CLINICAL VIGNETTE

Nitrate Hypersensitivity

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A 77-year-old male was admitted to the hospital for weakness. He has multiple chronic conditions including renal cancer status post left nephrectomy and prior immunotherapy, end stage renal disease on hemodialysis, prostate cancer, coronary artery disease with a history of cardiac stent, diabetes mellitus type 2, and hypertension. He was found to have gastrointestinal bleeding from hemorrhoids and anal fissures, and development of angina thought related to his anemia. He was treated with isosorbide dinitrate, and nitroglycerin ointment for his anal fissures. Four days after discharge he was readmitted with chest pain and a non-ST-elevation myocardial infarction. Coronary angiogram revealed multivessel disease that was suboptimal for percutaneous intervention due to risk of bleeding and dual antiplatelet therapy intolerance. He was transferred to a tertiary referral hospital for the consideration of coronary artery bypass graft surgery.

Upon transfer the patient reported onset of painful ulcers in the mouth and around the penis shortly after his initial discharge two weeks prior. His last immunotherapy for renal cancer was 3 months prior and he recalled similar ulcerations associated with his immunotherapy in the past. He also developed a pruritic rash on his back and arms shortly after the ulcers appeared. On physical exam, he had low grade fevers and markedly erythematous papules coalescing into thin plaques on the back, chest and posterior upper arms. Labs included a positive herpes simplex virus 2 (HSV2) swab from the penile lesions and he was started on acyclovir. He was also started on topical triamcinolone 0.1% for the body rash. However, his rash worsened moving across the entire trunk, becoming more confluent and Dermatology and Allergy & Immunology services were consulted. Due to concern for possible disseminated herpes simplex virus versus a drug reaction, repeat swabs for HSV and a punch biopsy were taken from the abdomen. Blood count showed eosinophilia. Repeat HSV swabs were negative from the trunk and the biopsy showed spongiotic dermatitis with subcorneal pustules and superficial perivascular and interstitial inflammation with eosinophils, neutrophils and lymphocytes. There were no viral cytopathic changes noted on the biopsy. The differential diagnosis based on the biopsy included drug eruption, contact dermatitis, and eczematous dermatitis. Based on review of outside records, given the temporal relation between when isosorbide dinitrate was started and onset of the rash, drug hypersensitivity was strongly suspected and all forms of nitrate therapy were stopped. The patient was started on antihistamines and oral prednisone. His rash resolved over a period of several days and the patient underwent successful coronary artery bypass surgery.

Discussion

According to the American Heart Association, short-acting nitroglycerin is indicated for patients with angina in stable ischemic heart disease and can be delivered via intravenous or transdermal route.[1] Long-acting nitrates are used for treatment of angina when additional therapy is necessary after beta blockers or nondihydropyridine calcium channel blockers.[1] Though systemic hypersensitivity to nitroglycerin and nitrates is rare, allergic reactions to both short-acting nitroglycerin and long-acting nitrates have been reported.[2-4] More commonly, topical and transdermal nitroglycerin drugs cause allergic contact dermatitis, a form of delayed hypersensitivity.[4] Though some patients may have contact dermatitis to topical nitroglycerin, many are still able to tolerate oral or sublingual nitroglycerin, as well as IV nitrates.[4] This is likely due to how the immunogenicity of a drug is affected by route of administration. Primary nitrate sensitization may occur via use of oral or IV drugs first with subsequent local skin reactions based on the observation that allergic contact dermatitis may follow years of oral nitrate use.[4] However, the converse may also be true in terms of initial sensitization with topical products, and potential development of or immediate or delayed hypersensitivity via oral or IV route thereafter.[2,3]

