Acute Generalized Exanthematous Pustulosis: An Enigmatic Drug-Induced Reaction

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Acute generalized exanthematous pustulosis (AGEP) is a diffuse pustular disorder that is primarily drug induced and characterized by acute, extensive, small, nonfollicular, sterile pustules that usually begin in intertriginous folds with widespread edema and erythema. This article reports a case in which thalidomide, dexamethasone, or meloxicam may have been the etiologic agent to induce AGEP and the skin condition may have worsened with administration of additional medications during hospital admission. A good thorough medical history, including a drug history, along with clinicopathologic correlation is extremely important in a patient presenting with acute diffuse pustular lesions.

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Acute generalized exanthematous pustulosis (AGEP) is a pustular reaction that is primarily drug induced in 90% of cases and characterized by acute, extensive, small, nonfollicular, sterile pustules that usually begin in intertriginous folds with widespread edema and erythema. It is a rapidly progressing, self-limiting disease with a good prognosis.[1-4] We discuss the clinical presentation, etiology, pathogenesis, and management of AGEP.

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How does AGEP present?

The clinical presentation, evaluation, and management of AGEP will be discussed based on a real-world case. A 70-year-old man presented to the emergency department with a chief concern of a fever (temperature, 38.4°C), an increasingly sore throat, and back pain. The patient recently had been diagnosed with end-stage IgG multiple myeloma and was being treated with thalidomide, dexamethasone, hydrocodone, ranitidine hydrochloride (HCl), omeprazole, promethazine HCl, meloxicam, lidocaine patch 5%, polyethylene glycol 3350 soluble powder laxative, and testosterone enanthate injections. He also received one infusion treatment of pamidronate disodium. On hospital admission, laboratory studies revealed the following values: white blood cell count, 1000/µL (reference range, 4500–11,000/µL) with 3% polymorphonuclear cells; hemoglobin, 7.3 g/dL (reference range, 14.0–17.5 g/dL); hematocrit, 21.2% (reference range, 41%–50%); and platelet count, 166,000/µL (reference range, 150,000–350,000/µL). The patient was admitted to the hospital for neutropenic fever. The chest x-ray showed no areas of consolidation. Blood cultures were positive for *Pseudomonas aeruginosa* and *Streptococcus salivarius*. The patient also had presented with oral thrush. Initially, he was administered intravenous (IV) cefepime HCl, IV vancomycin HCl, oral fluconazole, morphine sulfate, naloxone HCl, acetaminophen, pantoprazole

sodium, diphenhydramine HCl, heparin sodium, zolpidem tartrate, amiodarone HCl, alprazolam, and filgrastim. After receiving the results of the blood cultures, the antibiotic regimen was changed by the infectious disease department to IV meropenem, daptomycin, tobramycin, and caspofungin acetate.

The patient stated that he developed sudden onset of fever followed by a rash a few hours later on the right upper thigh on the day he was admitted to the hospital. Dermatology was consulted on the 11th day of hospitalization when the eruption worsened to cover almost his entire body. On physical examination, the patient had diffuse scaling, edema, and erythema of the trunk as well as the proximal lower and upper extremities, with white-studded nonfollicular pustules mainly on the chest and thighs. There also were few scattered bullae on both arms. Figures 1 and 2 depict the clinical presentation.

Two punch biopsies were performed from the right lateral thigh and chest. Histologic evaluation revealed subcorneal and intraepidermal pustule formations characterized by collections of neutrophils and necrotic cellular debris. The adjacent epidermis appeared hyperplastic with spongiosis and overlying basket-weave orthokeratosis. There was a perivascular infiltrate consisting of lymphocytes and neutrophils. Figure 3 demonstrates the histologic findings.

Special stains were negative for bacteria and fungi. The diagnosis of AGEP was favored within the clinical and histopathologic contexts; however, cultures to rule out infectious etiology were suggested. Also, with unknown history of psoriasis, acute pustular psoriasis could not be excluded with certainty. The following day, the patient experienced another episode of atrial fibrillation and became more lethargic and nonresponsive. The patient's family decided that hospice care was appropriate because of the patient's terminal condition and poor prognosis. The patient was transferred to another facility and was lost to follow-up.

What is AGEP?

