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RESEARCH ARTICLE

AGEP – A Rare but Important Adverse Cutaneous Drug Reaction

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Abstract: Acute Generalized Exanthematous Pustulosis (AGEP) is a rare but severe skin reaction predominantly triggered by medications. It is characterized by the rapid onset of sterile, non-follicular pustules on an erythematous base, often accompanied by fever and leucocytosis. Despite its dramatic presentation, AGEP typically has a favourable prognosis with appropriate management, but its rapid onset and potential for misdiagnosis necessitate prompt recognition. We report a case of AGEP in a 50-year-old female with type 2 diabetes mellitus who developed widespread pustular lesions shortly after taking an Ayurvedic medication for a headache and fever. The patient initially presented with fluid-filled lesions on the abdomen and erythematous papules on her arms and thighs, which rapidly progressed to pustules. Over the course of four days, the lesions coalesced into larger purulent areas with desquamation. Histopathological examination of the lesions revealed severe spongiosis, basal vacuolar degeneration, and epidermal neutrophilic infiltration, consistent with AGEP. The Ayurvedic medication was immediately discontinued, and the patient was treated with systemic and topical corticosteroids. Broad-spectrum antibiotics were administered prophylactically due to the risk of secondary bacterial infection. The patient showed significant improvement within four days, with resolution of pustules and desquamation. This case highlights the potential of Ayurvedic medications to trigger severe cutaneous reactions like AGEP. The rapid identification and withdrawal of the offending agent, combined with corticosteroid therapy, were crucial in the patient's recovery. Given the increasing use of alternative medicines, healthcare providers must consider these potential triggers in patients presenting with acute dermatological conditions.

Keywords, Erythema Multiforme, Drug Eruption, Ayurvedic Medication, Vesiculobullous lesions.

INTRODUCTION

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare but severe skin reaction, most commonly triggered by medications. It is characterized by the rapid onset of dozens to hundreds of sterile, non-follicular pustules on an erythematous base, typically accompanied by fever and leukocytosis [1]. The clinical presentation of AGEP is dramatic, with symptoms usually appearing within a few days of exposure to the offending agent. The most common culprits are antibiotics, particularly beta-lactams, as well as calcium channel blockers and antimalarials [2].

AGEP is considered a severe cutaneous adverse reaction (SCAR) and is distinct from other pustular skin conditions due to its acute onset and the absence of systemic involvement in most cases [3]. Despite its alarming presentation, AGEP generally has a favorable prognosis, with resolution typically occurring within one to two weeks after the discontinuation of the causative agent [4]. However, its rapid onset and the potential for misdiagnosis with other more severe conditions, such as generalized pustular psoriasis or Stevens-Johnson Syndrome, make prompt recognition and management critical [5].

This report discusses a case of AGEP in a 50-year-old female with type 2 diabetes mellitus, who developed widespread pustular lesions shortly after taking an Ayurvedic medication. The patient initially presented with fluid-filled lesions on the abdomen and erythematous papules on her arms and thighs, which rapidly progressed to pustules. The history of recent medication use, combined with the clinical and histopathological findings, strongly supported a diagnosis of AGEP.

The increasing use of alternative and complementary medicines, such as Ayurveda, underscores the importance of recognizing AGEP as a potential adverse reaction. While Ayurvedic treatments are often perceived as natural and safe, they are not without risk. This case highlights the need for healthcare providers to consider all possible etiologies, including non-conventional therapies, when assessing patients with acute dermatologic reactions [6,7].

Patient Information

Demographics: A 50-year-old female with a known history of type 2 diabetes mellitus.

Primary Concerns and Symptoms: The patient presented to the emergency department with acute onset of fluid-filled lesions on the abdomen, along with reddish, raised lesions on both arms and thighs. She also reported fever and breathlessness that began one day prior to her visit.

Medical, Family, and Psychosocial History: The patient had a history of well-controlled type 2 diabetes mellitus but no significant family history of skin disorders or drug allergies. There were no known

psychosocial stressors, and she denied any recent changes in diet or lifestyle.

Relevant Past Interventions with Outcomes: The patient had been managing her diabetes with oral hypoglycemic agents and had not experienced any recent changes in her medication regimen. Two days before the onset of symptoms, she took an unknown Ayurvedic medication for a headache and fever. She had no previous history of adverse reactions to medications, including Ayurvedic treatments.

