CLINICAL VIGNETTE

Treating Through a Delayed Maculopapular or Morbilliform Drug Eruption?

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A 19-year-old female with a history of IBS presented to the Allergy Immunology Clinic for evaluation of a rash. She had recurrent Streptococcal tonsillopharyngitis with recurrent sore throat associated with tonsillar swelling, difficulty swallowing, and fatigue. Following two ten-day courses of antibiotics (penicillin V, cefpodoxime) and two six-day methylprednisolone courses, her Primary Care Provider saw her for worsening sore throat and difficulty swallowing. The physical exam confirmed grade four enlarged tonsils bilaterally, and she was referred to the Emergency Department for risk of a compromised airway, peritonsillar cellulitis with abscess. In the ED, her enlarged tonsils were associated with absent uvula deviation, rash and petechiae. Laboratory data revealed an elevated white blood cell count, normal transaminases, and normal kidney function. Testing for Streptococcus DNA and Ebstein Bar Virus were negative. Computed Tomography (CT) Contrast imaging of the neck showed "*bilateral edematous tonsils compatible with tonsillitis. No tonsillar abscess identified."* She was prescribed a ten-day course of clindamycin, given a dexamethasone injection and advised to follow up with an otolaryngologist. She started the clindamycin and awoke on the third day with an itchy rash on the trunk. She called her Primary Care Provider, who advised drug discontinuation and a same-day allergy referral. The patient reported the rash was itchy but not painful and was spreading to the arms and legs. She denied difficulty breathing, and oral or genital lesions. She previously tolerated clindamycin without adverse drug reaction (ADR) and had no history of allergic rhinitis, asthma, or atopic dermatitis. She was a non-smoker and did not consume alcohol. The physical exam was significant for normal vital signs, bilateral tonsillar hypertrophy with erythema and absent oral lesions. The skin was notable for a diffuse, patchy blanching erythematous morbilliform rash of the trunk, bilateral upper arms, and legs down to the thighs with coalesced lesions on the abdomen and back. The rash spared the face, palms, soles, and mucosa. The patient had no axillary or intertriginous erythema or lymphadenopathy.

Cutaneous adverse drug reactions (CADR) are skin-related ADRs and represent 25-33% of all ADRs. They range from life-threatening forms like severe cutaneous adverse reactions (SCARs), such as Acute Generalised Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), to milder forms. Non-life-threatening CADRs include conditions like maculopapular/ morbilliform eruptions (MPE/MDE), urticaria, and photo-distributed drug eruptions. A third category comprises potentially severe forms such as MPE with systemic symptoms, Fixed drug eruption (FDE), and generalized bullous fixed drug eruption (GBFDE). The last category includes symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), whose severity is uncertain. Morbilliform rash, also known as "maculopapular" drug eruption (MPE), morbilliform drug eruption (MDE) and "exanthematous" drug eruption, represents 50-90% of all CADRs.[1] Morbilliform rash resembles the morphology and distribution of viral exanthems such as measles. It is characteristically diffuse, symmetric erythematous macules or papules coalescing into larger plaques and patches. Targetoid, annular and urticarial or polymorphous morphology may also occur. The rash typically starts on the extremities and spreads to the trunk but also frequently starts on the trunk and spreads to the extremities, sparing the axilla, groin, hands, feet, mucous membranes, hair, and nails. In severe cases, palms, soles, and face may be affected. Lesions generally blanch with pressure and rarely purpura, pustules and bullae may develop in the dependent areas of the lower extremities. MDE differs from SCARs (which often involve organs and mucosa) and may be associated with a mild low-grade fever of <100.4° F and various levels of pruritus.