Acute generalized exanthematous pustulosis is a pustular reaction most often caused by a drug. In reports, it has been referred to as amicrobial pustulosis, acute generalized pustular bacterid, pustular necrotizing angeitis, generalized pustular drug rash, acute generalized pustulosis manifestation of leukocytoclastic vasculitis, pustular eruption with eosinophilic abscesses, subcorneal pustules in erythema multiforme and in Sweet syndrome, and toxic pustuloderma.[1,5] In 1968, Baker and Ryan[6] described 5 of 104 cases of pustular psoriasis with no history of psoriasis in which the episode of pustular eruption was acute and quickly resolved. Baker and Ryan[6] referred to the condition as generalized exanthematous pustular psoriasis and suspected drugs and/or infections as cause for the pustular eruption. In 1980, Beylot et al[5] coined the term *pustuloses exanthématique aiguës généralisés* in French, which translates to AGEP.

What are the predominant clinical characteristics of AGEP?

The main clinical characteristics of AGEP are an acute eruption of numerous small (<5 mm),

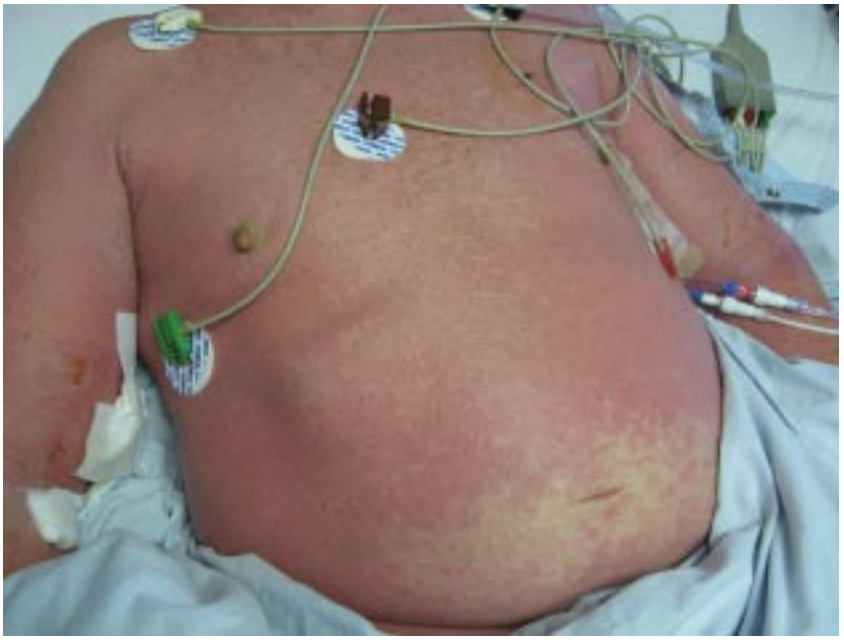

Figure 1. Diffuse edema and erythema.

