An 18-year-old male came with complaints of red rash over the trunk, back, and arms associated with itching for 3 days. He stated that these lesions had appeared first over the chest and had spread to involve the back and the arms gradually. At the time of presentation, the patient was afebrile but gave a history of starting category 1 antitubercular treatment consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide 5 days before the onset of rash in view of the recent detection of pulmonary Koch’s. His other past medical history was insignificant. Cutaneous examination revealed erythematous maculopapular eruption distributed over the trunk [Figure 1] and arms symmetrically. At a few places over the trunk, it had coalesced to form patches and plaques. The rash was blanching on diascopy and was nontender on examination. No evidence of icterus or pallor was noted. Patient was afebrile and recorded a pulse rate of 86/min, respiratory rate of 14/min, and was normotensive. Oral, conjunctival, and genital mucosa were uninvolved. There was no evidence of any lymph node enlargement or hepatosplenomegaly on systemic examination. Chest X-ray revealed a small patch of consolidation in the upper lobe of right lung. Complete blood count revealed leukocytosis and mild elevation of eosinophil count. Other biochemical investigations in the form of liver and renal function tests were within normal range. A biopsy from the lesion showed focal parakeratosis, spongiosis, superficial, and deep perivascular infiltrate of lymphocytes and scanty eosinophils [Figure 2]. Thus, based on history and examination, a diagnosis of maculopapular drug eruption secondary to antitubercular therapy (ATT) drugs was made. He was admitted for the evaluation of skin rash and was started on oral antihistamine and topical calamine-based soothing lotion. After 5 days of stopping the therapy, his lesions showed complete improvement, and he was restarted on escalating doses of individual antituberculosis drugs one after the other according to the WHO guidelines, looking for any recurrence of skin reactions. He tolerated isoniazid, rifampicin, and ethambutol till the full doses but on inclusion of pyrazinamide 500 mg, he developed the rash again. Pyrazinamide was withheld, and he was started on the second-line drug levofloxacain.

Questions

• Why the diagnosis of maculopapular drug rash/eruption was made in this case?
• Which are the other causative agents implicated in causing maculopapular drug eruption?
• If this patient requires antibiotic or analgesics what drug substitution should be done in this case?
• What is the differential diagnosis for a maculopapular drug eruption?
• What is the pathophysiology of a maculopapular drug eruption?
• How can a maculopapular drug eruption be prevented in future?
• Are there any reliable diagnostic tests for confirming the diagnosis and identifying causative agent of maculopapular drug eruption?
• How is maculopapular drug eruption treated?
Doshi and Manjunathswamy: Maculopapular drug eruption secondary to pyrazinamide

ATT drugs such as hospital patients. Morbilliform drug eruptions (MDEs) have been reported to occur in 3.6/1000 among causing maculopapular drug eruption? Which are the other causative agents implicated in postinflammatory fine desquamation can be noticed. As hemostatic pressure that is typically maximal on the legs. There may be noted occasionally on the legs secondary to seen, but mucosa is typically spared. Petechiae and macular the lesion resolves, it begins to look dusky and violaceous and hemostatic pressure that is typically maximal on the legs. As purpura may be noted occasionally on the legs secondary to seen, but mucosa is typically spared. Petechiae and macular the back in hospitalized patients. Facial involvement can be confluence and appear severe in dependent areas such as the arms, and thighs. There is the presence of significant temporal correlation between the intake of drugs and occurrence of rash beginning on the 5th day of intake. In addition, previous reports of similar adverse cutaneous reactions due to suspected drug in the literature helped in making causality assessment. Furthermore, reappearance of the rash on rechallenge with pyrazinamide confirmed the diagnosis in this case with a score of 9 (definite) according to Naranjo’s algorithm and probable/likely association as per the WHO-The Uppsala Monitoring Centre casualty category.

Literature mentions that onset of maculopapular drug eruption (morbilliform/exanthematous) typically occurs within 7–10 days after the initiation of the culprit drug. Occasionally, a 14-day window has been noted. On rechallenge with a drug that the patient has been sensitized to in the past, the eruption may occur within 24 h.[1]

The eruption usually begins on the trunk and upper extremities and progresses caudally. It is usually symmetric. It may get confluence and appear severe in dependent areas such as the back in hospitalized patients. Facial involvement can be seen, but mucosa is typically spared. Petechiae and macular purpura may be noted occasionally on the legs secondary to hemostatic pressure that is typically maximal on the legs. As the lesion resolves, it begins to look dusky and violaceous and postinflammatory fine desquamation can be noticed.