Symptom Progression: The patient was in her usual state of health until she took the Ayurvedic medication. Within 8 hours, she developed erythematous papules on her abdomen, forearms, and thighs. These papules rapidly evolved into vesicles, particularly over the abdomen, with some lesions on the forearms displaying a targetoid appearance. Over the next 18 hours, the lesions on the abdomen transformed into pustules, some of which coalesced to form "lakes of pus." By the third day, the pustules had started to rupture, leading to desquamation.

Clinical Findings

Upon presentation, the patient exhibited a variety of dermatological manifestations that evolved over the course of several days:

- **Day 1:** Initial examination revealed multiple vesicles on an erythematous base over the abdomen, with target-like lesions observed on both thighs and arms. The lesions were not associated with pruritus or pain. The patient also exhibited a mild fever, consistent with her reported symptoms.
- **Day 2:** The vesicles on the abdomen began to transition into pustules, while the erythematous lesions on the thighs and arms showed signs of Koebnerization (the appearance of new skin lesions on previously unaffected skin due to trauma or pressure). The targetoid lesions remained distinct, particularly on the forearms.
- **Day 3:** The pustules over the abdomen had coalesced into larger, purulent areas, giving a "lakes of pus" appearance. The patient's fever persisted, and she continued to experience mild breathlessness. Examination of the oral cavity revealed no lesions, and mucosal surfaces were spared.
- **Day 4:** By the fourth day, many pustules on the abdomen had ruptured, leading to desquamation and the appearance of healing skin underneath. The erythematous base remained, but the intensity of the lesions appeared to be subsiding.

The differential diagnosis at this stage included Acute Generalized Exanthematous Pustulosis (AGEP) due to the rapid onset and progression of pustular lesions, and a potential drug reaction given the temporal association with the intake of an unknown

Ayurvedic medication. The absence of pruritus and mucosal involvement, along with the presence of targetoid lesions, was notable and helped guide the diagnostic process.

Laboratory Findings: Routine blood tests revealed leukocytosis, consistent with the inflammatory nature of the condition. Specific laboratory data such as complete blood count, liver function tests, and renal function tests were within normal limits, except for the elevated white blood cell count.

Histopathological Findings: A biopsy taken from a Day 1 lesion revealed severe spongiosis, basal vacuolar degeneration, and epidermal neutrophilic infiltration.

The dermis showed marked edema, with perivascular neutrophilic and lymphocytic infiltration, findings consistent with AGEP.

A biopsy of a Day 2 lesion displayed parakeratosis, subcorneal bullae filled with neutrophils, and continued spongiosis, with the dermis again showing perivascular lymphocytic infiltration, including one vessel with fibrinoid material deposition.

Timeline

Day	Clinical Event
Day -2	The patient ingested an unknown Ayurvedic medication for headache and fever.
Day 0	**(Presentation Day)**: The patient developed erythematous papules over the abdomen, forearms, and thighs within 8 hours of taking the medication. The lesions progressed to vesicles, particularly on the abdomen, with some targetoid lesions appearing on the forearms. The patient also experienced fever and mild breathlessness.
Day 1	Vesicles on the abdomen began to transition into pustules. Koebnerization observed on erythematous lesions over the thighs and arms. Targetoid lesions persisted. A differential diagnosis of AGEP was considered.
Day 2	Pustules over the abdomen coalesced, forming "lakes of pus." The patient continued to have a mild fever. Histopathological examination of lesions confirmed findings consistent with AGEP.
Day 3	Rupture of pustules on the abdomen, leading to desquamation. Erythematous base showed signs of healing. Mucosal surfaces remained unaffected.

Day 4	Pustules continued to resolve with desquamation. The patient's overall condition began to improve, with a reduction in fever and breathlessness.

