Skin reaction with Eosinophilia and Systemic Symptoms after lenalidomide in peritoneal Dialysis

Case reports

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ABSTRACT
The Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a fatal and immune-mediated idiosyncratic drug reaction, with symptoms of fever, skin eruptions (that involves more than half of the body surface), facial oedema and hematological disorders, all presenting within the latent period following drug intake. Effects can also be seen on multiple organs, most notably hepatitis in liver and acute interstitial nephritis in kidney, generally post-administration of allopurinol. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) classifies the DRESS Syndrome cases as “definite”, “probable” or “possible”, based on clinical and laboratory features. Different pathogenetic mechanisms have been involved in this disease, including immunological reactions and HHV-6 reactivation. In our experience, a 72-year-old male, affected by myeloma in peritoneal dialysis, developed a rare case of DRESS syndrome after lenalidomide administration (less than ten cases are known) with HHV-6 reactivation. According to literature, we withdrew the drug and gave methylprednisolone 0,8 mg/kg orally and IVIG 1 gr/kg for two days. Despite this therapy, DRESS syndrome relapsed during steroid taper with rash, thrombocytopenia, hepatitis and high troponin level. A single cycle of intravenous immunoglobulin 0,5 g/kg for four days was enough for syndrome remission. Only few cases are reported in literature, but because of the increasing use of lenalidomide and the autoimmune sequelae of DRESS syndrome, a broad workup and a multidisciplinar careful approach could help in diagnosis, treatment and follow-up.

PAROLE CHIAVE: eosinophilia, systemic drug reaction, DRESS Syndrome, interstitial nephritis, multiple myeloma, Lenalidomide

Introduction

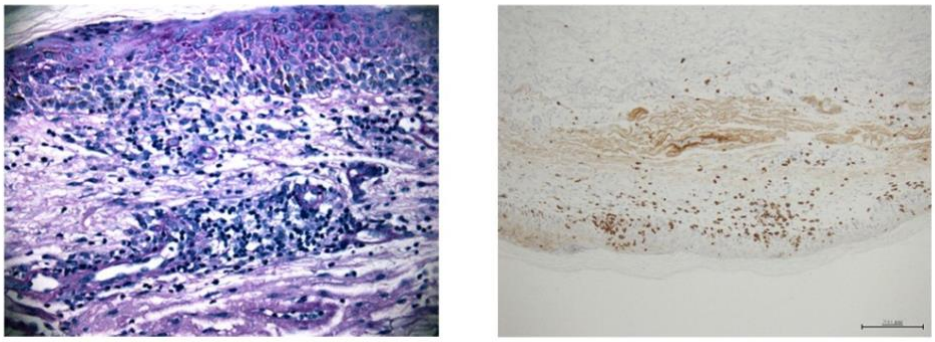
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare, immune-mediated idiosyncratic and fatal drug reaction, characterized by a latent period after intake of the inciting drug (2-6 weeks). Other signs and symptoms are fever higher than 38,5°C, skin eruptions, eosinophilia (in 66-95% of patients), mononucleosis-like atypical lymphocytes (27-67% of patients), thrombocytopenia, lymphadenopathy (in 54% of patients), and multiple organ involvement. The prevalence ranges from 1:1000 to 1:10000 of drug exposures; mortality has been estimated to be up to 10% because of myocarditis and liver failure [1]. It is difficult to pinpoint the exact moment at which the organ damage and blood alterations occur, except in the cases of already hospitalized patients [2]. Generally, the rash covers more than half of the body surface. Cutaneous lesions have polymorphic presentations: maculopapular, urticarial, exfoliative, lichenoid, pustular, bullous, target-like or eczema-like lesions. The facial oedema (found in 76% of patients) is the hallmark feature of the disease. In 50-60% of patients, two or more organs are affected, most frequently liver (hepatomegaly, hepatitis with ALT> 2 times and ALP> 1,5 times the upper limit), kidney (acute interstitial nephritis, most often induced by allopurinol) and lung (interstitial pneumonia). Cardiovascular involvement occurs lately (up to four months after recovery) with myocarditis, decreased LV function and elevated troponin [3]. The nomenclature of this syndrome has significantly evolved over the last 80 years. The current name, DRESS, as defined in 1996 by Bocquet et al [4], but in the past it was named “drug induced pseudolymphoma”, “anticonvulsant hypersensitivity syndrome” and “drug induced hypersensitivity syndrome” (DIHS). This syndrome requires a high index of suspicion by clinicians and exclusion of infectious, inflammatory, autoimmune and neoplastic conditions, besides other similar cutaneous drug reactions. DRESS syndrome could have long-term sequelae like the development of autoimmune disease, including thyroiditis, diabetes mellitus type I and systemic erythematosus lupus [5]. These manifestations can occur early, like in our patient, to years following the initial episode. There is no pathognomonic sign or diagnostic test for DRESS. The leucocyte transformation/activation test (LAT) measures T cells response to a drug. It lacks of sensitivity, but a positive LAT is useful to confirm the diagnosis, because of very low false positive results (only 2%) [6, 7]. Confirmation or exclusion of DRESS syndrome diagnosis is based on clinical and laboratory features. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) classifies the cases as “definite”, “probable” or “possible”.

