CASE SERIES

Case Series on Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS) with Different Ocular Manifestation

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ABSTRACT

"Drug reaction with eosinophilia and systemic syndrome" (DRESS) is a rare type of "severe cutaneous adverse reaction" (SCAR). We report 3 patients with DRESS who had different presentations. The first case developed DRESS following initiation of Allopurinol a month earlier. He presented with bilateral pseudomembranous conjunctivitis which resolved after 2 weeks. Two months later he presented with bilateral severe meibomian gland dysfunction (MGD), ocular surface disease (OSD) with severe dry eyes and left eye corneal perforation. The second case developed DRESS following initiation of allopurinol and had bilateral conjunctivitis. As for the third case, DRESS happened after taking Roxithromycin. She was diagnosed to have bilateral MGD, blepharitis and dry eyes. Case 2 and 3 did not develop ocular long-term complications. DRESS can cause acute and long-term ocular complications and therefore, following up patients with DRESS is essential to treat any complications with the aim to prevent corneal perforation.

Keywords: SCAR, DRESS, corneal perforation, MGD

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INTRODUCTION

There are 4 types of SCAR which consists of "Stevens-Johnson syndrome/toxic epidermal necrolysis" (SJS/TEN), DRESS, "generalized bullous fixed drug eruptions" (GBFDE) and "acute generalized exanthematous pustulosis" (AGEP) (1). DRESS is a rare type of SCAR(2) and could potentially present as a life-threatening adverse drug reaction (1). It is believed that medications or its reactive metabolites can initiate a severe hypersensitivity reaction in the body and cause fever, skin rashes, hematologic changes and internal organ impairment (1,3). While the well-recognized SJS/TEN is associated with severe ocular inflammation that can potentially cause blindness, (4) there is limited literature on the ocular presentation of DRESS. Thus, we report 3 cases of DRESS with different presentation ranging from acute conjunctivitis, blepharitis to chronic ocular sequelae of meibomian gland dysfunction (MGD), ocular surface disease (OSD) and cornea perforation. Informed consent was obtained from all three patients involved in this case series publication.

CASE SERIES

Case 1

A 63 years old gentleman with underlying gouty arthritis, hypertension and dyslipidemia was referred by the dermatology team for bilateral conjunctivitis. He presented with generalized skin eruption, fever, liver dysfunction, bilateral red eyes and hematological abnormalities which were eosinopenia (30µL), lymphocytopenia (890 µL) and neutrophilia (9460 µL), following initiation of allopurinol a month ago. There were no lymphadenopathy. In view of the suspicion of an allergic reaction, allopurinol was withheld. He was then diagnosed as DRESS based on the "Registry of for severe cutaneous adverse reaction" (regiSCAR) criteria score which scored 4 in this case. He was managed with intravenous hydrocortisone initially and transitioned to oral prednisolone later on. The ophthalmology team opinion was sought in view of his bilateral eye redness. He denies having blurring of vision, floaters or eye pain and visual acuity of the right eye (OD) was 6/36 while the left eye (OS) was 6/60. Bilateral injected conjunctiva with pseudomembrane over the lids were noted. The intraocular pressure (IOP) was 9mmHg OD and 15mmHg OS. Bilateral lens were cataractous while the examination of the fundi was normal. He had pseudomembranous conjunctivitis which resolved with gutt. levofloxacin 4

hourly and gutt. dexamethasone 8 hourly for a week. Both medications were tapered off slowly over a month's period. The vision improved to 6/12 OD and 6/18 OS during the one-month review visit. Two months later, he presented to the ophthalmology clinic with complaint of bilateral blurring of vision associated with redness and discharge. Vision deteriorated to 5/60 OD while OS had only perception of light. Further evaluation showed bilateral severe MGD, OSD with severe dry eyes and there was a left eye corneal perforation (3mm in size) with no corneal ulcer or hypopyon. (Fig. 1 and Fig. 2) The anterior chamber was quiet. He underwent left eye corneal gluing. (Fig. 2) Post operatively, intensive topical lubricants, oral doxycycline, topical antibiotics (cefuroxime, gentamicin and oxytetracycline) and strict lid hygiene were commenced. The corneal perforation healed after 6 weeks. The review at one year showed left eye visual acuity of 1/60. The left eye lids were clean, conjunctival was white, and there is a cornea scar seen obstructing visual axis located over lower paracentral region. (Fig. 3) Patient had bilateral dry eyes which was treated with gutt. artificial tears preservative free (ATPF) 6 hourly.

