Severe Cutaneous Adverse Reactions to Drugs (SCAR): Definitions, Diagnostic Criteria, Genetic Predisposition

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This paper is a review of the clinical characteristics, diagnostic criteria and main drug causes of the severe cutaneous adverse reactions to drugs (SCAR) that are studied by the RegiSCAR-group. These include acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (also called drug-induced hypersensitivity syndrome), Stevens-Johnson syndrome, and toxic epidermal necrolysis. (Dermatol Sinica 27: 203-209, 2009)

Key words: Adverse drug reactions, Drug hypersensitivity, Stevens-Johnson syndrome, Toxic epidermal necrolysis

Adverse drug reactions affecting the skin are frequent and present with a huge variety of phenotypes. The two most frequent are alterations of skin functions related to pharmacologic effect of medication (e.g. altered pigmentation, acne, hair loss…) and on the other hand mild “drug eruptions”. Severe forms are rare and account for less of 5% of drug eruptions observed in hospitalized patients.¹ We proposed the denomination of severe cutaneous adverse reactions (SCAR) for very rare disorders that share the following criteria: i) being severe (associated to a significant morbidity and mortality and usually leading to hospitalization, ii) non-predictable (idiosyncratic, and probably of immunological mechanism) and iii) most often induced by drugs.²

A multinational collaborative research team was established since 1988 to study SCAR.³ It initially associated mainly dermatologists and epidemiologists and progressively enlarged to geneticists and immunologists. It changed its name from SCAR-group to EuroSCAR- and lately RegiSCAR-group when enlarging the scope of diseases of interest and aggregating new participating teams. At present (Jan. 2009) the RegiSCAR-group is active in Austria, France, Germany, Italy, Netherlands, South Africa, Taiwan, and the United Kingdom. It is operating as a registry collecting detailed clinical data and biological samples on 3 varieties of SCAR, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), also called drug induced hypersensitivity syndrome (DIHS) and acute generalized exanthematous pustulosis (AGEP).
**ACUTE GENERALIZED EXANTHEMA-TOUS PUSTULOSIS (AGEP)**

AGEP was described in 1980 as a widespread pustular eruption resembling pustular psoriasis, but usually occurring as a drug reaction in patients without a history of psoriasis. Numerous, very small and mostly non-follicular pustules arise on a widespread edematous erythema. Pustules are mainly located in the main folds (neck, axillae, groin), trunk, and upper extremities. Confluence of pustules may result in superficial (subcorneal) detachment, not rarely misdiagnosed clinically as TEN. Edema of the face, purpura, vesicles, erythema multiforme-like lesions, and mucous membrane involvement are occasionally present. Proposed diagnosis criteria include: 1) an acute pustular eruption; 2) fever above 38°C; 3) neutrophilia with or without a mild eosinophilia; 4) subcorneal or intraepidermal pustules on skin biopsy; 5) spontaneous resolution in less than 15 days.

The time between the beginning of drug administration and the skin eruption is relatively short (less than 2 days) for antibiotics, whether a history of prior sensitization is found or not. The eruption lasts a few days, and is followed by a superficial desquamation. AGEP may be difficult to differentiate from acute pustular psoriasis. The pustules in both diseases are clinically indistinguishable; the histopathology can be helpful (absence of epidermal changes suggesting psoriasis, edema in the upper dermis). Antibiotics (such as aminopenicillins, pristinamycin) diltiazem, terbinafine, chloroquine/hydroxychloroquine, are the drugs most often implicated in AGEP. Drug specific T-cells were found within the skin lesions that produced neutrophil recruiting cytokines and chemokines.

**DRESS- DIHS- “HYPERSENSITIVITY SYNDROME”-**

The acronym of DRESS for Drug Reaction with Eosinophilia and Systemic Symptoms has been proposed as more specific than “hypersensitivity” which would apply to all types of “allergic” drug reactions. The name of DRESS points to 2 important characteristics: multi-systemic involvement and frequent eosinophilia. Dermatologists in Japan prefer the acronym of DIHS for Drug-Induced Hypersensitivity Syndrome.

