Maculopapular Drug Eruption versus Maculopapular Viral Exanthem

Maculopapular skin eruptions are characterized by an erythematous maculopapular rash coinciding temporally with the administration of a drug in the absence of underlying conditions unless it progresses to severe forms which are associated with extensive skin or mucosal involvement. A large number of drugs have been attributed to give rise to such eruptions. It is also one of the most common dermatologic manifestations in certain viral exanthems which are characterized by the prototypic morbilliform/maculopapular rash with or without an exanthem. Maculopapular rash is a common symptom in day-to-day clinical practice, and a large number of consultations and references are attributable to it. However, drugs initiated for the treatment of underlying infections can be a cause of a maculopapular eruption. In such a setting, it is a diagnostic dilemma to differentiate between the two. Table 1 enlists differences between the two so as to help physicians to differentiate between the two.

### Table 1: Differentiating features between maculopapular drug eruption and maculopapular viral exanthem

| Feature                                      | Maculopapular drug eruption                                                                 | Maculopapular viral exanthem                                                                 |
|----------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| **Definition**                               | Exanthematous drug eruption, also called morbilliform or maculopapular drug eruption, is the most common type of drug hypersensitivity reaction characterized by a diffuse and symmetric eruption of erythematous macules or small papules occurring approximately 1 week after the initiation of drug treatment[1] | A generalized eruption of erythematous macules and papules associated with systemic infection, often accompanied by fever and lymphadenopathy |
| **Epidemiology**                             | Adulthood, increased incidence in HIV-positive population and women[2]                     | Childhood, no particular sex predilection[3,4]                                             |
| **Etiology**                                 | Numerous drugs have been implicated such as antibiotics (most commonly beta-lactams, sulphonamides, cephalosporins, quinolones, tetracyclines), anticonvulsants (phenytoin, carbamazepine, lamotrigine), NSAIDs, and allopurinol are common culprits. Antitubercular drugs such as ethambutol and pyrazinamide, antiretroviral agents such as protease inhibitors, emtricitabine, and tenofovir[5] | Measles (Paramyxoviridae), rubella (Togaviridae), erythema infectiosum (Parvoviridae), Roseola Infantum HHV Types 6 and 7 belonging to the Roseolovirus genus, infectious mononucleosis by EBV or CMV. Rare etiologic agents are nonpolio enteroviruses, rhinovirus, adenovirus, paramyxovirus, respiratory syncytial virus, and influenza virus[6,7] |
| **Mechanism**                                | Maculopapular drug eruption is a T-cell-mediated delayed hypersensitivity (Type IV) type reaction[8] | After the entry of virus into the body, it incubates and enters the viremic phase where there occurs dissemination of viral particles to all tissues of the body. The exanthema occurs as a result of perivascular inflammatory reaction to the virus in the skin |
| **Onset of rash**                             | The eruption usually begins within a week upto 10 days after intake of the offending drug[7] on the trunk and upper extremities and progresses caudally | Prodrmal symptoms such as fever, conjunctivitis, rhinorrhea, cough, pneumonia, otitis media in measles, headache, sore throat, and myalgia, arthralgia, in rubella, cephalocaudal distribution of maculopapular eruption in measles and rubella[8,9] |
| **Temperature**                              | Low-to-moderate grade fever may be present | High-grade fever in erythema infectiosum, roseola infantum |
| **Cutaneous manifestation**                  | Erythematous maculopapular eruption appears on the trunk and upper extremities and then progresses caudally [Figure 1]. It is usually symmetric and may get confluent and severe in dependent areas, such as the back. Facial involvement can be seen. In severe forms, the mucosa (oral, conjunctival, nasa, or anogenital) and skin appendages (hair and nails) may be involved. Petechiae and macular purpura may be noted occasionally on the legs secondary to hemostatic pressure. Lesions are mostly pruritic | Cephalocaudal distribution of maculopapular (morbilliform) eruption [Figure 2] with sparing of palms and soles, may be associated with lymphadenopathy as in rubella or Koplik’s spots over the buccal mucosa in measles |
| **Diagnosis**                                | Diagnosis is clinical and requires a high index of suspicion. Temporal correlation with drug intake will be found. Appearance of rash on drug re-challenge is characteristic | Appearance of maculopapular rash following intake of ampicillin/amoxicillin in suspected cases of infectious mononucleosis |

Contd...
| Laboratory investigations | Maculopapular drug eruption | Maculopapular viral exanthem |
|----------------------------|----------------------------|----------------------------|
| Occasional derangement of liver function tests and raised eosinophil counts may be associated | Serologic investigations show elevated blood counts, lymphocytosis or lymphocytopenia, atypical lymphocytes, thrombocytopenia, transient aplastic anemia in parvovirus B19 infection |
| Histopathology from the maculopapular lesions shows focal spongiosis, with underlying focal-vacuolar interface changes, occasional necrotic keratinocytes, superficial and deep perivascular lymphocytes, and eosinophils | Histopathology features in viral exanthemata include a superficial perivascular infiltrate of lymphocytes without associated epidermal changes, a superficial-vacuolar interface dermatitis, sometimes associated with eosinophils and neutrophils, a lichenoid dermatitis, and a mild spongiotic dermatitis. All these patterns may also be encountered in drug eruptions |
| Skin intradermal/prick tests may show immediate reactions to penicillin and a few other drugs | Serum ELISA for IgM antibody against the viral antigen can be detected in the initial few days |
| Patch tests using the suspected drugs should be done to confirm the diagnosis | Viral PCR for specific diagnosis is useful in cases of Parvovirus B19 infection, HHV 6 and HHV 7 implicated in Erythema infectiosum |

| Laboratory investigations | Histopathology features in viral exanthemata include a superficial perivascular infiltrate of lymphocytes without associated epidermal changes, a superficial-vacuolar interface dermatitis, sometimes associated with eosinophils and neutrophils, a lichenoid dermatitis, and a mild spongiotic dermatitis. All these patterns may also be encountered in drug eruptions |
| Treatment | Can be prevented by available vaccinations for measles and rubella |
| Withdrawal of the offending drug and its further avoidance | Symptomatic treatment for fever with antipyretics, soothing calamine-based preparation |
| Symptomatic management with oral antihistamines, a short course of oral corticosteroids and topical calamine-based soothing agents | | |

| Response to corticosteroid | Resolution and clearing up of lesions with fine desquamation | Predisposition to development of secondary bacterial infections |

NSAIDs: Nonsteroidal anti-inflammatory drugs, HHV: Human herpesvirus, CMV: Cytomegalovirus, EBV: Epstein–Barr virus, PCR: Polymerase chain reaction

**Figure 1:** Drug-induced maculopapular rash in an adult involving the trunk.

**Figure 2:** Viral maculopapular exanthem over the face in a child.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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