BRIEF ARTICLES

Iohexol-Induced Acute Generalized Exanthematous Pustulosis (AGEP): Case Report

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a rare adverse drug reaction characterized by numerous non-follicular sterile pustules overlying edematous, erythematous plaques. The majority of AGEP cases are associated with antimicrobial medications, although other agents and etiologies have also been implicated. Here, we report a patient with recurrent angioimmunoblastic T-cell lymphoma (AITL) who presented with a pruritic and widespread pustular eruption one week following computed tomography (CT) with iohexol contrast administration. Notably, she had a documented prior mild reaction to contrast medium and was appropriately pre-medicated with diphenhydramine and prednisone before imaging. Biopsy revealed intra-epidermal pustules, epidermal spongiosis, and dermal infiltrate of lymphocytes, neutrophils, and some eosinophils – histological findings consistent with AGEP. Systemic and topical corticosteroids plus topical mupirocin resulted in complete resolution of symptoms. While cutaneous reactions to iodinated contrast are common and often self-limited, severe manifestations such as AGEP must be considered particularly in patients with a history of prior contrast allergy.

CASE REPORT

A 75-year-old woman with a longstanding history of angioimmunoblastic T-cell lymphoma (AITL) presented for dermatologic evaluation after developing a widespread pruritic rash of two weeks duration. She reported the itching and rash were initially localized to her arms but spread to the thighs, legs, chest, and back over several days. She was now complaining of a burning sensation in her inner arms, worsening redness, and swelling of the hands. She was otherwise feeling well, and review of systems was entirely unremarkable. Notably, she denied fever, chills, and recent infections.

AITL was originally diagnosed in 2008, with subsequent recurrence in 2009, 2016, and most recently 2017. At time of presentation, she had received four brentuximab cycles with good tolerance over the course of two months. She underwent computed tomography (CT) imaging with iohexol

contrast agent to assess tumor response one week prior to the cutaneous eruption. Importantly, she had a reported allergy to contrast dye, documented as a 'mild rash'. She was given 50 mg diphenhydramine at 1 hour before and 50 mg prednisone at 1, 7, and 13 hours before the CT scan, as instructed by guidelines for pre-medication in patients with contrast allergy.[1] She had previously taken prednisone without incident. Her only other medication was rivaroxaban, which she had been taking for over a year. No recent changes were made to her medication regimen. Dermatologic history was significant for excised stage pT1a melanoma, squamous cell carcinoma *in situ*, actinic keratosis, and lentigo. She had no personal history of eczema or psoriasis.

Exam was notable for scaly salmon-red papules coalescing into eczematous plaques studded with numerous pustules on the upper chest, upper back, and bilateral upper extremities (Figure 1). On the lower back beneath the waistband line, bilateral lateral thighs, and posterior knees, there were deep-red papules coalescing to plaques studded with numerous pustules. Bilateral upper arms and dorsal hands were edematous. Open fissures on flexural surface of arms appeared impetiginized. Palms and soles were uninvolved.

Punch biopsies were performed on the lateral thigh and upper arm. Sections demonstrated intra-epidermal pustules associated with mild epidermal spongiosis. Papillary dermis showed marked edema with separation of the epidermis from the dermis with a mixed inflammatory infiltrate of lymphocytes, neutrophils, and some eosinophils (Figure 2). Findings were consistent with a pustular drug eruption / hypersensitivity reaction, also known as acute generalized exanthematous pustulosis (AGEP).[2] Although less likely, pustular psoriasis was included in the histologic differential diagnosis. Of note, bacterial organisms were identified within the pustules focally, and wound culture grew 1+ methicillin-susceptible *Staphylococcus aureus*, consistent with our clinical suspicion of impetiginization. Indeed, a potential complication of AGEP includes impetiginization, particularly in older or immunocompromised individuals.[3] Complete blood count revealed leukocytosis with neutrophilia, consistent with a neutrophil-mediated inflammatory process of AGEP.[4] Complete metabolic panel was within normal limits, and there were no signs of organ involvement.

The patient was recommended to continue 60 mg prednisone taper and apply triamcinolone 0.1% and mupirocin 2% ointment twice daily. On follow up one week later, she exhibited significant improvement in erythema involving bilateral upper extremities, upper chest, and upper back compared to prior exam. Bilateral arms and hands were significantly less edematous, and linear superficial lesions were in the process of healing. There were scattered pink papules and plaques with minimal scaling on the thighs, but no pustules were noted anywhere on the skin. Her rash further improved and fully resolved by three months of topical steroid use, which is longer than standard AGEP therapy, indicating severe manifestation.[5] She continued to tolerate brentuximab infusions with excellent AITL response and no relapse of pustular rash. Future avoidance of contrast dye was strongly recommended, as re-exposure could again precipitate AGEP.[2]