Behind the different denominations there is a consensus of all experts on the originality and main characteristics of this syndrome, which include:

1. Drug-induced immunologic phenomenon
2. Later onset than for other drug reactions
3. Longer duration than common “drug rash-
4. Multi-organ involvement, often including severe skin eruption
5. Lymphocyte activation (node enlargement, lymphocytosis, atypical lymphocytes)
6. Eosinophilia
7. Frequent virus reactivation

Compared to other denominations, DRESS captures a little more, but still not all, of these salient features. DRESS has been estimated to occur in about one in 10,000 exposures to drugs such as antiepileptics and sulfonamides. In France these reactions were considered more frequent among persons of African ancestry. They begin 2 to 6 weeks after the onset of drug intake and may persist for several weeks after drug withdrawal. Some of the manifestations, especially hepatitis may be life-threatening, with a mortality rate of about 10%. DRESS is typically characterized by a severe eruption, lymphadenopathy, fever and hematological abnormalities. Visceral involvement differentiates this syndrome from common eruptions; it may include hepatitis, arthritis, pulmonary infiltrates, interstitial nephritis, and other.

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answers to many pending questions. In major published case series none of the 7 “main characteristics” of DRESS/DIHS was constant.\textsuperscript{11,12} The respective prevalence of lymphadenopathy, “atypical” or “activated” blood lymphocytes, eosinophilia, proof of viral activation all varied between 40 and 70%. We think, therefore, that it is unwise to consider the absence of any of them as exclusion criteria.

Until the mechanisms of visceral involvement (including the skin) are better understood, we estimated that the decision that an organ is involved by DRESS should rely on 2 criteria: clinical relevance and absence of other causes. As an example, liver is considered involved, if alanine aminotransferase levels are at least twice above the upper limit of normal values in the absence of another disease. The literature on drug-induced hepatitis and nephritis includes cases that resemble DRESS but occasionally without an eruption. The absence of skin lesions should, therefore, not be an exclusion criterion.

Differential diagnoses of DRESS comprise acute viral infections, multisystemic inflammatory diseases such as systemic lupus erythematosus, idiopathic hypereosinophilic syndrome, and cutaneous T-cell lymphoma. Skin pathology of DRESS is not yet fully characterized. Several reports pointed to the presence of a relatively dense perivascular infiltrate of lymphocytes in the dermis and/or lichenoid features in DRESS. Totally normal or very slightly altered skin histology is still compatible with a diagnosis of DRESS.

Several antiepileptic agents (phenobarbital, carbamazepine, phenytoin, lamotrigine), and allopurinol are the most frequent causes of DRESS worldwide. Anti-infectious sulfonamides, gold salts, dapsone may also induce this syndrome as well as many other drugs, varying with countries maybe on the basis of ethnic background (e.g. minocycline in French patients of African ancestry).

A specificity of DRESS appears to be virus activation. Several case reports and a few well documented series have evidenced markers of virus reactivation in many cases of DRESS. Human herpes virus 6 (HHV6) is the most frequently reactivated in Japan (62% of cases based on serology, 30% with positive PCR on serum). Two other herpes viruses: cytomegalovirus (CMV) and Epstein-Barr virus (EBV) can also be reactivated as well as HHV6.\textsuperscript{11} This reactivation is usually detected in the 2 weeks following the onset of the reaction and is related (and probably contributes) to late and prolonged clinical manifestation, such as fever, recurrent rash hepatitis, and encephalitis.

The mechanisms of DRESS remain unknown. The original mixture of drug "allergy" (proven by accelerated onset in cases of rechallenge, positive skin tests, and positive in vitro tests) and virus activation has been the source of many hypotheses, none being proven up to now.

