Acute generalized exanthematous pustulosis (AGEP) with systemic involvement in a 9-year-old boy given multiple antibiotics

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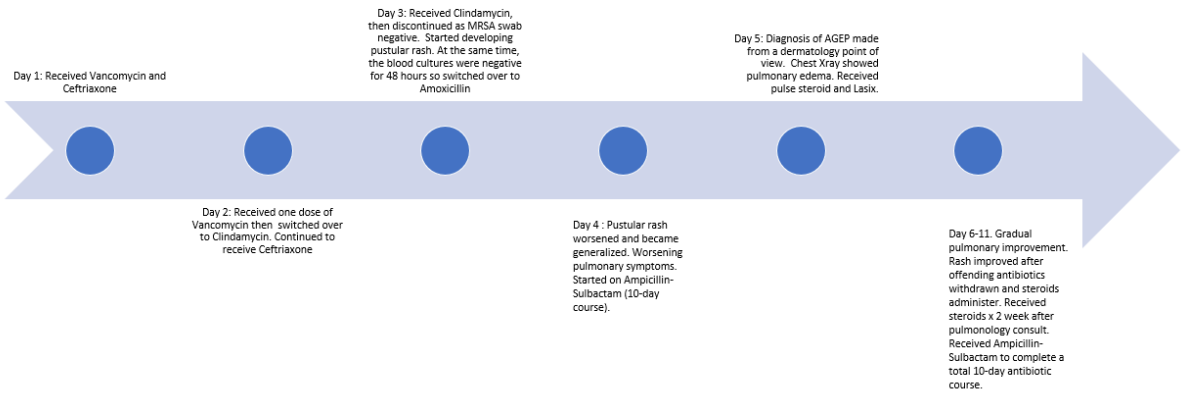
The case

A previously healthy 9-year-old boy presented to the emergency department with acute onset of sore throat, diffuse abdominal pain, poor oral intake, and vomiting. On arrival he was febrile to 40°C with heart rate of 164, blood pressure of 100/54mm Hg, respiratory rate of 34 saturating at 99%. He met the systemic inflammatory response syndrome criteria. Complete blood count (CBC) upon admission was significant for a left shift (total white blood cells [WBCs] 16.8, 88% Neutrophils [14.8K total], 7.3% Lymphocytes [0.51K total], and 0.1% Eosinophils [0.02K total]). A comprehensive metabolic panel revealed elevated blood urea nitrogen (BUN) and creatinine indicative of acute kidney injury in the setting of dehydration. Beta strep throat culture was positive for *Streptococcus pyogenes* (Group A). Chest x-ray (CXR), abdominal x-ray, and abdominal ultrasound were normal. Due to possible sepsis, he was started on ceftriaxone and vancomycin.

He continued to spike fevers over the next 24-36 hours, but the fever curve was improving. Antibiotic coverage was switched from vancomycin to clindamycin because the former is known to be more nephrotoxic. His BUN and creatinine stabilized over the next 2 days, and he started showing clinical improvement. He had remained afebrile for 24 hours, and antibiotics were further narrowed. Clindamycin was discontinued after a methicillin resistant *Staphylococcus aureus* swab returned negative and ceftriaxone was switched to amoxicillin after the blood culture was negative for 48 hours. However, right before he was given his amoxicillin dose, he developed a pustular, pruritic rash on his neck. Within a few hours it spread to his upper extremities, torso, abdomen lower extremities with the most severe lesions in the flexural creases (figures 1-5). His lips were swollen dry and chapped. He spiked fever again to 38.8°C and was tachycardic to 110s-130s, tachypneic to the 35-40s. T-max next day was 39.5. He was now hypoxic. A CXR showed pulmonary congestion, bilateral infiltrates, and edema. Repeat CBC was significant for marked eosinophilia (total WBCs 15.1, 70% Neutrophils [10.8K total], 16% Lymphocytes [2.43K total], and 6% Eosinophils [0.91K total]. He was started on triamcinolone cream twice daily for the rash. Due to pulmonary symptoms and worsening rash he was started on high dose methylprednisolone and lasix. Although the cause of the rash was unclear,

