Atypical DRESS Syndrome Induced by Lenalidomide in Chronic Hemodialysis

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Introduction

Drug adverse reactions manifested with cutaneous eruptions are not uncommon in chronic hemodialysis. Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS) syndrome is a prime example of a rare, potentially fatal cutaneous reaction attributed to drug hypersensitivity. It is typically characterized by a long latency period of two weeks to two months from drug exposure to rash emergence. The term was introduced by Bocquet et al. in 1996 [1]. Due to the variability in clinical presentation and the lack of clear diagnostic criteria imperfect definitions of this syndrome had been initially used such as “anticonvulsant hypersensitivity syndrome” and “drug induced hypersensitivity syndrome”. DRESS frequency has been reported to be 1 case among 1,000 to 10,000 drug exposures. In a prospective seven-year study, the annual incidence of DRESS syndrome in the general population was estimated at 0.9/100,000 [2]. Numerous drugs have been associated with DRESS syndrome. In a comprehensive literature review, 44 culprit drugs related to 172 case reports over a 12-year period were detected. The majority of cases were found to be related to aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital), allopurinol and sulfasalazine administration [3]. Clinical manifestations of DRESS syndrome include fever, lymphadenopathy, cutaneous eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis) and internal organ involvement, primarily of the liver. Data regarding DRESS syndrome in chronic hemodialysis patients are limited and the possible influence of uremia on the natural history of the syndrome has not been explored [4]. Two sets of diagnostic criteria have been independently introduced by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group and the Japanese consensus group to aid in the diagnosis and classification of suspected cases [5,6].

Lenalidomide, a derivative of thalidomide, is an immunomodulatory drug, which is indicated for treatment of multiple myeloma (MM) and myelodysplastic syndromes. The use of lenalidomide has been consistently associated with the development of skin rash. In a systematic review including 10 studies with 737 patients, the incidence of lenalidomide-associated all-grade rash was 27.2% [7]. Although Stevens-Johnson syndrome (SJS) is the most common cutaneous adverse reaction caused by lenalidomide [8], recent case reports have also linked this medication with DRESS syndrome [9,10]. To our knowledge, this is the first reported case of DRESS syndrome in a chronic hemodialysis patient five days after the lenalidomide commencement.

Case Report

A 62-year-old female on chronic hemodialysis (HD) was admitted for fever (38.5°C) and acute cutaneous eruption. She had been simultaneously diagnosed with end-stage renal disease and MM fifteen months ago for which she commenced treatment with bortezomib and dexamethasone. Five months ago, she developed progressive paralysis of the lower extremities due to spinal cord compression. Bortezomib and dexamethasone were discontinued and she underwent radiotherapy. Radiotherapy was complicated by bowel perforation treated with partial colectomy and palliative colostomy formation. Her latest medications consisted of oral furosemide, allopurinol, calcium carbonate, quetiapine, paroxetine, alprazolam and intravenous erythropoietin during HD sessions. Five days before admission the patient had been started on lenalidomide at a reduced renal dose of 5 mg per day to treat relapsed MM. The skin rash was characterized by diffuse, infiltrating erythema affecting equally the face, trunk and limbs. The patient also exhibited facial edema, pruritus, as well as mild cervical and axillary lymphadenopathy (Figures 1 and 2).

Figure 1: Palmar exfoliative dermatitis.
although they had been administered for many years and therefore
(0.5-1.5), sodium: 140 mmol/l (136-145), potassium: 5.3 mmol/l
DRESS syndrome due to lenalidomide.
(0-1.5), alkaline phosphatase: 79 IU/l (25-130), gamma-GT: 9 IU/l
AST: 11 IU/l (8-40), ALT: 10 IU/l (8-45), total bilirubin: 0.2 mg/dl
Discussion
37.1 mg/l (<5.0), urea: 123 mg/dl (10-50), creatinine: 9.9 mg/dl
Denying medical care and food intake and passed away eight weeks
antihistamines and a brief course of oral corticosteroids. However, she
failed to improve and the absolute eosinophil count remained over
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Application of the RegiSCAR scoring system in this clinical setting
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The rash soon progressed to extensive exfoliative erythroderma. Laboratory test results on admission were: Hemoglobin: 9.4 gr/dl (12.2-18.1), hematocrit: 32.4% (37.7-53.7), white blood cells: 12,300/mm³ (4,600-10,200) [neutrophils 54%, lymphocytes 13%,
3
CD8+ T-cells have been shown to expand during the acute phase of
DRESS syndrome may well occur and this should not impede
clinicians from prompt diagnosis and removal of the putative culprit
drug. Moreover, overlapping manifestations between DRESS syndrome and SJS may be observed, further complicating the diagnostic process.
Severe mucosal involvement with erosions and bleeding occurs in over
90% of cases of SJS, whereas mucosal involvement without erosions
occurs in approximately 50% of patients with DRESS syndrome. Most
importantly, eosinophilia and atypical lymphocytosis are not observed
in SJS. The exact mode of action of lenalidomide is incompletely
understood. However, MM patients on lenalidomide exhibit regulatory
T-cell activation [17] which has also been described as a pathogenetic
mechanism for DRESS syndrome.
The mainstay of therapeutic management of DRESS syndrome is the
withdrawal of the offending agent along with supportive care and
topical or systemic corticosteroids according to severity of internal
organ involvement. Systemic corticosteroids can be administered via
the oral or intravenous route. Cyclosporine and intravenous
immunoglobulin (IVIG) have been used in steroid-resistant patients in
isolated case reports [18]. Persistence or aggravation of clinical
disease onset.

agent commencement. The pathogenesis of DRESS syndrome is still
unclear. A strong association of DRESS syndrome with human herpes
virus 6 (HHV-6) reactivation has been proposed [11]. This has led the
Japanese consensus group to the inclusion of HHV-6 reactivation in
the diagnostic criteria of DRESS syndrome. Defective drug
detoxification process resulting in accumulation of toxic metabolites
has also been suggested [12]. Furthermore, drug specific CD4+ and
CD8+ T-cells have been shown to expand during the acute phase of
the disease leading to the release of pro-inflammatory interleukin 5 [13].
Intriguingly, the expansion of regulatory T-cells has also been
associated to HHV-6 reactivation and DRESS syndrome development
[14]. The histologic pattern of skin rash in DRESS syndrome usually
displays spongiosis, acanthosis and lymphocytic infiltration in the
superficial dermis with few eosinophils [15]. Timely recognition of this
entity is of utmost importance since it is associated with a significant
mortality rate of 10%-30%. Fulminant hepatic failure has been
reported to be the leading cause of death in DRESS syndrome [16].

The interesting features of the present case are the short latency
period of 5 days (between lenalidomide commencement and rash
onset) and the mild systemic symptoms - fever and lymphadenopathy.
No signs of liver or other vital organ involvement were detected. In a
recent review, Cacoub et al. reported that the latency period can be as
short as half week whereas 12% of the patients have no internal organ
involvement [3]. It is, therefore, obvious that atypical manifestations of
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clinicians from prompt diagnosis and removal of the putative culprit
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Discussion
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reaction to medications marked by the delayed onset after offending

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Conclusion
We reported a rare, atypical case of DRESS syndrome in a chronic
hemodialysis patient and recognized lenalidomide as the culprit
medication. DRESS syndrome diagnosis necessitates a high index of
suspicion because of the extended variability in clinical presentations. Immediate discontinuation of the suspected offending agent is a sine qua non for proper management. A multidisciplinary approach potentially involving dermatologists and clinical pharmacists apart from the attending physicians is often needed to attain successful outcomes.

References