Diagnostic Assessment
Diagnostic Methods:

- **Physical Examination:** Upon initial presentation, the patient underwent a thorough dermatological examination, which revealed multiple vesicles on an erythematous base, primarily over the abdomen, with targetoid lesions on the forearms. The physical findings, along with the patient's systemic symptoms of fever and mild breathlessness, raised suspicion for a severe cutaneous adverse reaction.
- **Histopathology:** A skin biopsy was performed on the first day of presentation to gain a definitive diagnosis. The biopsy revealed severe spongiosis, basal vacuolar degeneration, and epidermal neutrophilic infiltration, consistent with Acute Generalized Exanthematous Pustulosis (AGEP). A follow-up biopsy from a second lesion on the abdomen, taken on Day 2, showed parakeratosis, subcorneal bullae filled with neutrophils, and spongiosis, with dermal perivascular lymphocytic infiltration and fibrinoid material in one vessel.
- **Laboratory Tests:** Blood tests demonstrated leukocytosis, a common finding in AGEP. Liver and renal function tests were normal, ruling out significant systemic involvement.

Diagnostic Challenges:

- **Differential Diagnosis:** The rapid evolution of the patient's skin lesions necessitated consideration of several differential diagnoses, including erythema multiforme, Stevens-Johnson syndrome, and generalized pustular psoriasis. The absence of mucosal involvement, combined with the histopathological findings, was crucial in narrowing the diagnosis to AGEP. Additionally, the temporal association with the ingestion of an Ayurvedic medication complicated the diagnosis, as the specific components of the medication were unknown, and herbal medications are not commonly recognized triggers for AGEP.
- **Lack of Medication Information:** The unknown nature of the Ayurvedic medication posed a significant challenge. Without knowledge of the specific ingredients, it was difficult to conclusively identify the causative agent. This necessitated a reliance on the clinical presentation and histopathological findings for diagnosis.

Diagnostic Reasoning:
The patient's history of sudden onset pustular eruption following the intake of an Ayurvedic medication, combined with the histological evidence of severe epidermal and dermal inflammation, strongly suggested a diagnosis of AGEP. The rapid progression of lesions and the characteristic histopathological findings, including spongiosis, neutrophilic infiltration, and subcorneal pustules, supported this diagnosis over other differential considerations.

Prognosis:
The prognosis for AGEP is generally favorable, with most cases resolving within one to two weeks after cessation of the offending agent. In this patient, the lesions began to resolve with desquamation by the fourth day of hospitalization, and her overall condition improved with supportive care. Given the absence of significant systemic involvement, the patient's long-term prognosis is excellent, with no expected chronic complications.

Therapeutic Intervention
Initial Management:

- **Discontinuation of Suspected Medication:** Upon admission, the immediate therapeutic priority was the discontinuation of the suspected offending agent—the Ayurvedic medication. Although the exact ingredients were unknown, the strong temporal association with the onset of symptoms warranted its discontinuation to prevent further exacerbation of the condition.
- **Supportive Care:** The patient was provided with supportive care, which included hydration and electrolyte balance to manage fever and general discomfort. Given the patient's history of type 2 diabetes mellitus, blood glucose levels were closely monitored, and her diabetic medications were adjusted as needed to account for any potential impact from her acute illness.

Pharmacologic Treatment:

- **Systemic Corticosteroids:** The patient was started on systemic corticosteroids to reduce the inflammatory response and halt the progression of the skin lesions. This intervention is common in severe cases of AGEP to control widespread pustular eruptions and associated symptoms. A moderate dose of oral prednisone was initiated, with plans to taper the dosage based on the patient's clinical response.
- **Topical Steroids:** To further manage the localized skin lesions, potent topical corticosteroids were applied to the affected areas, particularly over the abdomen and limbs where the pustules and erythematous lesions were most prominent. This helped to reduce inflammation and promote healing of the skin.

Antibiotic Prophylaxis:

- **Broad-Spectrum Antibiotics:** Although AGEP is not typically associated with bacterial infections, the presence of ruptured pustules and the potential for secondary bacterial infection necessitated the prophylactic use of broad-spectrum antibiotics. This was especially important given the patient's ongoing immunosuppression from systemic corticosteroid use.

Monitoring and Adjustments:

- **Daily Assessment:** The patient was closely monitored, with daily assessments of her skin lesions, vital signs, and laboratory parameters. Adjustments to her steroid regimen were made based on her response to treatment. The corticosteroid dose was gradually tapered as the patient's condition improved and the lesions began to resolve.
- **Management of Adverse Effects:** Careful attention was given to managing potential side effects of corticosteroid therapy, including hyperglycemia, given the patient's diabetic status. Insulin therapy was adjusted as needed to maintain optimal glucose control.