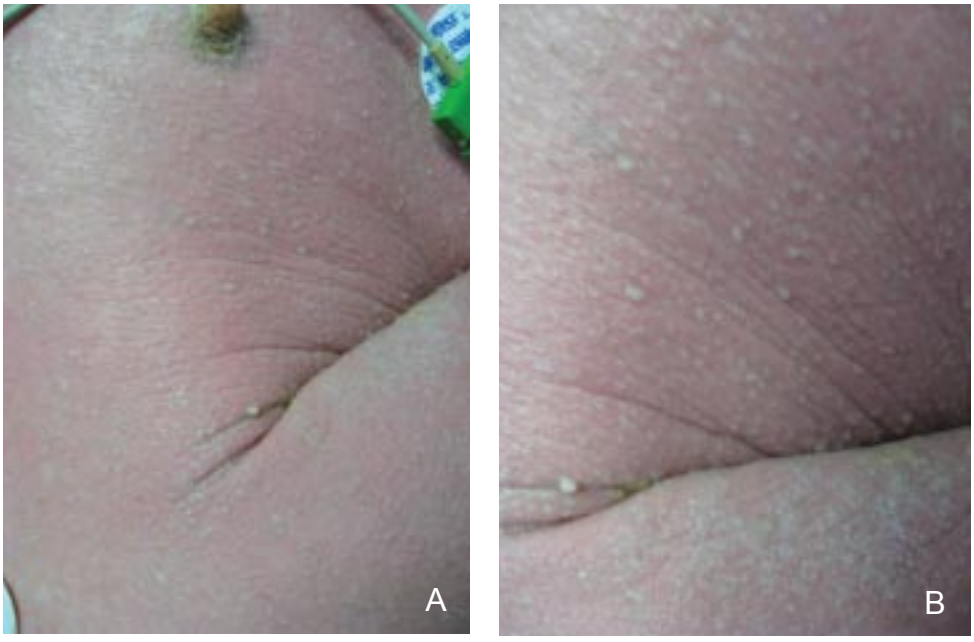

Figure 2. Numerous white-studded non-follicular pustules on trunk and axilla on an edematous and erythematous background (A and B).

nonfollicular, sterile pustules on a widespread edematous and erythematous base that usually begin in the intertriginous folds (neck, axillae, inguinal folds) or on the face and rapidly spread in a caudad direction to the trunk and upper extremities. Confluence of pustules may mimic a positive Nikolsky sign. Other skin involvement may include marked edema of the face; purpuric lesions, especially on the legs; and atypical targetoid lesions including blisters and vesicles, as seen in Stevens-Johnson syndrome. In most cases, the pustules spontaneously resolve within 15 days followed by a characteristic pinpoint desquamation lasting a few days. The mucous membranes may be involved in approximately 20% of cases, but involvement usually is mild and is mostly limited to the oral mucosa.[1-4]

Some of the systemic symptoms that may accompany skin eruptions include fever, leukocytosis mostly due to increased neutrophil count ($>7\times10^9$/L), mild eosinophilia in one-third of the patients, lymphadenopathy, slight reduction in creatinine clearance, and mild elevation of aminotransferases, with no involvement of other internal organs.[1-4]

Acute generalized exanthematous pustulosis is a self-limiting disease, usually arising rapidly within a few hours and resolving quickly within a few days without treatment. The overall prognosis is good, but high fever or cutaneous superinfection can lead to substantial complications affecting morbidity and/or mortality in patients who are older or debilitated by overall poor health, as demonstrated by our case report.[1,4] The death rate for AGEP has been reported to be up to 5%.[3]

Many times, the combination of high fever, leukocytosis, and pustules may be mistaken for acute infectious disease; therefore, early diagnosis of AGEP is important to avoid unnecessary administration of systemic antibiotic therapy that may potentially worsen the condition depending on its etiology,[1] as was the case for our patient.

What are the histologic characteristics of AGEP?

The histopathology of AGEP demonstrates subcorneal or intraepidermal pustules associated with marked edema of the papillary dermis and perivascular infiltrates of neutrophils, lymphocytes, and/or eosinophils, with focal necrosis of keratinocytes.[1,2] Direct immunofluorescence may show deposits of C3 and occasionally IgM at the vascular wall.[5] Figure 3 depicts histologic features of AGEP.

What is the incidence of AGEP?

The incidence of AGEP has been estimated to range from 1 to 5 cases per million per year. Males and females seem to be equally affected and AGEP can occur at any age.[1] The disease has been associated with HLA-B51, HLA-DR11, and HLA-DQ3.[7]

What is believed to be the etiology of AGEP?

It has been reported that more than 90% of cases of drug-induced AGEP are caused mainly by antibiotics such as aminopenicillins (β-lactams) or macrolides. Reactions to systemic antifungal agents including azoles and terbinafine also have been reported.[1-3,8-10]