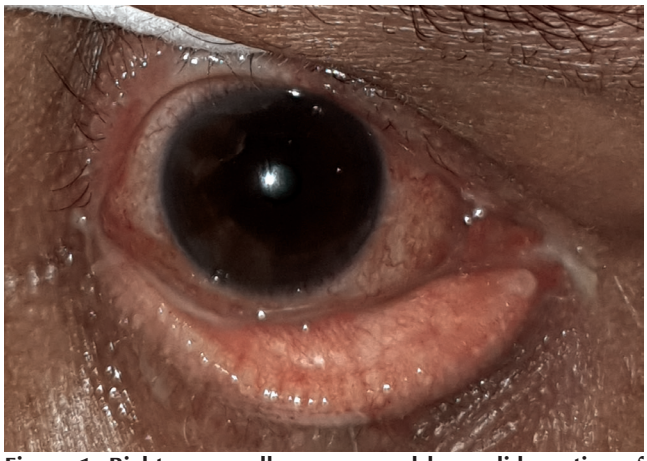

Figure 1: Right eye swollen upper and lower lid pouting of meibomian glands and presence of discharge. Conjunctiva appeared injected.

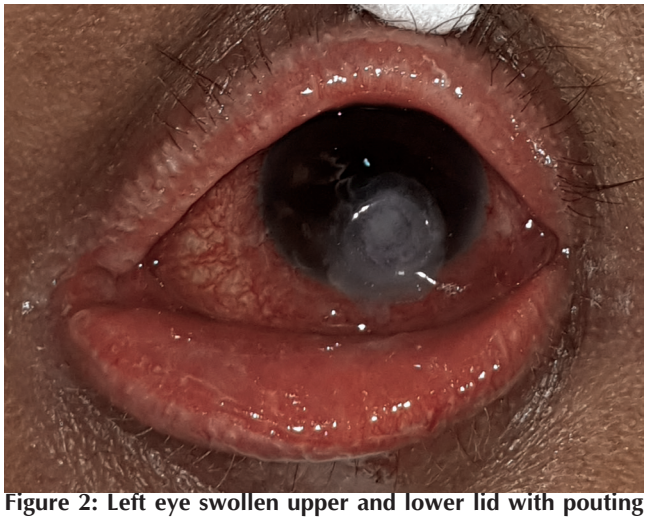

Figure 2: Left eye swollen upper and lower lid with pouting of meibomian glands and presence of discharge. Conjunctiva appeared injected. There was a cornea gluing located at paracentral region.

Figure 3: Left eye cornea scarring with cornea vascularization involving visual axis

Case 2

A 56 years old gentleman with underlying diabetes mellitus, hypertension, dyslipidemia and gouty arthritis was referred from the medical ward for bilateral conjunctivitis. He presented with generalized skin eruption, fever, hematological abnormalities which were eosinophillia (1980µL), leukocytosis (15900 µL), atypical lymphocytosis (3060 µL) and neutrophilia (9910 µL), acute kidney injury, liver dysfunction and bilateral red eyes following initiation of allopurinol for gout 2 months prior. There were no lymphadenopathy and other organ involvement. He was diagnosed as DRESS with regiSCAR score of 5 and treated with intravenous hydrocortisone 7 days followed by oral prednisolone prior to our review. On examination, patient was confused and disorientated, thus initial visual acuity could not be assessed. There were bilateral injected conjunctival and left eye small cornea epithelial defect measuring 2mm x 2mm. The IOP were 16mmHg OU. Lens were cataractous and fundi examination were unremarkable. Diagnosis of bilateral conjunctivitis without pseudomembrane and left eye cornea epithelial defect were made. The small cornea epithelial defect over left eye resolved after a day of gutt. moxifloxacin 4 hourly, gutt. dexamethasone 4 hourly, gutt. ATPF 2 hourly and hydroxypropyl methylcellulose ophthalmic gel on night. The bilateral conjunctivitis resolved after 7 days of therapy. The latest best corrected visual acuity (BCVA) 5 months after first presentation were 6/7.5 OD and 6/18 OS. Patient did not develop further complications like OSD.

Case 3

A 61 years old lady with underlying diabetes mellitus, hypertension and hypothyroidism was referred from medical ward for bilateral watery eyes with burning sensation. She presented with generalized skin eruption, fever and hematological abnormalities such

as eosinophillia (880µL), leukocytosis (13000µL), and neutrophilia (9900µL), following consumption of roxythromycin for an upper respiratory tract infection for 5 days. There were no lymphadenopathy and other organ involvement. She was diagnosed as DRESS with regiSCAR score of 4 and treated with intravenous hydrocortisone 6 days followed by oral prednisolone. She was then referred to the ophthalmology team for the ophthalmic symptoms. She denies having blurring of vision and eye pain upon questioning. On examination, unaided vision was 6/12 OD and 6/18 OS and there was bilateral pouting of meibomian glands and flacks on bilateral upper lashes. Bilateral corneas were clear with reduced tear break up time. IOP were 14mmHg OS and 16mmHg OD. The right eye was pseudophakic while the left eye was cataractous. Both eyes fundus examination were normal. She was also diagnosed to have bilateral MGD, blepharitis and dry eyes which resolved with ointment terramycin BD, gutt. dexamethasone 6 hourly, gutt. ATPF 4 hourly and lid hygiene. She underwent left eye phacoemulsification and posterior chamber intraocular lens implantation 3 months later and her latest BCVA were 6/7.5 OU. Patient still had dry eyes bilaterally and was symptomatically treated with gutt. ATPF 4 hourly.

