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Clinical spectrum of drug eruption

Speaker: LE French
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Drug eruptions are not uncommon and the incidence can be as high as 1-5% for certain type of medications such as NSAID, antibiotics and antiepileptics. When encountering a case of drug eruption, other differential diagnoses e.g. infection and autoimmune disease should be considered. A detailed drug list should be formed to ensure that the timeline and clinical picture is compatible.

Drug eruptions are the most common adverse event in hospitalised patients. Disseminated morbilliform drug eruption is the most common presentation of drug eruption. It will usually fade in a few days when the culprit drug is stopped. However, a disseminated morbilliform eruption could be the initial presentation of severe cutaneous drug eruption such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS). It is of utmost important to be familiar with features of severe cutaneous drug eruption. Mucosal involvement, blisters, bullae, greyish skin lesions, skin dislodgement, ulcer, purpura, pustule, facial oedema, angioedoema, lymphadenopathy, fever, blood eosinophilia and organ involvement are important red flag signs to be aware of. The following includes some pearls of the more commonly encountered severe cutaneous adverse drug eruptions.

Stevens- Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN):

Mucosal and conjunctival involvement occurs in >90% of cases. Early lesions may present with morbilliform or atypical targetoid lesions with later rapid confluence of lesions with bulla and skin dislodgement (positive Nikolsky sign). The onset is usually at around four weeks after exposure to culprit drug.

Acute generalised exanthematous pustulosis (AGEP):

This is characterised by the rapid appearance of sterile pustules (under 48 hours after exposure to the culprit drug) with fever and neutrophilia in the blood. Upon stopping the related drug, rapid spontaneous healing with desquamation is expected. If the resolution is not rapid (under two weeks), other differential diagnosis such as pustular psoriasis should be considered.

Drug reaction with eosinophilia and systemic symptoms (DRESS):
Onset is mostly 3-6 weeks after culprit drug. It usually starts with diffuse maculopapular exanthema with facial oedema, fever, lymphadenopathy. Eosinophilia is a typical feature. Atypical lymphocyte and systemic involvement e.g. hepatitis, nephritis, pulmonary infiltrate may be found.

Learning points:

It is important to recognise red flag signs which indicate underlying severe cutaneous drug eruption.

How to manage severe drug reactions- SJS/TEN

Speaker: W Hoetzenecker
Johannes Kepler University Linz | JKU Dermatology, Austria

Treating toxic epidermal necrolysis with systemic immunomodulating therapies: A systemic review and network meta-analysis.

The mortality rate of SJS is lower than SJS/ TEN overlap and TEN. Hence, when mortality is used as outcome, involving SJS in the pool may undermine the clinical relevance of results. Therefore, this is a network meta- analysis (NMA) involving patients with greater severity SJS/TEN overlap and TEN. In 66 studies included, only three were RCTs and six were prospective comparative studies. The NMA showed that combination therapy of IVIG with corticosteroid may lower mortality risks in patients with SJS/TEN and TEN (standardised mortality ratio SMR: 0.53; 95% CI, 0.31-0.93). Another meta-analysis using recovery time instead of mortality rate as an outcome also suggested the beneficial role of IVIG with corticosteroids. Other treatments e.g. cyclosporine, cyclosporine with IVIG, IVIG with plasmapheresis, and etanercept are potential treatment options but high quality evidence is still lacking. More high quality studies like RCTs are required.

Rapid identification and withdrawal of culprit drugs followed by optimised supportive is essential. IVIG with corticosteroid has been demonstrated to provide survival benefit in the latest meta-analysis while there is increasing evidence for cyclosporine being able to lower mortality rates.

Learning points:

In the latest meta-analysis, IVIG with corticosteroid has been demonstrated to have survival benefit.

Diagnosing non-immediate drug allergy

Speaker: M Goncalo
University of Coimbra, Faculty of Medicine and University Hospital, Coimbra, Portugal

The following framework to confirm culprit drug was introduced:

1. Pharmacological algorithms:
   French pharmacovigilance system
   Naranjo ADR probability scale
2. Complementary tests:
   Acute phase – in-vitro tests such as T cell proliferation
   After resolution – in-vivo tests such as skin test (cutaneous patch tests, intradermal tests), drug provocation test (oral rechallenge)

In-vitro tests include T-cell proliferation (LTT), T cell activation (flow cytometry), cytokine production (ELISA/ELIspot). The sensitivity and specificity depend on the culprit drug and the type

of adverse cutaneous drug eruption with high variability. Moreover, these tests can be time-consuming and are not widely available.

Regarding in-vivo tests, patch testing is generally safe even in severe cutaneous drug eruption. However, there may be minor reactivation of exanthems. It has a high specificity but variable sensitivity. Hence, a negative patch test may need to be confirmed with intradermal testing. Drug provocation tests are the gold standard to confirm a culprit drug. However, these are not recommended in severe cutaneous drug eruption.

Conclusion

The diagnosis of drug eruption relies heavily on history and physical examination and clinical judgement. It is of utmost important to be familiar with the usual timeline and clinical manifestations (particularly the red flag signs listed above) of severe cutaneous drug eruptions. Early identification and withdrawal of the culprit medication is the best and most effective way to halt the potential life-threatening events. Pharmacological algorithms such as Naranjo ADR probability scale and ALDEN, a specific algorithm for SJS/TEN, will definitely help physicians determine the culprit drug(s). In the rapid acute phase, patch test or intradermal tests may not be feasible and as such, in-vitro tests such as lymphocyte transformation test are gaining attention in these situations. More high-quality RCTs to define better treatment options in severe cutaneous drug eruptions are needed.

Learning points:

Pharmacological algorithms together with various complimentary tests can assist clinicians in finding the culprit drug.