

BRIEF ARTICLES

Positive Nikolsky sign and pinpoint “lakes of pus”

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ABSTRACT

A 54-year-old man with a past medical history of paraplegia, osteomyelitis, sacral decubitus ulcer, suprapubic catheter, and several reported drug eruptions was seen for evaluation of skin sloughing without any tenderness to palpation. He reported being on chronic oral antibiotics including amoxicillin/clavulanic acid and ciprofloxacin over the past two years for osteomyelitis. Two days prior to evaluation, he had been hospitalized for osteomyelitis of the left iliac bone and was treated with intravenous vancomycin and meropenem. Initial evaluation revealed widespread Nikolsky sign with extensive involvement of the back, abdomen, and extremities without any tenderness. Involving 30-40% body surface area were scattered deep red macules and patches. The histopathologic findings were consistent with the diagnosis of acute generalized exanthematous pustulosis (AGEP). Clinically, AGEP appears as diffuse erythema with several small, non-follicular pustules and possible peripheral neutrophilia or eosinophilia. A positive Nikolsky sign can be seen with AGEP, but it is not specific, and has been referred to as a ‘pseudo-Nikolsky sign.’ Systemic involvement, such as renal insufficiency, has been reported in AGEP. There are few reports in the literature describing AGEP with TEN-like features. We present an interesting patient with AGEP and TEN-like features who improved after cessation of vancomycin and meropenem and a short course of systemic steroids.

CASE REPORT

A 54-year-old man with a past medical history of paraplegia, osteomyelitis, sacral decubitus ulcer, suprapubic catheter, and several reported drug eruptions was seen for evaluation of skin sloughing without any tenderness to palpation. He reports being on chronic oral antibiotics including amoxicillin/clavulanic acid and ciprofloxacin over the past two years for osteomyelitis. Two days prior to evaluation, he had been

hospitalized for osteomyelitis of the left iliac bone and was treated with intravenous vancomycin and meropenem. He notes that when he was started on vancomycin, he developed Red Man Syndrome and had a similar rash in the past to vancomycin which resolved with slower infusion. He also reported the development of a rash to other antibiotics including ampicillin, gentamicin, and sulbactam sodium. He denied having mucosal involvement, skin sloughing, or a

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diagnosis of Stevens-Johnson syndrome with any medications in the past.

Initial evaluation revealed widespread Nikolsky sign with extensive involvement of the back, abdomen, and extremities without any tenderness. Involving 30-40% body surface area were scattered deep red macules and patches [Figure 1]. Focal areas of the arms and abdomen revealed several pinpoint pustules coalescing into “lakes of pus” [Figure 2]. Examination of the mouth revealed a non-tender, beefy red tongue. The oral mucosa, nasal mucosa, ocular mucosa, and genital mucosa were uninvolved. No purpuric, dusky, atypical targetoid lesions or hemorrhagic crusts were appreciated. A punch biopsy was performed for frozen section [Figure 3_100x] and hematoxylin and eosin staining [Figure 4_100x].

He was normotensive and afebrile. Laboratory evaluation showed a significant leukocytosis of 69.00 k/mm³ (3.70-11.0 k/uL normal range) with a differential significant for 97.0% neutrophils and an absolute neutrophilic count of 66.93 k/uL (1.45-7.50 k/uL normal range). The differential further included 1.0% lymphocytes with an absolute lymphocyte count of 0.69 k/uL (1.00-4.00 k/uL normal range), monocytes 2.0% and absolute monocyte count of 1.38 k/uL (0.00-0.86 k/uL), and no detectable eosinophils or basophilic cells. Creatinine 1.24 mg/dL (0.70 - 1.40 mg/dL), alkaline phosphatase 92 U/L (40 - 150 U/L), AST 18 U/L (7 - 40 U/L), and ALT 8 U/L (5 - 50 U/L) were all within normal limits. Of note, the patient’s baseline creatinine was 0.78 mg/dL.

Frozen section [Figure 3_100x] reveals desquamating basket weave orthokeratosis with intraepidermal bullous formation of the superficial epidermis. The remainder of the epidermis is mildly spongiotic. Within the

dermis, there is mixed and acute chronic inflammatory infiltrate. A GMS and gram stain fail to highlight fungal hyphae and bacterial organisms. The histopathologic findings are consistent with the diagnosis of acute generalized exanthematous pustulosis.

Permanent section by hematoxylin and eosin stain [Figure 4_100x] demonstrates an epidermis with mild spongiosis and scattered neutrophils within the stratum corneum. Within the superficial dermis, there is diffuse papillary dermal edema with numerous neutrophils. The histologic differential diagnosis is consistent with acute generalized exanthematous pustulosis.

Infectious Disease was consulted by the primary team and recommended stopping all antibiotics. Due to the progression of skin lesions after drug cessation, the patient was treated with 1.4 mg/kg/day (80mg BID) of methylprednisolone with marked improvement of skin lesions. By day three of treatment, the patient had a negative Nikolsky sign and no new pustules were appreciated. His creatinine decreased to 0.92 with steroid treatment. He was tapered off prednisone within a week and continued to re-epithelialize.

