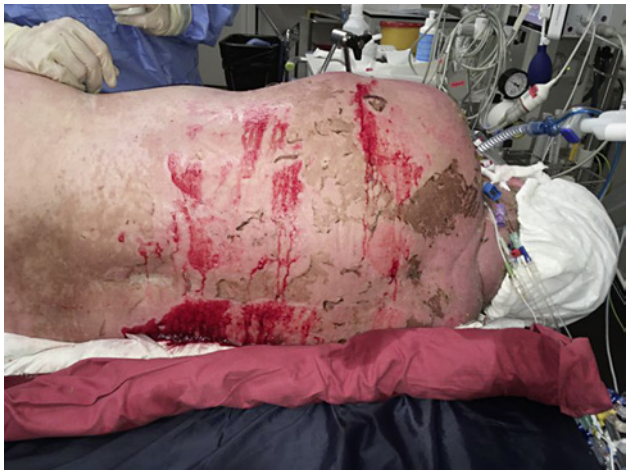

Fig. 2. Skin findings at the time of TEN/DRESS overlap syndrome.

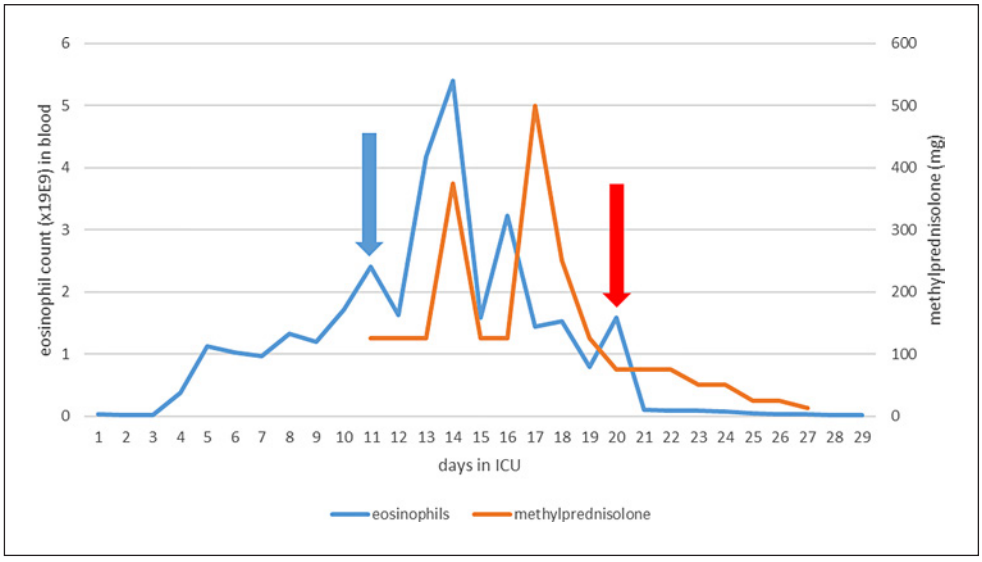

Fig. 3. Temporal development of eosinophilia in dependence on therapy; blue arrow: diagnosis of DRESS and start of steroid therapy; red arrow: single dose of benralizumab.

The current recommendation for treatment is a regimen of oral or intravenous glucocorticoids until clinical improvement and normalization of laboratory parameters, followed by a slow tapering to prevent relapse [13–15]. In our case, even slow and careful dose reduction of prednisolone provoked a quick rebound of blood eosinophilia and systemic inflammation.

In the absence of improvement with steroid therapy, we applied benralizumab, which is an IL-5-receptor alpha-chain-specific humanized monoclonal antibody (IgG1k). It depletes IL-5 receptor-bearing cells (eosinophils and basophils) via enhanced antibody-dependent cytolysis and blocks IL-5 binding to its receptor. IL-5 is mainly produced by T helper 2 cells and is a critical mediator responsible for differentiation, activation, and chemotaxis of eosinophils [16], which contribute considerably to organ damage in DRESS and drive allergic and inflammatory immune responses characterizing numerous other diseases. Benralizumab is approved as an add-on therapy in patients with severe asthma. Its efficacy in the reduction of annual exacerbation rates and health-related quality of life

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has been proven by several randomized, multicenter, placebo-controlled trials [17–19]. It has also shown a sustained reduction of the absolute eosinophilic count in patients with platelet-derived growth factor receptor alpha-negative hypereosinophilic syndrome [20].

Recently, the successful treatment of severe DRESS with benralizumab in two COVID-19 patients provided first evidence that IL-5Rα-blocking antibody is a treatment option for severe DRESS symptoms that do not respond to first-line treatment [21]. Hematologic and proteomics data derived from those two cases suggest that benralizumab has a rapid and profound effect on eosinophils. It also points to a benralizumab-mediated indirect regulatory effect on other cell types, possibly cytotoxic T cells. In the meantime, there have been further reports of successful treatment of DRESS in the setting of severe acute respiratory syndrome coronavirus 2 infection [22] and in non-COVID-19-related patients [23]. We are not aware of any report in which a TEN/DRESS overlap syndrome was treated with benralizumab.

Conclusion

Our case report shows that IL-5Ra blockade can be a valuable therapeutic option for refractory TEN/DRESS overlap syndromes in critically ill patients. The treatment with benralizumab has two important benefits. It causes less adverse effects than corticosteroids and other systemic immunosuppressants, and it can be administered in a single dose.

Statement of Ethics

Ethical approval was not required for this report in accordance with national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Felix K. Zeller collected case relevant and background information, performed literature review, and participated in writing the manuscript; Mirjam C. Nägeli provided her expert opinion and helped in the preparation of the manuscript; Patrick R. Bader and Philipp K. Bühler were involved in the diagnostic process and treatment of the patient and participated in writing the manuscript. Reto A. Schuepbach provided supervision throughout the treatment and publication period of this case.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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