Case Report

A 72-year-old male, affected by end-stage kidney disease (ESKD) because of nephroangiosclerosis and ischemic nephropathy in peritoneal dialysis, was diagnosed with micromolecular multiple myeloma kappa in June 2019. In November he stared lenalidomide 5 mg days 1-21 in 28-days cycle without steroids because of his comorbidities. The patient suffered from hypertension, ischemic cardiomyopathy with reduced ejection fraction of 25% (he had two NSTEMI, the last in March 2019), and chronic kidney disease for about six years and started automated peritoneal dialysis in March 2019.

After 18 days of therapy with lenalidomide, he presented a violet maculopapular rash covering more than 50% of his body, fever (38,5 °C), and leukopenia with negative C-reactive protein. Lenalidomide was withdrawn and oral steroid with anti-histamine were administered. One week later he was admitted to our Nephrology Unit for a syncopal episode. Laboratory tests revealed leukocytosis (white blood cells were 12250/mm^3), eosinophilia (until 56%, 4550/mm^3), and cholestatic-cellular liver damage (ALT 1448 U/l, ALP 308 U/l) requiring albumin infusion. In suspicion of a hidden infection, blood/peritoneal cultures and viral/bacterial tests were performed and a broad-spectrum

empirical therapy was prescribed. In the absence of liver and vascular abnormalities during an ultrasound abdominal study, an autoimmune workup was performed: ANA, ANCA, SMA, LKM, AMA were negative. Blood markers of HBV, HCV and herpetic viruses were negative, except for Human herpes virus 6 (HHV-6) reactivation with 420 copies/ml. Because of the persistence of the rash, the patient underwent a skin biopsy, that demonstrated sparse vacuolization of epidermis and dermal-epidermal inflammation with some eosinophils and CD8+ T cells, suggesting a drug reaction (shown in Figures IA and IB).



A B

Figure IA: Histopathological examination of the skin biopsy specimen revealing hyperkeratosis, spongiosis, dermis swelling and chronic perivascular inflammation with some eosinophils. IB: Immunohistochemical examination revealing CD8+ T cells dermal-epidermal infiltration, suggesting a drug reaction.