Which are the other causative agents implicated in causing maculopapular drug eruption?

Drug eruptions have been reported to occur in 3.6/1000 among hospitalized patients. Morbilliform drug eruptions (MDEs) were noted to be the most common drug eruption in these patients in a systematic review.[2,3] The rates varied between 73% and 91% of all drug eruptions. There is a higher risk of all drug eruptions in the HIV-positive population and in women.[2]

A multitude of drugs has been implicated in maculopapular drug rash. Antibiotics (most commonly beta-lactams, sulfonamides, cephalosporins, quinolones, and tetracyclines), anticonvulsants (phenytoin, carbamazepine, and lamotrigine), nonsteroidal anti-inflammatory drugs (NSAIDs), and allopurinol are common culprits.[3] ATT drugs such as ethambutol, pyrazinamide, antiretroviral agents, such as the protease inhibitors, emtricitabine and tenofovir, and telaprevir have also been reported.[4]

If this patient requires antibiotic or analgesics what drug substitution should be done in this case?

The offending drug should be avoided as far as possible. The antibiotic class or molecule of NSAIDs should be changed, and the patient should be alerted to keep a close watch on the occurrence of new eruption and stop the offending drug and immediately report to the physician. In case of antiretroviral therapy, nevirapine is the most common offending drug; this can be replaced with efavirenz or tenofovir.

A graded challenge by cautiously administering the drug to assess whether it is safe to give the drug can be done. This is used in patients who are unlikely to be currently allergic to the drug.[5]

Induction of drug tolerance can be[5] tried to modify a patient’s response to allow treatment to be given safely for patients who are known to be or highly likely to be allergic to the drug but have a strong clinical indication. For example, it may be useful to give aspirin to patients with aspirin-exacerbated reactive airways disease needing recurrent oral steroids, recurrent nasal polyps needing resection.[5]

However, this approach is not appropriate for patients who have experienced severe non-IgE-mediated reactions (Stevens–Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], etc.). Graded challenges usually start with about 1/100 of the normal dose; dose step up may be at intervals of a few days where non-IgE-mediated mechanisms would be more likely (e.g., an exanthematous reaction).[5]

Induction of drug tolerance involves progressive depletion of mediators (e.g., penicillin) or internalization of receptors (aspirin). Very small doses (about 1/10,000 of the usual dose) are to be given with a progressive escalation of dose over 6–12 h. Tolerance is generally maintained for as long as the drug is continued but will be lost if the patient ceases to take the drug.[5]

What is differential diagnosis of maculopapular drug eruption?

The following conditions should be considered in the differential diagnosis:
**Viral exanthems**

The history of upper respiratory tract symptoms and the presence of a lymphocytosis or lymphopenia on the white blood cell differential count (as opposed to eosinophilia) points toward a viral etiology.

**Toxin-mediated erythemas**

Toxin-mediated erythemas such as toxic shock syndrome and streptococcal shock-like syndrome may present with an eruption resembling MDE. These patients are typically sick with a high fever and hypotension.

**Acute graft versus host disease**

This diagnosis is made in the setting of a recent bone marrow or stem cell transplant and in the absence of a drug culprit. However, these patients are on multiple drugs, which complicate the clinical picture. The presence of symptoms and signs that suggest graft versus host disease (GVHD), such as diarrhea, and liver function abnormalities should be looked for. Skin biopsy may be helpful in that acute GVHD may manifest satellite cell necrosis.

**Stevens–Johnson syndrome/toxic epidermal necrolysis**

The initial lesions of SJS and TEN are purpuric or necrotic macules and targetoid lesions. These patients are look systemically ill with a fever. Skin pain/tenderness is a distinguishing feature, as opposed to itch that accompanies MDE.

**Scarlet fever**

A sandpaper-like eruption accompanies a sore throat and fever. Scarlatiniform eruptions such as Kawasaki syndrome should also be considered. In these patients, a prolonged fever accompanies the rash, cervical lymphadenopathy, oral mucous membrane involvement, and/or conjunctival injection along with palmoplantar desquamation.