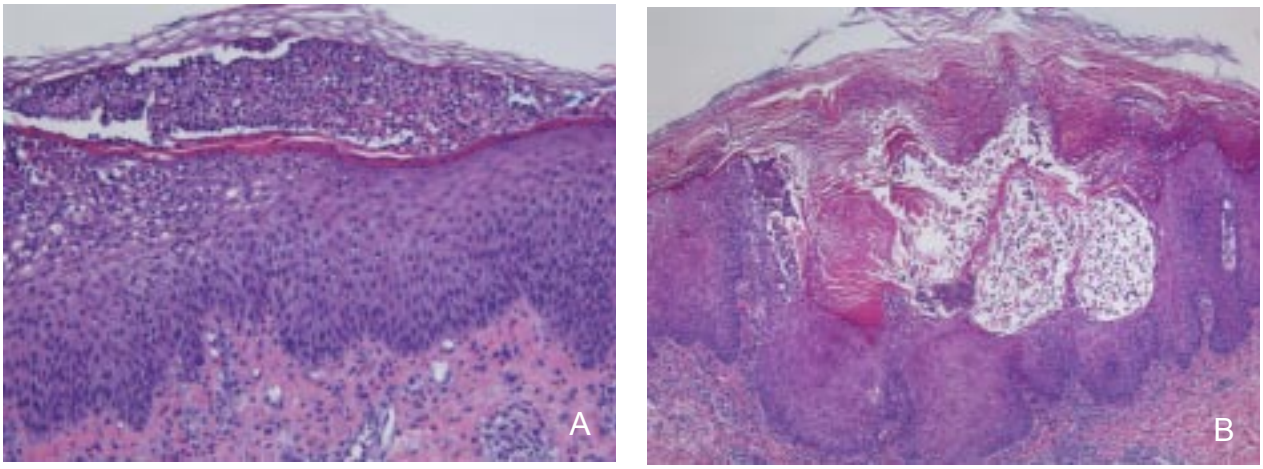

Figure 3. Subcorneal and intraepidermal pustules formed by collections of neutrophils. There is psoriasiform epidermal hyperplasia, relatively. Note the overlying basket-weave orthokeratosis (A and B)(H&E; original magnifications ×40 and ×10, respectively).

Other etiologic agents that have been reported to trigger AGEP are viruses including coxsackievirus A9, coxsackievirus B4, cytomegalovirus, enterovirus, Epstein-Barr virus, hepatitis B virus, and parvovirus B19. Mercury and *Mycoplasma pneumoniae* also have been implicated in causing AGEP.[1,8,9,11] The Table lists many of the agents associated with AGEP.

The most striking feature is the short interval between drug administration and onset of AGEP. In a European Study of Severe Cutaneous Adverse Drug Reactions (EuroSCAR) study, Sidoroff et al[4] observed a similar pattern, as did Roujeau et al,[2] in their analysis of AGEP cases. There was a different pattern for antibacterials versus other drugs on the time of onset from drug intake to emergence of the eruption and developing AGEP. The median time of onset was one day after exposure to antibiotics and approximately 11 to 18 days for other drugs.[2,4] This pattern of rapid onset may be explained by prior sensitization and/or immunologic recall phenomenon induced by T-cell reactivation.[2,4] The widespread use of systemic and topical antibiotics support this hypothesis.[1,4,10] Reports of many cases in which a first episode of AGEP occurred 2 to 3 weeks after a new drug was administered and recurrence followed rechallenge within 2 days support the pattern involving an extended interval.[50-52]

What is the underlying mechanism believed to be associated with the pathogenesis of AGEP?

Britschgi et al[53] suggested the involvement of T cells and proposed that drug presentation elicits a drug-specific $CD4^+$ and $CD8^+$ T-cell activation and secretion of neutrophil-recruiting factors, such as the chemokine CXCL8 (IL-8), IL-4, and IL-5, causing aggregation of neutrophils and eosinophils.[54,55] Other factors such as granulocyte-macrophage colony-stimulating factor, interferon-γ, and RANTES (regulated on activation of normal T cells expressed and secreted) also are secreted because of T-cell activation.[53,54] The release of inflammatory cytokines such as interferon-γ may stimulate keratinocytes to secrete IL-8 and other factors. Also, T cells are further stimulated by drug-presenting Langerhans cells. At the same time, $CD4^+$ and $CD8^+$ T cells migrate to the epidermis and cause the formation of vesicles via keratinocyte destruction by perforin, granzyme B, and the Fas/Fas ligand-mediating mechanisms. Positive patch and lymphocyte transformation tests further support T-cell involvement and suggest a delayed-type hypersensitivity reaction.[53-55]