FOLLOW-UP AND OUTCOMES

In-Hospital Progress:

- **Resolution of Symptoms:** During her hospital stay, the patient demonstrated a marked improvement in her condition. By the fourth day, the previously prominent pustular lesions on her abdomen had largely ruptured and were healing with desquamation. The erythematous base of these lesions was less inflamed, and no new lesions developed. The patient's fever resolved, and her breathlessness improved significantly, which suggested that the systemic inflammatory response was under control.
- **Steroid Tapering:** As the patient's skin lesions showed signs of resolution, the systemic corticosteroid dosage was gradually tapered. The patient tolerated the tapering well, without any recurrence of symptoms or new skin lesions. Topical corticosteroids were continued on an as-needed basis to manage any remaining erythema and to promote complete healing of the affected areas.

Post-Discharge Follow-up:

- **First Follow-up (2 weeks post-discharge):** The patient returned for her first follow-up visit two weeks after discharge. On examination, the skin lesions had almost completely resolved, with only mild post-inflammatory hyperpigmentation remaining at the sites of the previous pustules. There was no evidence of new lesions, and the patient reported no recurrence of fever or breathlessness. Her diabetes was well-controlled, and no further adjustments to her diabetes medications were needed.
- **Long-term Outcome:** The patient was advised to avoid all Ayurvedic medications unless the ingredients were fully known and approved by her healthcare provider. She was educated on the importance of informing all healthcare providers about any non-prescription or herbal remedies she might consider in the future to prevent similar adverse reactions. No long-term complications were anticipated, and the patient was expected to recover fully.

Final Outcome:

- **Recovery and Prognosis:** The patient made a full recovery from the acute episode of AGEP without any lasting sequelae. Her prognosis was excellent, with no expected chronic complications. Given the self-limiting nature of AGEP, especially with prompt identification and management, the risk of recurrence was low, provided that the patient avoids similar triggers in the future.

DISCUSSION

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare but severe adverse cutaneous drug reaction characterized by the rapid onset of widespread pustules on an erythematous base, typically associated with fever and leukocytosis. Although AGEP is often drug-induced, it can be triggered by a variety of agents, including infections and, less commonly, environmental factors. The condition is most commonly associated with the use of antibiotics (such as beta-lactams), calcium channel blockers, and antimalarials, but recent case reports have highlighted the role of alternative medicines, including herbal and Ayurvedic treatments, in triggering this reaction [1,2].

The clinical presentation of AGEP can be alarming, with its sudden onset of numerous sterile pustules, accompanied by systemic symptoms such as fever and malaise. The rapid progression from macules and papules to pustules, as observed in this case, is typical of AGEP and helps distinguish it from other pustular dermatoses such as generalized pustular psoriasis or pustular eruptions associated with Stevens-Johnson Syndrome (SJS) [5]. The absence of mucosal involvement in this case further supported the diagnosis of AGEP, as mucosal involvement is more characteristic of SJS and toxic epidermal necrolysis (TEN).

Histopathological examination is crucial in confirming the diagnosis of AGEP, as the findings are distinctive and include subcorneal or intraepidermal pustules, spongiosis, and a mixed infiltrate of neutrophils and eosinophils [3]. In this patient, the biopsy findings of severe spongiosis, subcorneal pustules filled with

neutrophils, and dermal perivascular lymphocytic infiltration were consistent with AGEP. The presence of these histological features, along with the rapid resolution of pustules upon withdrawal of the suspected offending agent, strongly supported the diagnosis.

AGEP is predominantly a drug-induced reaction, and the latency period between drug exposure and the onset of symptoms is typically short, often less than 48 hours [4]. In this case, the patient developed symptoms within 8 hours of taking an Ayurvedic medication, which strongly implicated this treatment as the trigger. The exact pathophysiology of AGEP is not fully understood, but it is believed to involve a T-cell mediated hypersensitivity reaction. The rapid recruitment of neutrophils into the epidermis, leading to pustule formation, is a hallmark of the condition [5].