For clinical, laboratory and pathological features, according to RegiSCAR score system this case has been evaluated as “definite DRESS” with score 6, because of rash, eosinophilia and liver damage. We started intravenous immunoglobulin 1 g/kg for 2 days and oral methylprednisolone with reduced dose for comorbidities (50 mg/die for 0,8 mg/kg daily). After one week the patient had fully recovered and was discharged home with methylprednisolone 37,5 mg/die (for 0,6 mg/kg). Seven days after discharge, the patient showed a pruritic rash. Laboratory tests showed elevated ALT, AST and troponin (until 330 ng/l) and thrombocytopenia (platelets 50.000/mm^3). HHV-6 was undetected. Hospital admission was not necessary and an outpatient follow-up was started. Because of the high risk of late onset of myocarditis with elevated troponin, we performed an electrocardiogram (normal) and an echocardiogram that showed a low ejection fraction like the previous. Despite the clinical suspicion, heart magnetic resonance imaging (MRI) ruled out this complication. Most likely, the elevation of troponin was related to an increased hydro-saline retention, which was responsive to the enhancement of peritoneal dialysis treatment. Taking into account the renal failure, the chronic ischemic heart disease and the DRESS syndrome relapse, we treated the patient with only intravenous immunoglobulin (IVIG) 0,5 g/kg for four consecutive days with clinical and laboratory benefits. After recovery, a multiple myeloma second-line therapy with orally Cyclophosphasmide 300 mg once weekly and prednisone 25 mg/die was started, but it was interrupted two weeks later because of melena and clinical worsening. Sixteen weeks after discharge the patient is still alive, he undergoes nephrological/hematological outpatient visits twice a week and receives palliative therapy. Liver tests and troponin levels are normal.

Discussion

DRESS syndrome is an idiosyncratic hypersensitivity reaction to a medication. Mortality has been estimated to be up to 10% because of myocarditis and liver failure. Renal involvement is usually secondary to liver (about 11-28% of patients); renal damage could be related to interstitial nephritis or to acute tubular necrosis, but sometimes the patient could develop vasculitis with renal failure.

Sometimes patients need short-term or long-term hemodialysis. In a survey conducted by Asian Research Committee on Severe Cutaneous Adverse Reactions (ASCAR) on 145 patients affected by DRESS syndrome [5], four of them with underlying diseases (IgA nephritis, renal disease and chronic renal failure) developed end-stage renal disease and culprit drug was allopurinol in two cases. 24 patients with Drug-Induced Hypersensitivity Syndrome were evaluated in a French study [8]: 11 patients on 24 (46%) were immunocompromised, the median latency time of onset was 15 days and myocarditis appeared in several cases with hypotension. Our patient developed these features and the suspicion of late myocarditis was very high because of troponin elevation, low cardiac ejection fraction and severe clinical impairment; however cardiac MRI showed that it was secondary to hyperhydration and previous cardiac disease. Furthermore, several studies suggest that myocarditis is often underestimated, because it needs a post-mortem histopathologic examination. The pathogenic bases of DRESS syndrome are still unclear. Some authors suggest that drug reactive metabolites, secondary to detoxification defect, could stimulate a delayed immunological reaction mediated by CD-8 T-lymphocyte and eosinophil degranulation; interestingly, the medication could also trigger viral reactivation, usually HHV-6. Cacoub et al reported 172 cases of DRESS: the most frequent “trigger-drugs” were carbamazepine, allopurinol, sulfasalazine, phenobarbital, nevirapine, and HHV-6 reactivation was positive in 80% of studied cases [9].

Generally, patients affected by DRESS syndrome develop renal complications presenting with creatinine elevation, sterile pyuria and sometimes with proteinuria and hematuria [10]. In our experience it was not possible to identify renal involvement, because our patient was already treated with peritoneal dialysis. Genetic predisposition to DRESS syndrome has been demonstrated: HLA-B*5801 in Chinese population treated with allopurinol is associated to kidney involvement in DRESS syndrome [11]. A French study [8] highlighted that 20 of 24 patients developed DIHS during winter, as our case, and that 75% of them had low level of Vitamin D. It is widely known that the nephrological population has chronic Vitamin D deficiency and that it has anti-inflammatory properties, so we can believe that it could be a risk factor for our patients treated with “trigger” drugs. Nevertheless, assessing clinical features of patients affected by DRESS syndrome described in literature, chronic kidney disease does not represent a risk factor for this syndrome (shown in Table 1).

