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CASE REPORT

A case of acute generalized exanthematous pustulosis associated with polyarteritis nodosa, responding to systemic steroids

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A patient with a known biopsy of polyarteritis nodosa diagnosis presented with cyclic fevers, acute kidney injury, and progression of rash from macular to pustular, worsening despite being on antibiotics, without evidence of infection on multiple cultures. The patient had a pathological diagnosis from a skin biopsy of acute generalized exanthematous pustulosis syndrome, with a total resolution of rash, fevers, and acute kidney injury on treatment with pulse steroids.

Keywords: *AGEP*; *PAN*; *Systemic Steroids*; *Skin Lesions*; *Pustules*

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Skin lesions of patients can be related to multiple etiological factors and can be confusing in patients with several active illnesses; however, a skin biopsy and finding the correct diagnosis can lead to the appropriate management.

Acute generalized exanthematous pustulosis (AGEP) is a rare condition with incidence of 1–5 million cases per year. AGEP is described as an acute eruption which is characterized by the development of numerous non-follicular sterile pustules on a background of edematous erythema (1, 2). The rash is usually associated with high fever ($>38^{\circ}C$) and high blood neutrophil counts ($>7{,}000$ cells/mm^3).

In our case, findings of extensive exanthematous pustulosis skin lesions and a biopsy confirming AGEP syndrome with assistance of dermatology guidance led to the systemic steroid treatment which drastically improved the patient's rash and the systemic manifestation that was representative by the acute kidney injury.

We also point out that skin lesions that are typically associated with certain antibiotics, anti-malarias, and some of calcium channels blockers still could be an atypical manifestation of an underlying autoimmune process such as vasculitis, polyarteritis nodosa (PAN) in a case such as this.

Case presentation

A 60-year-old man presented with a medical history significant for biopsy proven PAN (on prednisone and cyclophosphamide with prior failure on cyclophosphamide alone), paroxysmal atrial fibrillation, hypertension (not on calcium channels blocker), dyslipidemia, non-insulin dependent diabetes mellitus, with multiple prior admissions for PAN flares in the past, and with a history of an admission for septic shock 2 years prior to the current admission without any identifiable sources of infection.

The patient initially presented with a scrotal pain, a fever of 103°F, and fatigue. The patient was also found to be tachycardic to 130 beats per minute, hypotensive to 103/40 mm Hg.

Hospital course

The patient was initially started on broad-spectrum antibiotics consisting of vancomycin and Zosyn (piperacillin/tazobactam) in the emergency department followed by an admission under medicine service. During the hospital course the patient's kidney function worsened leading to a switch in antibiotics to meropenem. Despite switching antibiotics, the creatinine level continued to rise. The patient was on 40 mg of prednisone daily making a suspicion of acute interstitial nephritis less likely. Meanwhile, he continued to spike fevers without a specific source of an infection found in any of the blood, urine, and sputum cultures. Also, no focus was found on the CT chest, abdomen, and pelvis which led to stopping all antibiotics.

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After a time span of 1–2 weeks our patient started developing a previously present macular rash that progressed slowly to involve his axillary area, later including his chest, head, neck, and abdomen. Accompanied with these symptoms, the patient suffered an incendiary mental status than what was previously noted during the orientation exam. This was followed by a worsening of skin lesions with an element of bullae and vesicles. The dermatology team was involved, and a biopsy was obtained with a recommendation of initiating local steroid cream for the diagnosis of AGEP because of the given skin distribution and biopsy result, along with kidney injury, neutrophilia, and cyclic fevers. Nine days after the initial appearance of the rash, the rash became pustular, accompanied by high grade fever of 109°F leading to a transfer to the intensive care unit with a protocol of cooling. Given prior discussions with rheumatology, nephrology, and infectious disease, the patient was administered pulse steroids, given low suspicion of infection and his prior history of PAN flares and the general probability of autoimmune process.

After completion of the third day of pulse steroids, the patient's fever subsided and subsequent improvement of the initial rash was observed, along with a decreased progression of sloughing and complete resolution of acute kidney injury. A taper in steroids followed pulse steroids.

