Triad of acute generalized exanthematous pustulosis, delirium, and lactic acidosis due to azithromycin

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INTRODUCTION

Azithromycin is a relatively safe drug, uncommonly associated with acute generalized exanthematous pustulosis (AGEP). Furthermore, AGEP has not been previously reported as a triad with delirium and lactic acidosis. Ninety percent of AGEP cases are caused by drugs, whereas the remaining 10% are caused by viral infections. AGEP is associated with high fever, leukocytosis, and pustules and sometimes mistaken for an acute infection. The early diagnosis of AGEP is critical to avoid unnecessary investigations and administration of antibiotics with associated risks. We report a case of azithromycin-induced AGEP, delirium, and lactic acidosis occurring as a triad.

Abbreviation used:

AGEP: acute generalized exanthematous pustulosis

CASE REPORT

A 16-year-old previously healthy male presented with fever for 2 days and erythema and pustules for 1 day. He had been prescribed azithromycin daily for acne. On day 1, he developed malaise and fever 5-6 hours after taking azithromycin in the morning. The following day, he took a second dose in the morning. His fever persisted, and he developed erythema on the trunk and extremities, along with pustules, which were mostly observed on the elbows (Figs 1 and 2). He was admitted to the hospital with a temperature of 101.5°F (38.6°C) (Table I). At presentation, his total leukocyte count was 28,000/mm^3, with 93% neutrophilia. Over the next 2 days, the erythema and pustules spread on the remaining area of his trunk and extremities. There was no mucosal involvement. A skin biopsy showed the presence of spongiform subcorneal and intraepidermal pustules consisting of numerous neutrophils, accompanied by papillary edema. Based on a EuroSCAR validation score of 12, a diagnosis of AGEP was made (Table II).[1]

Azithromycin was discontinued following the second dose. On the third day, he developed delirium, which consisted of restlessness, agitation, and rambling with nonsensical speech. A neurologic examination did not reveal any localizing signs or neck rigidity. His arterial blood gas analysis revealed lactic acidosis (lactic acid level, 5.8 mmol/L); the rest

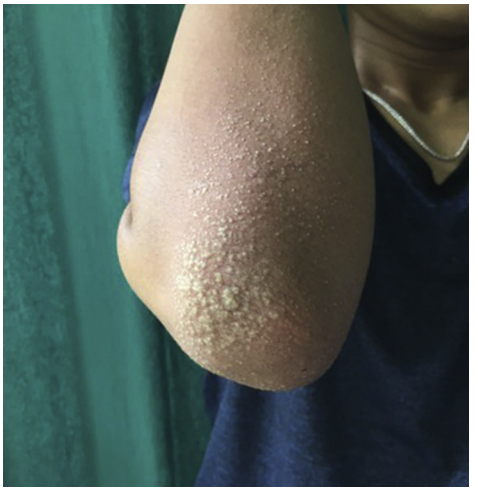

Fig 1. Numerous pustules on the right elbow.

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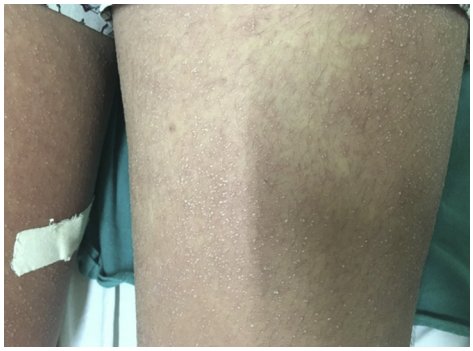

Fig 2. Pustules and erythema on the thighs.

of the arterial blood gas parameters were within the normal limit. In addition, he had hyponatremia and slightly elevated transaminase levels (Table I). Renal function test results were normal. HIV and viral hepatitis test results were negative. Blood, skin, and urine culture results were negative. Because of a high index of suspicion of AGEP and delirium due to azithromycin, he was continued on supportive care with close monitoring and given fluid supplementation, prophylactic antibiotic therapy with ceftriaxone, and paracetamol thrice daily for the first 2 days and as needed thereafter. The delirium subsided within 8 hours. He was afebrile by the fifth day; the leukocytosis decreased, rash waned, and lactic acid levels normalized by the seventh day. The clinical course and laboratory parameters are summarized in Table I.

DISCUSSION

AGEP is mainly associated with antibiotics, especially beta lactams and macrolides, although it has also been associated with oral antifungals, antimalarials, calcium-channel blockers, and anticonvulsants, as well as viral infections, making it of paramount importance to recognize the potential associations of AGEP. Azithromycin has rarely been associated with AGEP.[2] We present a case of azithromycin-induced AGEP associated with delirium and lactic acidosis. The diagnosis of AGEP was made based on the clinical features and confirmed by histopathology. A psychiatry consultation confirmed that the delirium was due