FIGURES



Figure 1: 30-40% body surface area with deep red macules and patches and widespread Nikolsky sign



Figure 2: Focal areas of the arms and abdomen with several pinpoint pustules coalescing into "lakes of pus"

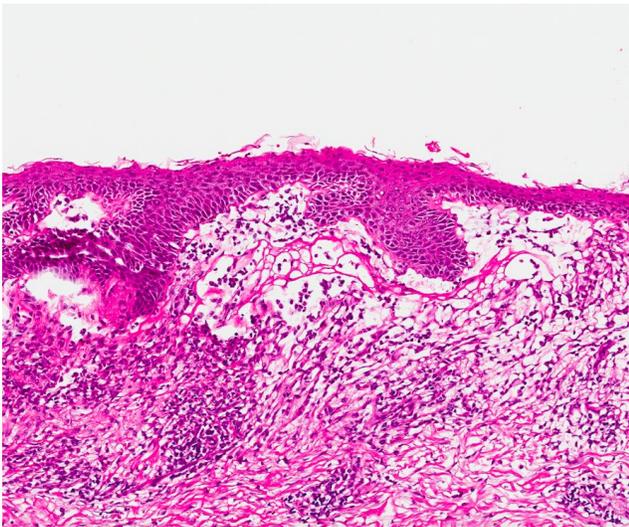


Figure 3: 100x frozen section reveals desquamating basket weave orthokeratosis with intraepidermal bullous formation of the superficial epidermis

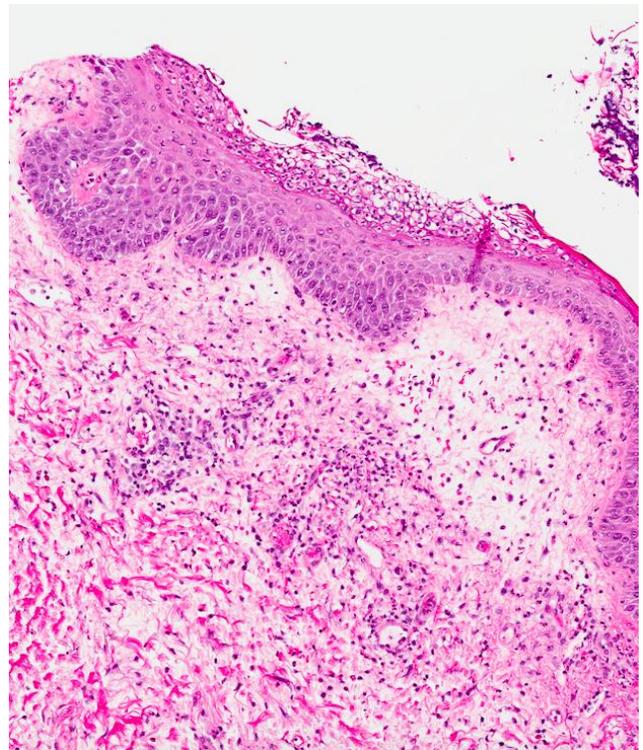


Figure 4: 100x hematoxylin and eosin stain demonstrates epidermis with mild spongiosis and scattered neutrophils within the stratum corneum

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DISCUSSION

Acute generalized exanthematous pustulosis (AGEP) is considered one of the severe forms of a cutaneous adverse drug reaction. Clinically, AGEP appears as diffuse erythema with several small, non-follicular pustules and possible peripheral neutrophilia or eosinophilia. It has been associated with up to a 2% mortality rate¹ compared to TEN which is associated with a 25-30% mortality rate.² Leukocytosis is typically seen at an elevated neutrophil count above $7.5 \times 10^9/L$.² Classically, skin lesions develop between 24-48 hours after exposure to the offending drug or infectious agent.⁴ Both meropenem and vancomycin have been described in the literature as inciting agents of AGEP.^{5,6} Systemic involvement, such as renal insufficiency, has been reported in AGEP.⁷ A positive Nikolsky sign can be seen with AGEP, but is not specific, and has been referred to as a 'pseudo-Nikolsky sign.'⁸

Our patient presented with a clinical picture that resembled an overlap between AGEP and toxic epidermal necrolysis (TEN). There are reports in the literature describing AGEP with TEN-like features. Van Hattem and Kardaun presented a case of AGEP with TEN-like features due to flucloxacillin with the patient developing similar superficial erosions of erythematous areas, studded with pustules.⁸ They further reviewed the literature describing ten additional cases describing TEN-like features clinically with AGEP diagnosed on histopathology. Bouvresse et al. reviewed 216 cases with histologically data confirming discharge diagnoses and described an overlap of AGEP and SJS in 21% of those patients assessed.⁸

Histopathology aids in distinguishing these two entities. TEN will present as an interface dermatitis with full-thickness necrosis of the epidermis and a mild perivascular lymphocytic infiltrate and dyskeratotic keratinocytes.¹⁰ In contrast, AGEP reveals spongiform features with subcorneal or intraepidermal pustules, neutrophils, and eosinophils. We present a patient with AGEP and TEN-like features who improved after cessation of vancomycin and meropenem and a short course of systemic steroids.

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