Investigations

Skin biopsy
Urine analysis
CT chest/abdomen/pelvis
CBC/BMP/coagulation

Differential diagnosis

1. Generalized acute pustular psoriasis (von Zumbusch type)
2. Acute generalized exanthematous pustulosis (AGEP)
3. Drug reaction with eosinophilia and systemic manifestation (DRESS)
4. Steven Johnson syndrome
5. Leukocytoclastic vasculitis
6. Subcorneal pustular dermatosis (Sneddon–Wilkinson disease)
7. Cutaneous candidiasis

Discussion

AGEP is a rare condition with incidence of 1–5 cases per million cases per year. AGEP is described as an acute eruption, characterized by the development of numerous non-follicular sterile pustules on a background of edematous erythema (1, 2). The rash is usually associated with a high fever ($>38°C$) and high blood neutrophil counts ($>7{,}000$ cells/mm^3) (Fig. 1).

The pathophysiology of AGEP is a T cell-mediated neutrophilic inflammation involving $CD4^+$ T cells, cytotoxic $CD8^+$ T cells, and inflammatory cytokines and chemokines, which produce large amounts of CXCL8, GM-CSF, and reduce neutrophil apoptosis (3–8). This is reflected on histological features by superficial, interstitial, and mid-dermal infiltrate rich in neutrophils. PAN's mechanism is still unknown, but it was described as an immune complex-mediated disease that leads to medium-sized arterial inflammation and yet spares arterioles, capillaries, and venules.

AGEP is a condition which usually manifests as a rapid development of small sized pustules on a background of edematous erythema with flexural accentuation (1, 2). In a series of 97 cases of AGEP, the median time between drug exposure and development of AGEP was 1 day for antibiotics and 11 days for all other drugs (9). The rash begins on the face, and extends to the trunk and limbs with a diffuse or patchy distribution.

During the acute phase, the patient has a fever above 38°C (100.4°F), leukocytosis with a neutrophil count $>7{,}000$ cells/mm^3, and usually mild eosinophilia. Organs are not usually affected by AGEP, but can be, particularly in older or compromised patients. A mild and reversible reduction in the creatinine clearance has been reported in some patients (1, 2, 10). In a retrospective study of 58 patients with AGEP done by Hotz and his group, 17% had evidence of at least one organ affected. Liver and/or kidney function tests were abnormal in seven patients, two developed acute respiratory distress, and one agranulocytosis (11).

Our case

Our PAN patient, who had a fever and leukocytosis, was started on vancomycin and Zosyn, and developed acute kidney injury, which can often be associated with the use of Zosyn. Giving this factor, the patient was switched to meropenem. Despite switching the Zosyn, the patient's creatinine level continued to rise. This was followed by a macular back rash and after 1–2 weeks progressed slowly to involve his axillary area and later his chest, head, neck, and abdomen, accompanied by a decline of his mental status, followed by a worsening of skin lesions and also an element of bullae and vesicles. Around 9 days after the first day of noticing the rash, the rash became pustular, and the patient developed a high grade fever of 109°F. This required initiation of pulse steroids. Three days following the pulse steroids, the patient's fever subsided with a drastic decline in the patient's rash and progression of sloughing, along with a complete resolution of acute kidney injury. The pulse steroids were gradually decreased in dosage.

The biopsy of the skin showed intra- and subcorneal (Fig. 2) spongiform, with superficial, interstitial, mid-dermal infiltrate rich in neutrophils, and dermal edema.