	Cacoub et al [9]	Mona Ben m'rad et al [8]	Kano Y et al [5]	Avancini J et al [15]
Number of patients	172	24	145	27
Age (years)	40,7 ± 20,9	50,4 ± 17,1	51 ± 18,8	36 ± 16,4
Male	53 %	50 %	40,7 %	62,9 %
Onset weeks (mean)	3,9 ± 2,3	2	–	5,6 ± 5,3
Liver involvement	94 %	54 %	–	85,2 % (23 patients)
Kidney involvement	8 %	17 %	HD in 4 patients with pre-existing renal disease	33,3 % (9 patients)
Cases resulting in death	5,2 %	0 %	–	3,7 % (1 patients)
Autoimmune sequelae	–	–	23,4 % (34 patients)	–

Table 1: Comparison of clinical features and outcomes of patients affected by DRESS syndrome observed in four different mentioned studies. HD: chronic hemodialysis.

As described by Vlachopanos [12], DRESS syndrome after receiving Lenalidomide for multiple myeloma in people in renal replacement therapy has a very unfavorable course. According to literature (Table 2), the culprit drug should be withdrawn and, in cases of visceral involvement, systemic steroids are indicated (oral methylprednisolone 1 mg/kg/die with slow taper over 3-6 months). Rapid tapering is associated with relapse, like in our patient, and the benefit of antiviral medications is unclear. In severe and corticosteroid-resistant cases, other immunosuppressant

medications including cyclosporine, azathioprine, and mycophenolate have been used, sometimes alongside adjunctive treatment with IVIG and plasmapheresis [13, 14]. In our experience IVIG has been a good ally to control DRESS syndrome relapse.

Primary disease	Age	Medical history	Therapy	Time after LND	Virus	Systemic involvement	Treatment	Reference
MM IgG kappa	65 years	UN	LND 25 mg[A] – DXS[B]	6 weeks	No	AIN Hepatitis	PS 80mg	Shaaban H. et al [16]
MM IgG lambda	75 years	Diabetes mellitus hypertension heart failure CKD stage III	LND 5 mg[A] – DXS[B]	4 weeks	UN	Acute on CKD	MPSL 80 mg	Shanbhag A. et al [17]
MM	78 years	Hypertension Diabetes mellitus	LND 25 mg[A]	4 weeks	HHV-6	AKI Hepatitis	PS 20mg	Foti C. et al [18]
MM	62 years	CKD on hemodialysis	LND 5 mg[A]	5 days	UN	Non erosive oropharyngeal mucositis dysphagia	PSL	Vlachopanos G. et al [12]
MM	59 years	UN	Bortezomib-DXS[B]-LND	5-6 weeks	HHV-6 CMV	None	PS 20 mg/die	Osada S. et al [19]
MM IgA lambda	67 years	UN	Carfilzomib-DXS-LND 25 mg[A]	7 weeks	CMV	Hepatitis	PSL 1mg/kg/die Relapse: IVI G 0,5 g/kg/die for 4 days	Gajewska M. et al [20]

Table 2: Summary of lenalidomide-induced DRESS syndrome described in literature. Comparison of clinical features, multiple myeloma therapy, organ involvement of DRESS syndrome, virus reactivation and therapy. Abbreviations: Multiple Myeloma: MM; Lenalidomide: LND; Dexamethasone: DXS; Prednisone: PS; Methylprednisolone: MPSL; Prednisolone: PSL; Unavailable: UN. A: Lenalidomide 25 mg/die on days 1-21 in 28-days cycle. B: Dexamethasone 40 mg/die once a week in 28-days cycle.

Statements

1. The variety of drugs, the clinical course with slow resolution and relapse and HHV-6 reactivation suggest that drugs cannot be the sole etiology of DRESS.
2. Drugs with immunomodulatory activity or immunosuppression could contribute to the hypersensitivity reaction of DRESS syndrome.
3. Few cases of DRESS syndrome in end-stage kidney disease are reported in literature, but because of the increasing use of drugs and its several autoimmune sequelae, a broad workup and a multidisciplinary careful approach could help in diagnosis, treatment and follow-up.
4. Patients affected by chronic kidney disease may develop renal failure if DRESS Syndrome is complicated by severe acute interstitial nephritis or vasculitis.
5. Therapy: oral methylprednisolone 1 mg/kg/die with slow taper over 3-6 months; quick taper encourages relapse, which could be treated only with IVIG 0,5 g/kg for 4 days.

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