concern about the antibiotics resulted in permanent discontinuation of ceftriaxone, vancomycin, and clindamycin. Over the next 2 days he showed gradual improvement in the rash and pulmonary symptoms. Gram stain from pustules showed few eosinophils, and neutrophils and no bacteria. Epstein-Barr virus, HIV and cytomegalovirus (CMV) work up was unremarkable. Ampicillin-sulbactam was continued over the next few days to complete 10-day course for streptococcal pharyngitis. Dermatology consultation supported the diagnosis of Acute generalized exanthematous pustulosis (AGEP). The pulmonologist believed his systemic symptoms and pulmonary infiltrates and edema were most likely due to a drug-related hypersensitivity.

Timeline of symptoms and antibiotic administration



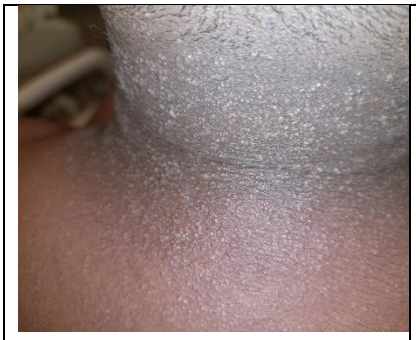
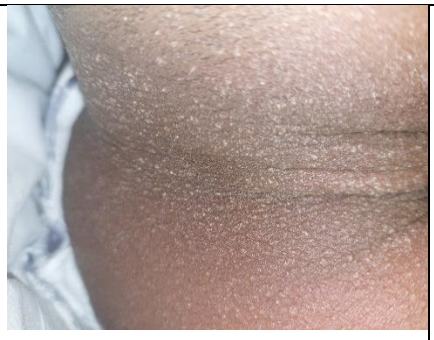
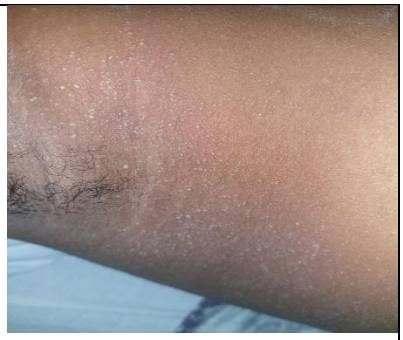
		

Figure 1: Pustules in the neck (anterior)	Figure 2: Pustules in the neck (posterior)	Figure 3: Pustules in the axilla

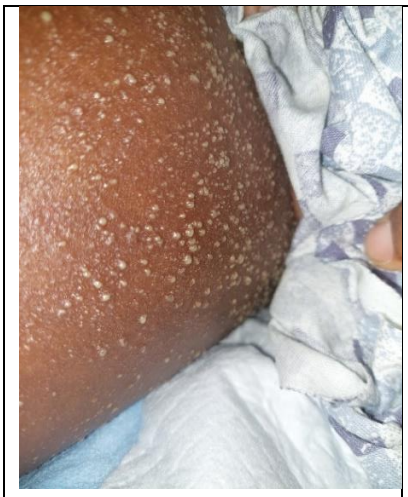
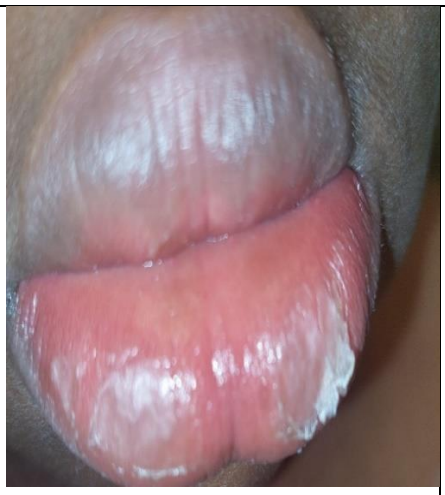
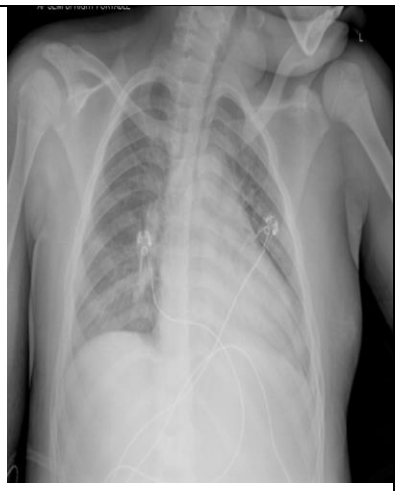
		