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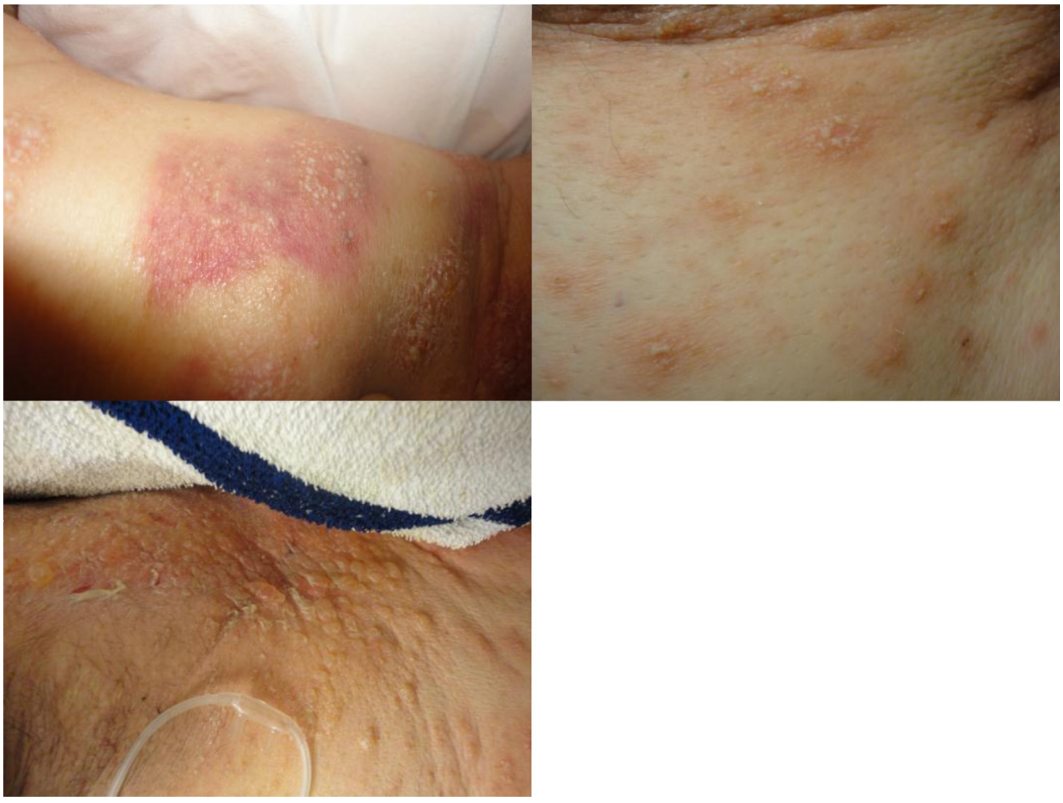

Fig. 1. Non-follicular sterile pustules on erythematous background.

The differential diagnosis in our patient included: AGEP syndrome, DRESS, GPP, a PAN typical rash, Steven Johnson syndrome, leukocytoclastic vasculitis, subcorneal pustular dermatosis (Sneddon–Wilkinson disease), and cutaneous candidiasis.

Both AGEP and GPP could be accompanied by a fever, neutropenia, and systemic manifestations (11). However, GPP is more commonly associated with cholestasis and hepatic involvement in around 90% of cases. Also, in retrospect our patient did not have any family history of psoriasis, or psoriasis. Skin manifestations of PAN may include: tender erythematous nodules, purpura, livedo reticularis, ulcers, and bullous or vesicular eruption (12–14). These are different from our patient's rash. Excluding this factor, the biopsy showed a better description of AGEP, giving the dermal edema, and multiple spongiosis. Other rashes that potentially have such a degree of skin reactions could be DRESS, Steven Johnson syndrome, and leukocytoclastic vasculitis which were unlikely given the biopsy result. Subcorneal pustular dermatosis (Sneddon–Wilkinson disease) was also in our deferential diagnosis list; however, on histology there was a subcorneal accumulation of neutrophils without spongiosis or keratinocyte damage and a perivascular infiltrate of neutrophils (15–19). Another differential diagnosis could be cutaneous candidiasis. However, given the negative blood cultures when the patient first was presented, and the clinical scenario, with significant improvement on pulse steroids, this diagnosis was unlikely.

Our final step of analysis is to look for a culprit. A vast majority of AGEP cases are secondary to antibiotics, and it usually start 1–2 days after starting the agents. However, there are some patients that do not have known etiology. Given that our patient started with fevers and acute kidney injury prior to instating any antibiotics and also having a rash which started more than a week after initiating Zosyn makes it less likely as an etiology. This also did not reoccur when the patient re-challenged with meropenem and vancomycin. Our final thought about our patient with PAN, being difficult to control with multiple admissions for PAN flares, and having poor responses to cyclophosphamide, is that his AGEP skin rash, could have been a manifestation of his autoimmune process that led to his prior PAN manifestations.