Theoretically, rechallenging the patient with the suspected drug can confirm a certain drug as the cause of AGEP. Patch testing may serve as a substitute for rechallenge by simulating AGEP both clinically and histologically at the patch test site only, though there have been reports of reactions spreading beyond the patch site, most of them attributed to diltiazem HCl. Importantly, patch testing with the causative drug may not provoke a reaction in up to 50% of patients who have experienced an AGEP reaction to a drug.[9,56] Lymphocyte transformation tests measure proliferation of T cells to a drug in vitro indicating sensitization. Drugs can interact directly with the T-cell receptor without previous metabolism or earlier binding to protein. As with patch testing, a positive lymphocyte transformation test helps define the culprit drug, but negative tests do not definitively rule out drug hypersensitivity.[12] The macrophage migration inhibition factor test and the mast cell degranulation test also have been

Agents Reported to Induce Acute Generalized Exanthematous Pustulosis[1,2,4,8-49]

Antibiotics

Aminopenicillins (β-lactams)
- Amoxicillin
- Ampicillin
- Cephalosporins
- Imipenem
- Penicillin
- Piperacillin sodium/ tazobactam sodium

Macrolides
- Erythromycin
- Pristinamycin
- Roxithromycin
- Spiramycin

Quinolones
- Ciprofloxacin
- Pipemidic acid

Aminoglycosides
- Gentamicin sulfate

Tetracyclines
- Doxycycline
- Tetracyline

Sulfonamides
- Trimethoprim-sulfamethoxazole

Other Antibiotics
- Chloramphenicol
- Clindamycin
- Metronidazole
- Nifuroxazide
- Vancomycin HCl

Antifungals
- Amphotericin B
- Fluconazole
- Griseofulvin
- Itraconazole
- Nystatin
- Terbinafine HCl

Antiparasitics
- Chloroquine phosphate
- Diaphenylsulfone
- Hydroxychloroquine sulfate
- Pyrimethamine

Antimycobacterials
- Isoniazid
- Rifampicin

Antivirals

Protease Inhibitors
- Lopinavir
- Ritonavir

Anticonvulsants
- Carbamazepine
- Clobazam
- Phenobarbital

Anti-inflammatory
- Dexamethasone

Antidiabetic
- Carbutamide

Antipyretics
- Acetaminophen (paracetamol)

NSAIDs
- Diclofenac
- Nimesulide
- Oxicam NSAIDs
  - Meloxicam
- Valdecoxib

Cardiovascular
- Diltiazem HCl
- Enalapril
- Furosemide
- Labetalol
- Nadoxolol
- Nifedipine
- Propafenone HCl
- Prostaglandin E_1
- Quinidine
- Terazosin HCl

Antiulcer
- Cimetidine
- Lansoprazole

Antihistamine
- Clemastine fumarate
- Hydroxyzine

Anticholesterol
- Simvastatin

Antipsychotics
- Clozapine
- Olanzapine

Antithrombotics
- Heparin
- Heparin derivatives
  - Dalteparin sodium
  - Enoxaparin sodium
- Ticlopidine HCl

Chemotherapy
- Bleomycin sulfate
- Cytarabine liposome
- Gefitinib
- Imatinib mesylate
- Pemetrexed

Other Drugs
- Allopurinol
- Amoxapine
- Bufexamac
- Buphenine
- Disulfiram
- Fenoterol
- *Ginkgo biloba*
- Illicit street drugs
  - Cocaine
  - Marijuana
- Morphine
- Pentoxifylline
- Pseudoephedrine
- Sennosides
- Sulbutiamine
- Sulfasalazine
- Tetrazepam
- Thalidomide
- Topical agents

Viral Infections
- Coxsackievirus A9
- Coxsackievirus B4
- Cytomegalovirus
- Enterovirus
- Epstein-Barr virus
- Hepatitis B virus
- Parvovirus B19

Miscellaneous
- Bromic acid vapor
- Chromium picolinate
- Dog bite
- IV nonionic contrast media
- Mercury
- *Mycoplasma pneumoniae*
- Pneumococcal vaccine
- PUVA
- Spider bite
- Sulfuric acid vapor
- Thallium

Abbreviations: HCl, hydrochloride; NSAIDs, nonsteroidal anti-inflammatory drugs; IV, intravenous; PUVA, psoralen plus UVA.

shown to be helpful in detecting the causative drugs in AGEP.[57]

What is the differential diagnosis of AGEP?