In regards to diagnosis of cutaneous drug reactions, particularly generalized exanthems similar to that of our patient, history is one of the most important diagnostic tools along with clinical exam. Skin biopsy, though not necessary, may be helpful in determining the type of drug reaction and ruling out other skin diseases.[5] Most generalized drug eruptions consist of classic pruritic maculopapular rashes that will coalesce into plaques spreading outward to the extremities.[5] These reactions are often considered delayed-type hypersensitivity reactions that evolve after several days of prior exposure to the drug.[5] Skin testing, both prick and intradermal, as well as patch testing to nitroglycerin products has been reported, though it is unclear if skin testing is a useful diagnostic tool as nitroglycerin may act as a hapten (lacking antigenicity alone).[2-4] Other components of nitroglycerin patches, such as glycerin and lanolin, are known to cause both irritant and allergic contact dermatitis as well, making determination of the causative agent within the patch difficult to discern unless patch testing is completed with components.[4]

There is only one reported case of successful nitrate desensitization. This patient developed repeated generalized pruritic maculopapular rash to multiple forms of nitrates including sub-

lingual nitroglycerin, transdermal nitroglycerin patch, and oral isosorbide mononitrate.[3] Given this patient's persistent angina after multiple coronary stents, both skin prick and intradermal testing were performed, and positive at the lowest dilution on intradermal testing. This positive intra-dermal test was presumed to be due to possible irritant effect, or local vasodilatory effect of nitroglycerin as the patient's history was more consistent with a delayed hypersensitivity as opposed to an immediate IgE-mediated reaction (e.g. urticaria, angioedema, bronchospasm, etc.). Given high suspicion for delayed hypersensitivity to nitrates, an oral nitrate desensitization protocol was successfully completed using both isosorbide dinitrate and isosorbide mononitrate over a period of 48 hours.[3]

There are 3 distinct types of cutaneous drug reactions known as Severe Cutaneous Adverse Reactions (SCARs) which include Acute Generalized Exanthematous Pustulosis (AGEP) with non-follicular sterile pustules, Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) with large scale epidermal apoptosis and mucosal involvement, and Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) with multi-organ involvement and eosinophilia.[5] Both patch testing and intradermal skin testing is controversial particularly in SCARs due to risk of inducing a severe reaction.[5] However, intradermal and patch tests have been used diagnostically in both severe and non-severe delayed-type drug reactions, and are suggested in algorithmic approaches to confirmatory diagnosis in delayed drug exanthems prior to drug provocation challenges.[6] Drug provocation challenges and desensitization are contraindicated in SCARs.[6]

Revisiting our patient, his history revealed no new drugs other than the oral and topical nitrates started prior to the onset of his rash. Though more distant records were not available, given his history of known coronary artery disease and previous cardiac stent, it is likely he had prior exposure to either topical, oral, and/or IV nitrates in the past that led to initial sensitization. Though there was initial concern for disseminated HSV2, his lack of clinical response to acyclovir and his skin biopsy were useful in ruling out disseminated viral infection and indicating drug eruption. Cardiology requested restarting oral isosorbide mononitrate with the assistance of Allergy & Immunology after the isosorbide dinitrate was stopped. Due to the severity of his rash and concern for cross reactivity, this was not recommended. The option of desensitization was considered based on the single case report of successful desensitization for delayed hypersensitivity[3]. However, due to severe cutaneous adverse reaction features of oral ulcerations, this was not pursued and all nitrates were avoided. It was noted that his oral ulcerations may have been due to HSV2 infection, similar to his genital lesions; however, this could not be definitively determined and thus, it was prudent to avoid desensitization, as the plan was to undergo coronary artery bypass surgery regardless.

This case demonstrates the need for a thorough historical investigation and multidisciplinary cooperation in the diagnosis and management of suspected delayed hypersensitivity reactions. It also highlights the use of current medical literature in considering an appropriate investigative technique such as skin patch testing, and treatments including drug desensitization for delayed drug hypersensitivity. Nitrates are commonly used with different administration modalities that can lead to sensitization and subsequent development of allergy. Though relatively rare, physicians need to be aware of the potential for both immediate and delayed hypersensitivity reactions to nitrates.

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