Table I. Summary of clinical and laboratory parameters

Day	Dose of azithromycin	Clinical course	Investigations	Treatment given
Day 1	First dose of azithromycin	Fever after 5-6 hours	NA	NA
Day 2 (admitted)	Second dose of azithromycin	Fever persisted (101.5°F), erythema on the trunk and extremities, tiny papules and pustules on the elbows and knees	NA	Ceftriaxone started empirically
Day 3	Stopped	Fever continued (range, 99°F-101°F), rash progressed, delirium observed in the morning, which subsided by evening	Lactic acid, 5.8 mmol/L Sodium, 124 mmol/L TLC, 28,000/mm^3 AEC, 150 ALT, 61 AST, 70	Supportive treatment* Ceftriaxone continued
Day 4	NA	Fever decreased (range, 98°F-99.8°F), delirium subsided, rash progressed	Lactic acid, 3.7 mmol/L Sodium, 132 mmol/L TLC, 18,100/mm^3 ALT, 83 AST, 59	Supportive treatment Ceftriaxone continued
Day 5	NA	Fever subsided, rash started improving	Lactic acid, 2.5 mmol/L TLC, 12,500/mm^3 Sodium, 137 mmol/L (N) ALT, 66 AST, 33	Supportive treatment Ceftriaxone continued
Day 7	NA	Rash further improved	Lactic acid, 1.5 mmol/L (N) TLC, 12,100/mm^3 AEC, 1560/mm^3 ALT, 41 AST, 30	Supportive treatment

AEC, Absolute eosinophil count (N, 40-440/mm^3); *ALT*, alanine transaminase (N < 41); *AST*, aspartate transaminase (N < 38); *N*, normal range; *NA*, not applicable; *TLC*, total leukocyte count.
*Supportive treatment consisted of fluid supplementation, paracetamol as needed, topical corticosteroids, and regular monitoring of vital and laboratory parameters.

Table II. AGEP Validation Score of the EuroSCAR Study Group[1]

Variable	Score
Morphology	
Pustules	
Typical*	+2
Compatible†	+1
Insufficient‡	0
Erythema	
Typical	+2
Compatible	+1
Insufficient	0
Distribution/pattern	
Typical	+2
Compatible	+1
Insufficient	0
Postpustular desquamation	
Yes	+1
No/insufficient	0
Course	
Mucosal involvement	
Yes	−2
No	0
Acute onset (≤ 10 days)	
Yes	0
No	−2
Resolution (≤ 15 days)	
Yes	0
No	−4
Fever (≥ 38°C)	
Yes 1	+1
No 0	0
PMN (≥ 7000/mm$^{3)}$	
Yes 1	+1
No	0
Histology	
Other diseases	−10
No representative/no histology	0
Exocytosis of PMN	+1
Subcorneal and/or intraepidermal nonspongiform or NOS pustule(s) with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary edema	+2
Spongiform subcorneal and/or intraepidermal pustule(s) with papillary edema	+3

Patients were not included in the study if only localized pustules were reported, the pustular rash had already lasted longer than 3 weeks, or a clear alternative diagnosis was made by a dermatologist.

AGEP, Acute generalized exanthematous pustulosis; *NOS*, not otherwise specified; *PMN*, Polymorphonuclear cells, Interpretation: ≤0, no AGEP; 1-4, possible AGEP; 5-7, probable AGEP; 8-12, definite AGEP.

*Typical: typical morphology.

†Compatible: not typical but not strongly suggestive of other disease.

‡Insufficient: lesions cannot be judged (mostly because of the late stage of the disease or poor quality of images).

to azithromycin, and delirium is a known adverse effect of therapeutic doses of azithromycin.[3] The lactic acidosis posed a dilemma as it is typically associated with a severe infection. Given the high-grade fever, delirium, and pustular eruption, a lumbar puncture and other investigations were suggested to rule out infection, and several antibiotics were considered to target the potential organisms causing this condition. However, due to the absence of neck rigidity, normal neurologic examination results, and normal limits of the remaining laboratory parameters, except for an increased total leukocyte count with neutrophilia (which is a common finding in AGEP), it was decided to keep the patient under close observation, and the lactic acid levels were monitored frequently. The delirium subsided within 8 hours. The lactic acid levels decreased daily and returned to normal on day 7, within 4 days from initial development.

Delirium has been reported to be associated with azithromycin use.[3,4] Lactic acidosis has been reported to be associated with other drugs, and when it is not associated with tissue hypoxia, it is known as type B lactic acidosis. There have been several reports on lactic acidosis associated with the use of linezolid, which is another antibiotic that inhibits bacterial protein synthesis by binding to the 23S ribosomal RNA residues of the 50S large subunit. Linezolid likely inhibits the 16S rRNA of the large 28S subunit of the mitochondrial ribosome. This can lead to the inhibition of protein synthesis, resulting in a decreased production of respiratory chain complexes in the mitochondria. This may result in the reduction of endogenous respiration and, hence, lead to lactic acidosis. However, this is likely to occur after some days as the pre-existing mitochondrial protein levels are decreased.[5,6]

Azithromycin binds to the 50S rRNA near the peptidyltransferase center, thereby preventing peptide chain elongation.[7] Hence, it may be postulated that azithromycin may similarly cause the inhibition of mitochondrial rRNA and result in lactic acidosis. In our case, lactic acidosis occurred on the third day after the first dose of azithromycin, which may have been precipitated early due to the decrease in the existing mitochondrial protein levels owing to their increased demands due to the high fever and extensive pustular eruption associated with AGEP, predisposing the patient to lactic acidosis.

In a previous case of azithromycin-associated AGEP, the patient tolerated clarithromycin but not azithromycin on rechallenge.[2] However, no rechallenge was attempted in our case. A patch test was not performed, which is a limitation.

The manifestations of AGEP can mimic those of other diseases and may result in unnecessary therapy

and morbidity if not recognized early. Potential associations should be kept in mind when dealing with AGEP cases. Further reports may be helpful in consolidating evidence regarding this unique triad of AGEP, delirium, and lactic acidosis.

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