Figure 4: Pustules on the abdomen	Figure 5: Lip swelling	Figure 6: Chest X-Ray shows bilateral pulmonary infiltrates and pulmonary edema

Discussion

AGEP is rare, severe, drug reaction associated with a generalized cutaneous pustular eruption. Typically, within 48 hours of ingesting the causative agent acute onset of fever (>38°C), pustulosis, and leukocytosis (7.5×10^9 /L) is seen[1] as in our patient. The pattern is consistent with multiple nonfollicular sterile pustules occurring with diffuse, edematous erythema most prominent in the skin folds and on the face.[1-3] The list of AGEP-inducing agents is broad, but it is most commonly associated with drugs including antibiotics, antimalarials, and calcium channel blockers. Case reports have also rarely reported AGEP with commonly used medications such as ibuprofen. Occasionally it has been associated with viral infections such as parvovirus, mycoplasma, and CMV.[1] Systemic symptoms such as pulmonary, hepatic, and renal involvement occurs in about 20% of cases.[1,2] With a mortality rate of less than 5%,[1] AGEP secondary to ceftriaxone in the pediatric population has been reported.[4]

Pathophysiology

AGEP is a phenomenon mediated by the T-cells. Multiple studies have shown that after exposure to the inciting drug (antigen), antigen presenting cells activate T-cells, specifically CD4+ T cells, cytotoxic CD8+ T cells that subsequently activates CXCL8, a chemokine that causes neutrophilic aggregation.[1]

Diagnosis

Diagnosis is mostly clinical but a biopsy if done early may reveal spongiform intracorneal, sub corneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophilic and eosinophilic infiltrates. Other features are necrotic keratinocytes along with absence of tortuous blood vessels. A helpful tool is the scoring system developed by the EuroSCAR group which considers the morphology, distribution, onset of disease, fever, leukocytosis and histology features.[3]

Differentials:

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	AGEP can seldom be difficult to distinguish from SJS/TEN, especially when there is mucosal involvement, such as lip involvement in this case (picture 5). However, the onset of symptoms takes a longer period of exposure in SJS, typically 1-3 weeks as opposed to the acute onset seen in AGEP. Mortality is also typically higher in SJS/TEN.
Drug reaction with eosinophilia and systemic symptoms (DRESS)	DRESS syndrome also could be confused with AGEP but has a morbilliform rash with severe systemic symptoms and the course typically takes 2-6 weeks.
Pustular psoriasis	In individuals with a history of psoriasis, it may be difficult to distinguish between pustular psoriasis and AGEP. The duration of pustular eruption and fever usually last much longer in pustular psoriasis, and the skin lesions often become confluent and much larger. The association with causes mentioned above for AGEP is typically not seen in pustular psoriasis.

Bullous impetigo	Commonly occurs in the pediatric population and may have a vesicular and/ or pustular appearance. Gram stain typically shows gram positive cocci though.

Treatment and course

Recognition and discontinuation of the offending drug(s) is critical as well as supportive care. Resolution of the pustular eruption, and generalized desquamation is noted in most cases within 15 days. Emollients and topical steroids may be used for symptomatic relief. However, for severe systemic symptoms, such as in our patient with pulmonary involvement, systemic steroid use has been reported, but more evidence and trials are needed. .

Follow up

He followed up at the pulmonology clinic after a 2-week prednisone taper. Repeat CXR was within normal limits.

BIO

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