The differential diagnoses of pustular eruptions include pustular psoriasis (von Zumbusch type); subcorneal pustular dermatosis (Sneddon-Wilkinson disease); pustular vasculitis; drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms [DRESS] syndrome); toxic epidermal necrolysis; and all follicular eruptions, such as bacterial folliculitis, pustular contact dermatitis, and pustular dermatophyte infections.[1,10,56]

How is AGEP distinguished from pustular psoriasis?

One of the main issues of discussion in the literature is if AGEP is its own entity or has a similar clinical presentation as pustular psoriasis of the von Zumbusch type.[1,2] Sidoroff et al[4] described many differences between AGEP and pustular psoriasis. Oftentimes there is no history of psoriasis in patients with AGEP, but in pustular psoriasis, there frequently is a history of psoriasis. The distribution of pustules in AGEP begins predominantly in the intertriginous folds with a shorter total duration of the eruption. More generalized distribution at the onset with a longer duration of pustular lesions tends to occur in pustular psoriasis. Patients with AGEP usually have a shorter duration of fever, may have a history of drug reaction, and typically exhibit a history of recent drug administration. Most cases of drug-induced AGEP occur within less than 1 week to 3 weeks after initiation of the etiologic agent. Patients with pustular psoriasis have longer duration of fever, an uncommon history of prior drug reaction, and a less frequent history of recent drug administration.[1]

Histopathology also may help distinguish AGEP from pustular psoriasis. Both diseases are characterized by subcorneal or intraepidermal spongiform pustules, but the addition of edema of the papillary dermis, possible vasculitis, exocytosis of eosinophils, or single-cell necrosis of keratinocytes suggest AGEP, while papillomatosis and acanthosis suggest pustular psoriasis.[1,2] A thorough medical history along with physical and histologic examination are important to differentiate the 2 diseases.

What is the recommended management approach for AGEP?

The first step in treatment of AGEP is to discontinue the offending drug. Systemic corticosteroid treatment generally is not considered necessary because of the benign self-limited course of the disease.[1,10] In an analysis of patients with AGEP in Asia, most were administered IV hydrocortisone, whereas the others were treated with oral prednisolone or methylprednisolone, or topical agents alone. No differences in outcome were found between the treatment regimens regarding the course and duration of the disease or the length of fever.[8] A systemic antipyretic can be given if it is not suspected as the causative drug. Antibiotics are best avoided unless presence of infection is documented.[1,10]

How does one evaluate the potential drug-induced causes of AGEP?

The patient discussed in this case report received many medications that have been reported to induce AGEP. The medications taken for approximately 2 to 3 weeks at the time of diagnosis of multiple myeloma and prior to his hospital admission that have been reported to trigger AGEP were thalidomide, dexamethasone, and meloxicam (an oxicam nonsteroidal anti-inflammatory drug). One of these drugs may have been the inciting factor. A less likely possibility is that the one infusion treatment of pamidronate disodium may have been the cause of AGEP. These medications were discontinued on hospital admission; however, the patient's skin condition continued to worsen, possibly related to a variety of confounding factors because of the complexity of his underlying medical status. During his hospital stay, many other medications were administered that have been implicated in AGEP, including cephalosporins, vancomycin HCl, fluconazole, morphine, acetaminophen, and heparin and its derivative enoxaparin sodium. It was difficult to determine the exact cause of AGEP in this patient. It is possible that thalidomide, dexamethasone, or meloxicam caused the initial presentation on hospital admission, but additional medications administered in the hospital may have further exacerbated the inciting event to a more full-blown case of AGEP. Worsening of the condition and administration of additional antibiotics may have been prevented by consulting the dermatology department at an earlier time. Due to the gravity of the patient's medical status, it was difficult to obtain a thorough medical history, including a history of psoriasis, list and duration of medications taken prior to hospital admission, and any history of a drug-induced reaction. Therefore, the diagnosis was based on clinicopathologic correlation. A thorough history, including a medication history, along with histologic examination, is important in reaching an accurate diagnosis and proper management in a patient presenting with an acute diffuse pustular reaction.

Conclusion

Unfortunately, there is no single definitive and confirmatory diagnostic test for AGEP. Additionally, in the presence of a complicated drug history with multiple, newly prescribed medications, it is not always possible to determine the causative agent. Correlation of the clinical presentation with the histologic findings in these cases can be used to support the diagnosis of AGEP.

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