MDE usually appears one to two weeks into drug therapy or several days after completion. In previously sensitized patients, onset can range from six hours to three days post-drug exposure. Most MDEs are mild to moderate in severity, and patients fully recover. Early on, MDE can mimic DRESS, complicating diagnosis. Trubiano et al. highlighted overlapping features between MPE and DRESS, suggesting a continuum between both diseases. "MPE with systemic symptoms, have been described, and minor forms of DRESS, also called overlapping MPE-DRESS (MR/DR), severe MPE, and mini-DRESS." There are limited data on risk of progressing to DRESS from severe MPE if the incriminated drugs are continued.[2,3] In comparison to MDE, DRESS has a more delayed onset occurring two to eight weeks post medication use and a more erythematous and extensive eruption, almost always associated with facial edema and erythema. Thus, the presence of "alarm signs" and MDE warrants hospitalization and assessment. Alarm signs include a high fever >38°C/100.4°F, facial edema with erythema, erythroderma (>90% body surface area involvement), skin tenderness or pain, blistering, pustules, palpable purpura, significant fatigue/malaise, mucosal involvement, end-organ damage (liver, kidney, blood, lungs, heart) or lymphadenopathy.[2,3] Patients with MDE should undergo

assessment for SCARs and have laboratory data collected at least once to assess for systemic involvement including eosinophilia, decreased kidney function or transaminitis. In patients with the appropriate risk factors, an infectious evaluation including rapid Strep, heterophile antibody test and CRP may be helpful to narrow the differential. Peripheral eosinophilia is supportive but not diagnostic of a drug eruption. Singh et al. compared peripheral eosinophil counts in patients with viral exanthem and MDE and found higher median absolute eosinophil count (AEC) and serum CRP in the MDE cohort. The median AEC in viral exanthem was 269 (range: 7.8-1295) and 500 in the MDE (range: 28-6177). Median CRP was 12.8 mg/L in the MDE exanthem group (range: 0.19-105.6 mg/L) and 5.25 mg/L in the viral exanthem group (range: 0.23-124.5 mg/L.[4] Interestingly, mild transaminitis is still compatible with a diagnosis of MDE; however, a greater than two-fold increase of AST, ALT or decreased renal function suggests SCARs. MDE risk factors include polypharmacy, reduced liver or renal function, co-incident or concurrent viral infection, immunodeficiencies and autoimmune disorders. Viral infections particularly confer increased risk of CADRs and systemic symptoms. For example, 100% of patients with acute EBV infections will develop MDE with co-administration of an aminopenicillin antibiotic. Antibiotics, antiepileptics and allopurinol pose the highest risk for MDE, but any drug can trigger MDE. Most common drugs have a CADR rate of>1%.[5]

If no alternative to a necessary drug is available, "treating through" MDE with close medical supervision is possible. Treating through refers to continuing a drug in the setting of a mild cutaneous hypersensitivity reaction such as MDE. Trautmann et al. used a retrospective case series to evaluate treating through in severe cellulitis with MPE based on efficacy and risk while closely monitoring patient data. The "decision to treat through was made when the suspected antibiotic (β-lactams, clindamycin, ciprofloxacin) were clinically effective and the benefits of continued treatment outweighed potential risks."[2] In 2021, Trubiano et al. stated that treating through in MDE "avoids unnecessary antibiotic discontinuation or use of inappropriate or inferior antibiotics" in the setting of mild delayed CADR. Clinicians must assess the severity of the CADR based on known phenotypes, the presence of systemic symptoms, "red flag" symptoms and signs to determine the appropriateness of treating through. Avoid treating through if "mucosal involvement, bullous lesions, atypical target lesions, extensive pustulosis, painful skin, facial edema, widespread, dark-red erythema, severe asthenia, systemic involvement (renal, hepatic or other), eosinophilia of concomitant onset and worsening, especially if greater than 1500/mm^3 The authors noted that "caution is required if coexisting eosinophilia and hepatitis are present because these were seen in cases of treat-through failures."[2,3] When considering treating through, weigh the benefits and risks of the continued therapy against worsening or progression of the exanthem. Co-administration of systemic corticosteroids and oral antihistamines can mitigate risks. At least one clinical or laboratory severity sign is a contraindication to treating through.