After mentioning a rational of diagnosis we reach the point of choosing the most appropriate management in this patient. Management from the prospect of clinical manifestation for the AGEP in this case, would be weaning off the steroids as AGEP is a self-resolving disease. However, with a severity of fevers, we believe pulse steroids are the best treatment at this point. Initiating other immunosuppressive would have been a premature decision and inaccurate given the nature of AGEP. However, because of the history of difficult to control PAN, and the lack

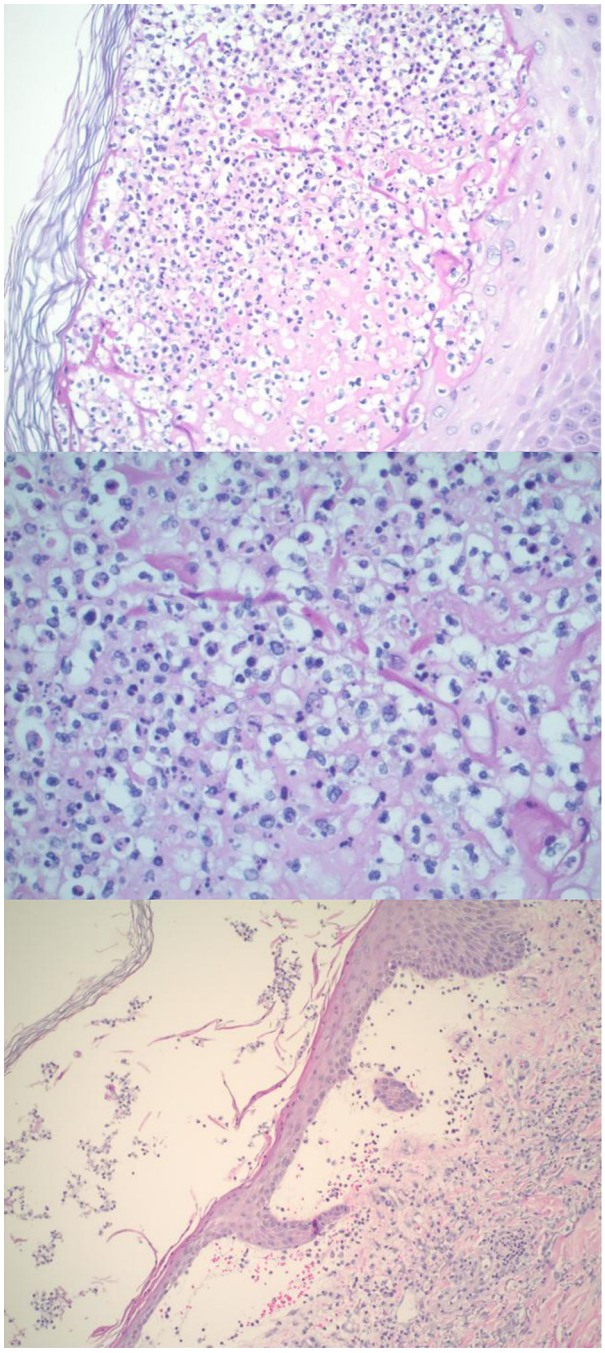

Fig. 2. Intra- and subcorneal spongiform, with superficial, interstitial, and mid-dermal infiltrate rich in neutrophils, dermal edema was also seen.

of explanation of AGEP syndrome, the patient would eventually benefit from immunosuppressive management guided toward his PAN. Yet, AGEP associates well with penicillin, which would make it prudent clinically to abstain from using penicillin antibiotics in such a patient.

Our case, nevertheless, is remarkable in several ways. First, the association between AGEP and the patient's history of PAN opens further questions about etiology of PAN and possibilities of involvement of T cell proliferation inducing neutrophilic proliferation in the pathogenesis.

Second, AGEP is a self-limiting disease with a favorable prognosis. Management includes withdrawal of the offending drug, supportive care, and symptomatic treatment of pruritus and skin inflammation. In our case, AGEP was extensive, and the etiology was unknown, with unresponsiveness after switching the antibiotics. This opens the door for the use of systemic steroids, which was followed by dramatic improvement in the patient's rash and his kidney function. Systemic corticosteroids have been used to treat AGEP, but evidence that they shorten the disease course is still unknown (20–22).

Finally, the severity of the case, AGEP usually resolves spontaneously. Our patient presented with systemic manifestations that followed with an extensive rash. Systemic manifestations involved a very high fever that required ICU admission, and the functioning of the kidneys.

Learning points

1. Clinician should be aware that pustular skin lesion could be autoimmune rather than infection.
2. Prior autoimmunity manifested as vasculitis can predispose to other process such as AGEP in this case.
3. AGEP progression can start with other generalized manifestation then progress with skin lesions.
4. Autoimmune process such as AGEP can lead to severe fevers.
5. Consideration of immunosuppression should be thought as primary treatment when clinical suspicion is high, especially with negative cultures.

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