DISCUSSION

DRESS incidence ranges from 1:1000 to 1:10000 (3) and carries a fatality rate of 10% (1). There were multiple diagnostic criteria used in diagnosing and managing DRESS (2). The RegiSCAR criteria was used in all 3 patients and the score is as shown in Table 1 (3). Pathogenesis of this syndrome have yet to be elucidated, however it is believed to be related with genetic predisposition, immunological mechanisms such as the delayed cell-mediated immune response, reactivation of the herpes viruses, and deficiency in drug metabolism and its reactive metabolites.(3) The clinical features of DRESS which are complex and broad usually appears 3 to 8 weeks after taking the culprit drug. The signs of DRESS are fever, cutaneous eruption, lymphadenopathy, hematological abnormalities (eosinophilia, leukocytosis, etc.), and internal organ involvement (1).

DRESS with ocular presentation is rare and with only few cases reported. It includes uveitis (anterior, intermediate, and panuveitis), angle closure glaucoma, choroidal folds in macula, serous elevation of retina and intraretinal haemorrhages (5). Bohm KJ et al., reported one case of DRESS syndrome where the patient presented with bilateral pseudomembranous conjunctivitis and conjunctival denudation in acute setting. After recovery, the patient exhibit residual conjunctiva cicatrization (4). It is to our best knowledge that there are no reports in the literature on cornea perforation due to DRESS.

In the first case, the patient exhibited severe ocular mucosal inflammation which lead to severe MGD and ocular surface disease. Even though patient had recovered systematically, the ocular mucosal inflammation persisted. The chronic changes of mucosal inflammation led to severe dry eyes, impairment of tear film formation and cornea erosion leading to cornea perforation. The other two cases however did not develop such chronic complications.

The management of DRESS includes early recognition of the disease and the withdrawal of the causative drug promptly. Earlier drug withdrawal has been shown to lead to a better prognosis (1). All 3 cases had different drug withdrawal time. Treatment while largely supportive and symptomatic, hinges upon the use of corticosteroids as the mainstay of treatment (1). In all 3 cases, symptoms and signs resolved with topical dexamethasone during the acute setting albeit Case 1 who unfortunately developed corneal perforation. There are limited studies on the treatment of ocular complications in DRESS. In first patient, the cornea perforation healed with cornea gluing, intensive lubrication, oral doxycycline and

Table I: Scoring system of Registry of severe cutaneous adverse reaction (RegiSCAR) criteria for diagnosing Drug reaction with eosinophilia and systemic syndrome DRESS

Score	-1	0	1	2	Min	Max
Fever ≥ 38.5°C	No/U	Yes			-1	0
Enlarge lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			700-1499/µL	≥1500/µL		
Eosinophils, if leukocytes <4000			10-19.9%	≥20%		
Atypical Lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Rash extent (>50% BSA)		No/U	Yes			
Rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ(s)		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes: Serological tests like ANA, HAV/HBV/HCV, Chlamydia, Mycoplasma, Blood culture, etc. Negative or Positive ≥3 of above					0	1

Final score <2: No case, 2-3: Possible case, 4-5: Probable case, >5: Definite case; U = unknown/unclassifiable;
*After exclusion of other explanations: 1=1 organ, 2 = ≥ 2 organs
BSA: Body Surface Area, DRESS: Drug Reaction with Eosinophilia and Systemic Syndrome, ANA: Antinuclear antibodies, HAV: Hepatitis A virus, HBV: Hepatitis C virus

topical antibiotics. We suggest that patients with DRESS should be carefully monitored especially on the ocular surface and lids even after the acute event has settled as this can help in early detection of ocular surface disease and offer prompt early treatment if needed. Maintenance of lubricants is important in preventing severe dry eyes and long-term complications.

CONCLUSION

DRESS can be associated with several ocular presentation in the acute phase ranging from bilateral pseudomembranous conjunctivitis, non-pseudomembranous conjunctivitis, blepharitis, MGD and dry eyes. It can also induce long-term ocular complications such as MGD, OSD and corneal perforation. Thus, it is important to follow up patients with DRESS in order to treat its complications as well as to prevent corneal perforation.

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