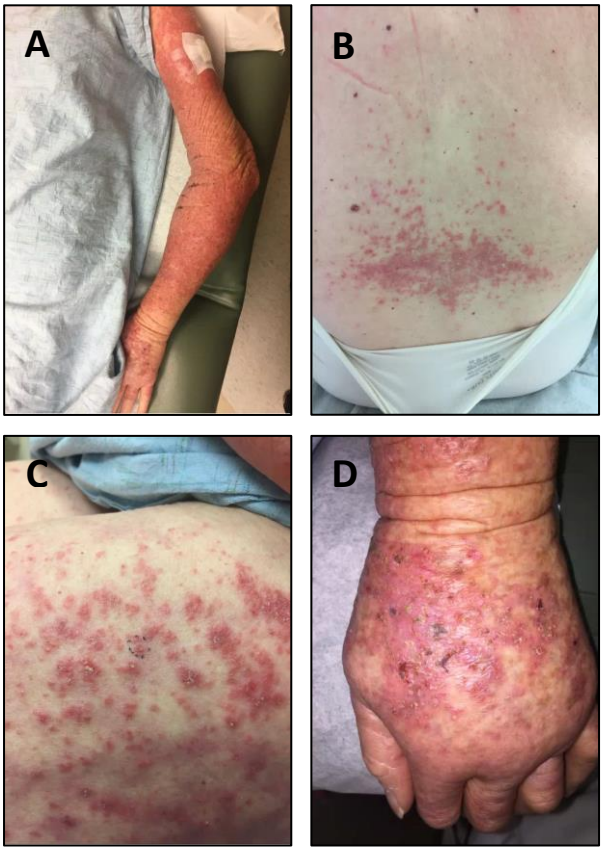

Figure 1. Extensive papules coalescing to eczematous plaques studded with numerous pustules involving the upper chest, upper extremities (A), upper back, lower back (B), and lateral thighs (C). Dorsal hands were edematous and appeared impetiginized (D).

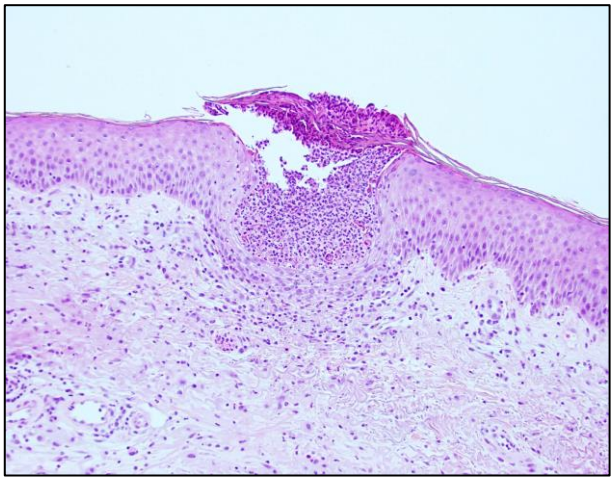

Figure 2. Histopathology reveals an intra-epidermal pustule associated with mild epidermal spongiosis and lymphocytic infiltrate with neutrophils and some eosinophils within the papillary dermis. Findings are consistent with AGEP. Magnification 100X.

DISCUSSION

AGEP is a rare adverse pustular eruption with 1 to 5 cases per 1 million, usually associated with antibiotics – particularly beta-lactams and macrolides.[6] Additional medications like antifungals, anticonvulsants, and antihypertensives have also been implicated.[7] In this report, we are the first to present a case of iohexol-induced AGEP despite prophylactic prednisone in a patient with previously documented mild contrast allergy. Differential diagnosis included acute generalized pustular psoriasis (Von Zumbusch) due to the overlapping clinical presentation with AGEP. Interestingly, pustular psoriasis may be precipitated by abrupt withdrawal of systemic corticosteroids or worsened by systemic corticosteroid therapy – which was not observed in our patient.[8] Moreover, most cases occur in the setting of diagnosed psoriasis, and generalized malaise, fever, and arthralgia are common. Histologic features distinguishing AGEP from pustular psoriasis include absence of tortuous, dilated blood vessels in the papillary dermis and absence of psoriasiform changes.[2] While AGEP is primarily characterized by non-follicular sterile pustules, bacterial super-infection may develop as seen in our patient and must be appropriately treated to prevent further morbidity.[3]

Iodinated contrast agents are utilized in roughly 50 million imaging procedures every year and are often necessary for accurate diagnosis. Patients with mild contrast dye allergy who require contrast for diagnostic purposes are pre-medicated with prednisone to reduce risk of acute (i.e. urticarial) adverse cutaneous reactions.[1] However, data on the efficacy of corticosteroids in preventing delayed adverse reactions

(DARs) are inadequate.[9] Indeed, prophylactic prednisone was ineffective at averting AGEP in our patient. This may be attributed to the unique pathogenesis of AGEP via a T cell-mediated type IV hypersensitivity reaction that is distinct from other DARs.[9] In conclusion, this interesting case augments the limited literature on iohexol-induced cutaneous reactions and encourages clinicians to consider AGEP as part of their differential diagnosis in DARs to contrast media.[10-12]

Conflict of Interest Disclosures: None

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