Management of MDE entails stopping the drug, prescribing antipruritic therapy, and assessing for SCARs. In general, MDE tends to resolve within one to three weeks. Second-generation antihistamines taken twice daily and high-potency topical corticosteroids used twice daily until resolution are advised for symptom relief. For severe or widespread rash, systemic corticosteroids can be used. As the rash improves, the skin can look dusky and violaceous, and the macules and plaques may take on a targetoid appearance followed by fine desquamation like a mild sunburn. Literature indicates "delayed hypersensitivity to clindamycin is seen in 1% with delayed maculopapular exanthems predominantly seen. Moreover, most adverse reactions to clindamycin are mild, and the drug can be continued safely."[6]

We advised the patient that her mild MDE to clindamycin is manageable by treating through due to the lack of SCAR alarm signs. Clindamycin was ideal for our patient, who failed two β-lactam antibiotics for recurrent Strep. We outlined the possible outcomes with continued clindamycin: rash resolution, persistence or, very rarely, progress to erythroderma and evolve into a SCAR. Most studies do not view exanthematous drug eruptions as SCAR precursors [2,3,6] We ordered labs and prescribed second-generation H1 and H2 blockers and oral corticosteroids. A one-week follow-up in allergy clinic was scheduled.

This case demonstrates that not all delayed MDEs are life-threatening and can be distinguished from early SCARs by distinct features. A thorough history, physical exam, and laboratory data can guide clinicians in choosing between the use of inappropriate or inferior antibiotics and treating through MDE with supportive medications and close observation.

REFERENCES

1. **Mockenhaupt M**. Drug Allergy and Cutaneous Adverse Reactions. *Handb Exp Pharmacol*. 2022;268:195-212. doi: 10.1007/164_2021_490. PMID: 34219202.
2. **Trautmann A, Benoit S, Goebeler M, Stoevesandt J**. "Treating Through" Decision and Follow-up in Antibiotic Therapy-Associated Exanthemas. *J Allergy Clin Immunol Pract*. 2017 Nov-Dec;5(6):1650-1656. doi: 10.1016/j.jaip.2017.03.032. Epub 2017 May 9. PMID: 28499779.
3. **Trubiano JA, Soria A, Torres MJ, Trautmann A**. Treating Through Drug-Associated Exanthems in Drug Allergy Management: Current Evidence and Clinical Aspects. *J Allergy Clin Immunol Pract*. 2021 Aug;9(8): 2984-2993. doi: 10.1016/j.jaip.2021.04.008. Epub 2021 Apr 17. PMID: 33878455.
4. **Singh S, Khandpur S, Arava S, Rath R, Ramam M, Singh M, Sharma VK, Kabra SK**. Assessment of histopathological features of maculopapular viral exanthem and drug-induced exanthem. *J Cutan Pathol*. 2017 Dec;44(12):1038-1048. doi: 10.1111/cup.13047. Epub 2017 Oct 13. PMID: 28914958.
5. **Ernst M, Giubellino A**. Histopathologic Features of Maculopapular Drug Eruption. *Dermatopathology (Basel)*.

2022 Mar 30;9(2):111-121. doi: 10.3390/dermatopathology9020014. PMID: 35466243; PMCID: PMC9036233.

6. **Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, Breslow RG, Brockow K, Buchheit KM, Cahill KN, Cernadas J, Chiriac AM, Crestani E, Demoly P, Dewachter P, Dilley M, Farmer JR, Foer D, Fried AJ, Garon SL, Giannetti MP, Hepner DL, Hong DI, Hsu JT, Kothari PH, Kyin T, Lax T, Lee MJ, Lee-Sarwar K, Liu A, Logsdon S, Louisias M, MacGinnitie A, Maciag M, Minnicozzi S, Norton AE, Otani IM, Park M, Patil S, Phillips EJ, Picard M, Platt CD, Rachid R, Rodriguez T, Romano A, Stone CA Jr, Torres MJ, Verdú M, Wang AL, Wickner P, Wolfson AR, Wong JT, Yee C, Zhou J, Castells M**. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. *J Allergy Clin Immunol Pract*. 2020 Oct;8(9S):S16-S116. doi: 10.1016/j.jaip.2020.08.006. Erratum in: *J Allergy Clin Immunol Pract*. 2021 Jan;9(1):603. Erratum in: *J Allergy Clin Immunol Pract*. 2021 Jan;9(1):605. PMID: 33039007.