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Short Communication

Current Understanding of Severe Cutaneous Adverse Reaction (SCAR)

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DESCRIPTION

Severe Cutaneous Adverse Reaction (SCAR) is a rare but life-threatening emergency. It encompasses a spectrum of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Generalized Bullous Fixed Drug Eruptions (GBFDE) [1]. All of them have a common presentation of extensive skin eruptions induced by drug intake. SCAR to drugs is associated with intensive care management, long term morbidity, health care costs, multi-disciplinary care and high mortality rates [2]. The incidence of SCAR is difficult to assess due to its rarity but the incidence of DRESS syndrome in new users of antiepileptic drugs has been estimated to be around one per 1000 and the incidence of SJS/TEN is estimated to be around two per 1 million people [3] Although rare, but high index of suspicion and adequate knowledge among physicians is the key to early diagnosis, prompt stoppage of the offending drug and timely initiation of definitive care. The key clinical and histopathology features of the major subsets of SCAR are shown in Table 1.

Table 1: Clinical and histopathological features of SCAR.

	Drug to rash interval	Systemic features	Skin findings	Laboratory parameters	Organs involved	Histopathology features
SJS=Stevens-Johnson Syndrome TEN=Toxic Epidermal Necrolysis	4 days to 4 weeks	Fever, sore throat	Skin detachment (less than 10% in SJS, 10-30% in SJS-TEN overlap, more than 30% in TEN), hemorrhagic crusting of mucosa, positive Nikolsky sign, Bullous lesions and purpura	Eosinophilia, renal and hepatic impairment, transitory neutropenia	Skin (acute skin failure), mucosae, respiratory tract, liver, kidney	Full thickness epidermal necrolysis, necrotic keratinocytes, mixed dermal infiltrate, dermal oedema, negative Direct immunofluorescence
AGEP=Acute Generalised Exanthematous Pustulosis	1 day to 2 weeks	Fever	Generalized non follicular sterile pustules, flexural erythema, epidermal desquamation, mucosal involvement is rare	Neutrophils ≥ 7000 cells per µL Mild leukocytosis, mild eosinophilia	Predominantly skin	Intraepidermal subcorneal spongiform pustules with papillary oedema with neutrophilic infiltrate, focal necrotic keratinocytes with occasional vasculitis
DRESS=Drug Reaction with Eosinophilia and Systemic Symptoms	DRESS=Drug Reaction with Eosinophilia and Systemic Symptoms	Fever, malaise, loss of appetite jaundice	Facial edema, icterus, macula-papular rash, erythroderma, focal mucosal involvement	Eosinophilia, atypical lymphocytes, transaminitis, impaired renal function, rarely herpesvirus family reactivation (HHV6, HHV7, EBV, CMV), parvovirus B19)	Skin, liver, kidneys, lymph nodes, pancreas	Interface dermatitis, spongiosis, focal necrotic keratinocytes, focal neutrophilic and eosinophilic infiltrates

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Pathogenesis

The clinical plethora of SCAR can be explained by the activation of effector or regulatory T lymphocytes secreting specific cytokines and finally leading to keratinocyte necrosis [4-6]. Non immediate hypersensitivity reaction to the drug is considered as the basic pathomechanism in all SCARs. Four proposed subgroups of inflammatory cascade areas follows:

1. T helper (Th1) T cells mediated

2. Th2 T cell mediated eotaxin cytokines and interleukins 5, 4, and 13 (AS IN DRESS)

3. Cytotoxic T cell mediated as in SJS/TEN

4. T cells and neutrophil mediated *via* chemokine (C-X-C motif, ligand 8 (CXCL-8) and granulocyte-macrophage colony-stimulating factor cytokines (as in AGEP)

Following drug stimulation *via* HLA-encoded MHC proteins, immune-cytokine mechanisms of SCARs include the activation of drug-specific cytotoxic T cells, inflammatory cells, or regulatory T cells (T-regs).

Several genetic factors that cause a predisposition to SCARs have been previously reported-eg, metabolic enzyme mutations, or specific HLA-A, B, or C alleles. A strong (100%) association has been established in Taiwan (Han-Chinese) between the HLA-B*15:02 allele and carbamazepine-triggered and the HLA-B*58:01 allele and allopurinol-induced SJS & TEN.

Assessment of SCARs

Patient assessment relies on the eruption's clinical appearance (eg, potentially drug or virus related), how long the eruption has been present, associated symptoms (eg, fever, pruritus, lymphadenopathy), and the time elapsed between drug intake and SCAR onset. Body surface area involvement, Nikolsky sign and comorbidities define further management. A high index of suspicion is the key to early diagnosis and timely initiation of definitive treatment.

Management and treatment

SCAR-management strategies are predominantly symptomatic, involving intense nursing care aimed at avoiding short-term morbidity and mortality and severe long-term sequelae. Stopping of the offending drug at the earliest and initiating immune suppressive therapy is the key to successful early outcome. Skin and mucosa care in a Dermatology ICU or burns unit is ideal as it prevents cross infection. Reverse barrier nursing, monitoring the vitals and body surface area involvement, care of eyes, mouth and focus on diet is of paramount importance. Definitive immunesuppresion with oral corticosteroids is a double edged sword as it predisposes to delayed wound healing and secondary bacterial infection. Several immunosuppressants or immunomodulatory treatments (eg, corticosteroids [7], calcineurin inhibitors like cyclosporine [8], cyclophosphamide [9], anti-TNF therapies [10], Intravenous Immunoglobulins [IVIg], [11,12] or plasmapheresis) have had controversial results. There have been no head to head trials on any randomized control trials on this subject yet.

CONCLUSION

We would like to conclude that a high index of suspicion can timely diagnose and prevent this rare but life threatening clinical entity. Drugs are important part of clinical medicine and drug reactions are part and parcel of the deal. Polypharmacy, increased longevity and comordities complicate the clinical picture and pose management challenges. Clinicians should be aware of the potential role of high-risk medication in triggering SCARs, especially when predisposing factors are present.

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