**EPIDERMAL NECROLYSIS (SJS/TEN)**

Based on the results of a large case-control study,\textsuperscript{13} we established that SJS and TEN can be considered as severity variants of a single disease, different from erythema exsudativum multiforme majus (EEMM). Actually, SJS/TEN and EEMM differ by demographic characteristics of patients, associated diseases, severity, causality and treatment. Some unifying denomination could be helpful. Several were proposed: acute disseminated epidermal necrolysis (ADEN),\textsuperscript{14} acute syndrome of apoptotic panepidermolysis (ASAP),\textsuperscript{15} to which we could add epithelial necrolysis. Waiting for a larger agreement, the RegiSCAR-group stays with SJS/TEN.

The main features of SJS/TEN are well known by dermatologists: acute onset and rapid progression of painful lesions of the skin and mucous membranes that develop to
blisters and erosions with severe constitutional symptoms and extensive detachment of the epidermis. The mortality rate is 25% during hospitalization for SJS/TEN, depending on age and the extent of skin detachment. The majority of survivors suffer from sequelae that impair often seriously their quality of life.

Extensive death and detachment of the epidermis resulting from apoptosis of keratinocytes on the full or nearly full thickness of the epidermis is characteristic. Direct immunofluorescence is negative. Differential diagnoses include rare cases of acute autoimmune blistering disorders that may mimic SJS/TEN, especially paraneoplastic pemphigus and drug-induced linear IgA bullous disease. Thermal or caustic burns are occasionally diagnosed as TEN when history is unclear. In very early stages SJS is often misdiagnosed as chickenpox (varicella).

Medications are the main cause of SJS/TEN.\(^\text{16}\) A drug causality can be established in two third of cases.\(^\text{17}\) The remaining one third of cases comprises a very small minority (much less than 5%) of cases with another cause (acute infection, especially with\(\text{Mycoplasma pneumoniae}\)). About thirty percent of cases remain idiopathic.

Recent progresses were done on the mechanisms of SJS/TEN. Drug specific cytotoxic T-cells are found at the site of the lesions.\(^\text{18}\) Widespread apoptosis seems to result from the massive release of a variety cytokines and especially granulysin.\(^\text{19}\) In our experience, no specific treatment has been proven to be effective. The best available evidence has been provided by the Euro-SCAR-cohort analysis.\(^\text{20}\) The results showed no benefit from using intravenous immunoglobulin and a strong (but not significant) potential reduction of mortality with the use of corticosteroids. These results should lead to further studies on the possible usefulness of corticosteroids and immunosuppressive agents.

**ARE SUCH SUB-CLASSIFICATIONS USEFUL?**

Many dermatologists still feel uncomfortable with the above classifications because they often see patients with ambiguous diagnosis. That is in large part dependant on the need to get information on pathology and on the course of the disease for a final diagnosis. When using all our scoring systems simultaneously in a large population of patients suspected of SCAR we obtained several “possible” diagnoses in about 20% of cases but in less than 2% at the level of “probable/definite” diagnoses. These observations suggest that the use of our classifications is feasible. We also consider they are useful because associated disorders are different, drug causes are not similar and effector mechanisms also differ.

**ADVANCES ON PREDISPOSITION GENES**

Two papers from Taiwan found a 100% association between SJS/TEN and HLA-B for two high risk drugs: carbamazepine and allopurinol.\(^\text{21, 22}\) These results strongly re-enforced the hypothesis of predisposing genes in SJS and TEN and raised the hope that genetic testing could become an effective way of prevention.

In Europe, among 12 cases related to carbamazepine, four were positive for B*1502, an allele so rare in Europe that the association would be highly statistically significant. But all four positive patients were from Asian ancestry, while none of 8 European patients had neither B*1502, nor any other associated allele.\(^\text{23}\)

On the other hand, among allopurinol-related SJS/TEN-cases we observed the same association with HLA-B*5801 as in patients from Taiwan.\(^\text{24}\) The association was weaker than in Taiwan anyhow (60% instead of
CONCLUSION
Tremendous advances were made in the last 10 years on knowledge of SCAR. Despite being rare SCAR deserve continuous interest, not only for improving the safety of medications but also because improved knowledge on the mechanisms of lesions in SCAR will apply to other fields of medicine. Because of the extreme rarity of SCAR, international collaboration is critical to further progress.

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