**What is the pathophysiology of a maculopapular drug eruption?**

Maculopapular drug eruption is a T-cell-mediated delayed hypersensitivity (Type IV) type reaction. Type IV hypersensitivity has been subdivided into four groups, depending on whether monocytes (Type IVa), eosinophils (Type IVb), or neutrophils (Type IVd) are predominantly activated or whether there is T-cell-mediated apoptosis (Type IVc).

MDE has been classified both as Type IVb and Type IVc. In Type IVc hypersensitivity, Langerhans cells present drug happens to cytotoxic CD8+ cells, which then initiate apoptosis of keratinocytes through perforin/granzyme B and Fas/Fas ligand pathways. Eosinophil-rich MDE has been classed as Type IVb reactions. Here, Th 2 cells secrete interleukins 4, 13, and 5, which call eosinophils into the infiltrate, among other functions.[6]

**How can a maculopapular drug eruption be prevented in future?**

Once confirmed that patient has had MDE due to a particular drug, the patient should be counseled and educated about it and explained that such episode may recur in the future with intake of offending drugs. A drug allergy card should be given to patient mentioning offending drug. Patients should be instructed to always carry the card and show it to the consulting physician.

**Are there any reliable diagnostic tests for confirming the diagnosis and identifying causative agent of maculopapular drug eruption?**

The diagnosis is made based on the typical clinical appearance in concert with an appropriate drug history, temporal association and the absence of systemic involvement.

Complete blood count will show the presence of eosinophilia or mid-derangement of liver function tests in the absence of toxic features clinically. In typical cases, a biopsy is not required. However, histopathologic specimens that are performed in cases where a differential diagnosis exists will show epidermal changes, including small areas of spongiosis, which may or may not arise above areas of vacuolar change of the basal layer. A few apoptotic keratinocytes and focal parakeratosis may be found.[7]

In the dermis, there is a lymphocytic infiltrate with eosinophils. There may be vascular dilatation and mild edema in the upper dermis. In a recent series, eosinophils were seen in 50% of cases and an interface dermatitis in 53%.[7]

Skin intradermal/prick tests can be undertaken by allergologist/immunologist to check for immediate reactions to penicillin and a few other drugs. Patch tests are sometimes performed using drugs thought to have caused exanthems but can be difficult to interpret.[5]

Graded rechallenging of the suspected offending drug is the only known test to possibly discern the causative agent once the rash resolves completely.

**How is maculopapular drug eruption treated?**

The offending agent should be discontinued if possible. In cases where it is not possible to do this, such as an antibiotic that is crucial to a drug regimen, symptomatic and supportive treatment while continuing the drug therapy is a feasible option.

Topical calamine-based soothing lotion can be given to allay the itch. Mid- or high-potency topical steroids (such as triamcinolone acetonide 0.1%, fluocinonide 0.05%, betamethasone dipropionate 0.05%, or clobetasol 0.05%) may help to relieve pruritus. Creams or lotions are useful for large surface areas. Lower potency topical steroids such as desonide 0.05% can be given for the face and folds. Antihistamines are useful when itch is severe.

Although the clinical course is often relatively mild, these exanthems may sometimes progress to erythroderma or represent the beginning of even more severe drug reactions such as SJS, TEN, or a drug rash with eosinophilia and systemic symptoms or erythroderma in some. Here, a short course of oral prednisolone at a dose of 0.5 mg/kg/day in tapering doses can be given till complete clearance, unless contraindicated by their underlying illness.
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References
1. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 2011;71:684-700.
2. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol 2003;149:1018-22.
3. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents – A 6 year series from Chandigarh, India. J Postgrad Med 2001;47:95-9.
4. Strazzula L, Pratt DS, Zardas J, Chung RT, Thiim M, Kroshinsky D. Widespread morbilliform eruption associated with telaprevir: Use of dermatologic consultation to increase tolerability. JAMA Dermatol 2014;150:756-9.
5. Frew A. General principles of investigating and managing drug allergy. Br J Clin Pharmacol 2011;71:642-6.
6. Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D. Drug hypersensitivity reactions: Pathomechanism and clinical symptoms. Med Clin North Am 2010;94:645-64, xv.
7. Gerson D, Sriganesan V, Alexis JB. Cutaneous drug eruptions: A 5-year experience. J Am Acad Dermatol 2008;59:995-9.