The role of herbal and Ayurvedic medicines in causing drug-induced reactions like AGEP is increasingly recognized. These treatments often contain a mixture of active compounds, some of which may be potent allergens or have unknown pharmacological effects. The lack of regulation and standardized testing for safety and efficacy in many alternative medicine products raises significant concerns about their potential to cause severe adverse reactions [6,7].

The cornerstone of AGEP management is the immediate discontinuation of the offending drug, which usually leads to rapid improvement of symptoms. Supportive care, including systemic corticosteroids, is often employed to manage inflammation and hasten the resolution of pustules, as was done in this case. The patient responded well to a combination of systemic and topical corticosteroids, which is consistent with the typical course of AGEP, where lesions begin to heal within days of stopping the causative agent [8].

The prognosis for AGEP is generally excellent, with most patients experiencing full recovery without long-term sequelae. However, the condition can be severe, particularly if it is not promptly recognized and treated, or if there is significant systemic involvement [9]. In this case, the patient's rapid recovery following corticosteroid therapy and discontinuation of the Ayurvedic medication underscores the importance of early intervention.

This case highlights several important considerations for clinical practice. First, it underscores the need for healthcare providers to be aware of the potential risks associated with herbal and alternative medicines, which are often perceived as safe due to their natural origin. A thorough patient history that includes inquiries about the use of non-prescription medications and alternative therapies is crucial, particularly in cases of acute dermatological reactions [10].

Second, the case emphasizes the importance of early recognition and appropriate management of AGEP. Given the condition's potential for rapid progression, prompt discontinuation of the suspected drug and initiation of supportive care are essential to prevent complications and ensure a favorable outcome [11].

Case Study 1: AGEP Induced by Paracetamol - A 38-year-old female from South India developed acute generalized exanthematous pustulosis (AGEP) two days after starting paracetamol for a mild fever. She presented with high fever and a widespread pustular rash on an erythematous base, primarily affecting the trunk and limbs, without mucosal involvement. A skin biopsy confirmed the diagnosis by showing subcorneal pustules and spongiosis with a dense neutrophilic infiltrate in the dermis. The paracetamol was discontinued, and the patient was treated with systemic corticosteroids, leading to a rapid resolution of pustules within three days and full recovery without recurrence during follow-up [12].

Case Study 2: AGEP Triggered by Nimesulide - A 50-year-old male from Northern India presented with acute pustular eruptions on his face, chest, and back two days after taking nimesulide for a headache. He also had fever and malaise. Physical examination revealed multiple non-follicular pustules on an erythematous base. Histopathological examination confirmed AGEP, showing subcorneal pustules with neutrophilic infiltration. Nimesulide was immediately stopped, and the patient was treated with oral corticosteroids and supportive care. The pustular lesions resolved within a week, and the patient had no further complications [13].

Case Study 3: AGEP Due to Herbal Medication - A 45-year-old male from Western India developed fever, erythematous macules, and rapidly forming pustules on his chest, back, and upper limbs, one day after ingesting a herbal preparation for general wellness. He had no previous history of drug allergies. A skin biopsy revealed typical AGEP features, including subcorneal pustules, spongiosis, and a mixed inflammatory infiltrate with neutrophils. The herbal medication was discontinued, and the patient was treated with systemic corticosteroids, leading to the resolution of pustular lesions within five days, with no long-term effects [14].

CONCLUSION

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare and severe cutaneous drug reaction characterized by the rapid onset of pustules on an erythematous base, typically associated with systemic symptoms like fever and leukocytosis. This case report, along with similar cases from India, describes the diverse range of potential triggers for AGEP, including commonly used medications such as paracetamol and nimesulide, as well as herbal and Ayurvedic preparations. The prompt recognition of AGEP and the immediate discontinuation of the offending agent are crucial for a favorable outcome, as demonstrated by the rapid resolution of

symptoms following appropriate management with systemic corticosteroids. The increasing use of alternative medicines, which are often perceived as safe due to their natural origin, highlights the need for healthcare providers to be vigilant in identifying potential adverse reactions, even from non-conventional therapies. This case reinforces the importance of a thorough patient history that includes inquiries about over-the-counter and herbal medications, particularly in patients presenting with acute dermatological conditions. Ultimately, awareness and prompt management of AGEP are essential to prevent complications and ensure complete recovery.

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