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AMOXICILLIN HYPERSENSITIVITY: UNVEILING A HIDDEN ADVERSE REACTION

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ABSTRACT
Amoxicillin, a commonly used penicillin-class antibiotic, is effective against various infections. However, it can cause hypersensitivity reactions ranging from mild skin rashes to severe systemic responses. A 44-year-old female with no significant medical history was prescribed amoxicillin 500 mg for heat boils. On day 4 of treatment, she developed a rash on her palms, hands, lips, and legs, followed by skin discoloration, peeling, generalized weakness, and a loss of consciousness. Clinical examination revealed elevated blood pressure, hyperpigmented lesions, and skin peeling scars. Blood investigations showed raised inflammatory markers. MRI findings suggested chronic small vessel ischemia. A Naranjo Adverse Reaction Probability Scale assessment indicated a probable adverse drug reaction to amoxicillin. The drug was discontinued, and the patient was managed conservatively with dermatological treatments, antihypertensive medication, neurological evaluation, and physiotherapy. Beta-lactam antibiotics, including amoxicillin, are associated with hypersensitivity reactions, potentially life-threatening. Early detection, prompt discontinuation of the offending drug, and appropriate management are crucial. This case highlights the importance of recognizing amoxicillin-induced hypersensitivity reactions and suggests that careful patient history, skin testing, and close monitoring are essential to prevent adverse outcomes. Reporting such cases contributes to pharmacovigilance efforts and promotes safer medication practices.

KEYWORDS: Amoxicillin, hypersensitivity, adverse drug reaction, beta-lactam antibiotics, pharmacovigilance.

INTRODUCTION
Amoxicillin is a semi-synthetic antibiotic that is acid stable and belongs to the Penicillin class of antibiotics. In the treatment of various infections and diseases, amoxicillin is more effective against gram positive bacteria than gram negative bacteria. Additionally, it has demonstrated greater efficacy to other antibiotics, e.g. ampicillin, azithromycin, clarithromycin, cefuroxime and doxycycline in treatment of various infections/ diseases.[1] Over the past decades, amoxicillin has been shown to be helpful in the treatment of a variety of indications. It is used to treat infections of the tonsils (tonsillitis & tonsillopharyngitis), throat, larynx (laryngitis), pharynx (pharyngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract (UTI), skin and for the management of gonorrhoea. Amoxicillin, both alone and in combination, continues to be a crucial treatment for various infections, especially those of the respiratory tract, globally, due to the development of higher dosing regimens and pharmacokinetically enhanced formulations. Amoxicillin is a bactericidal agent that works by inhibiting the synthesis of cell wall mucopeptide during bacterial multiplication, which is effective in killing susceptible micro-organisms. Penicillin, in this case, Amoxicillin binds to the penicillin-binding protein 1A (PBP-1A) in bacterial cell walls. The enzyme is acylated by amoxicillin, which renders it inactive and inhibits the formation of cell walls. This is essential for the shape and division of cells. Penicillin kills bacteria by both lytic and non-lytic processes that impact cell division and morphology.[1]

Amoxicillin is commonly used in conjunction with clavulanic acid or sulbactam, a beta-lactamase inhibitor. Beta-lactamase inhibitors link permanently to the catalytic site of bacteria's beta-lactamase enzyme thereby initiating inhibition of beta-lactamase enzyme activity, leading to increased efficacy of beta-lactam antibiotics. These medications do not have bactericidal action like amoxicillin, but when coupled with it, they can broaden its spectrum of activity.[3] The main side effect to watch out for is amoxicillin-induced hypersensitivity responses. Reactions of type I, II, III, or IV can occur with amoxicillin. It's crucial to distinguish between type-I and type-IV hypersensitivity reactions, as one may be more dangerous than the other.[3] Beta-lactams, whether

naturally produced or synthetic, can cause allergic reactions. In recent years, numerous case reports and case series have been published on amoxicillin-induced skin rashes, highlighting the potential risks associated with these medications.[4]

CASE REPORT

44-year-old female who is not a known case of hypertension, not on any other medications had a recent history of heat boils over back and limbs 15 days back for which she was prescribed with Amoxicillin 500mg tablet. At day 4 on treatment, she developed rash over palm and dorsum of both the hands, lips and legs. She also noticed blackish discolouration of skin and skin peeling for 3 days later which she complained of generalized weakness associated with 1 episode of loss of consciousness and stiffness in hands and legs for 10 days. The patient did not provide any history of febrile status.

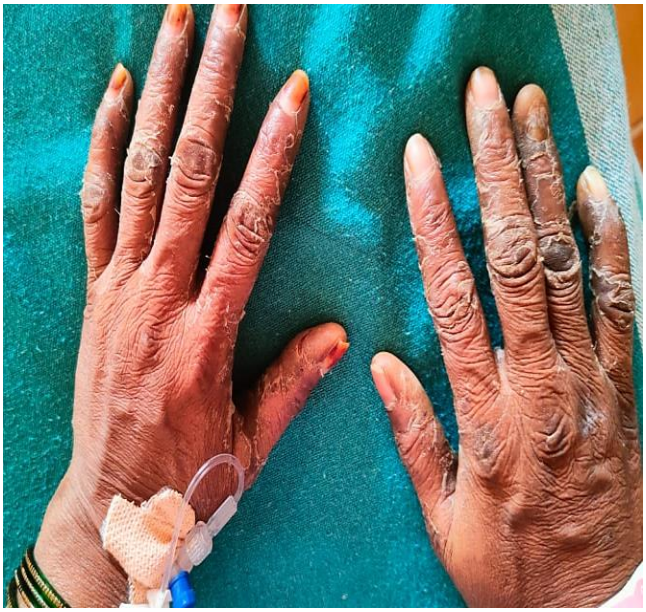

Figure 1 and 2: Rashes over hands.

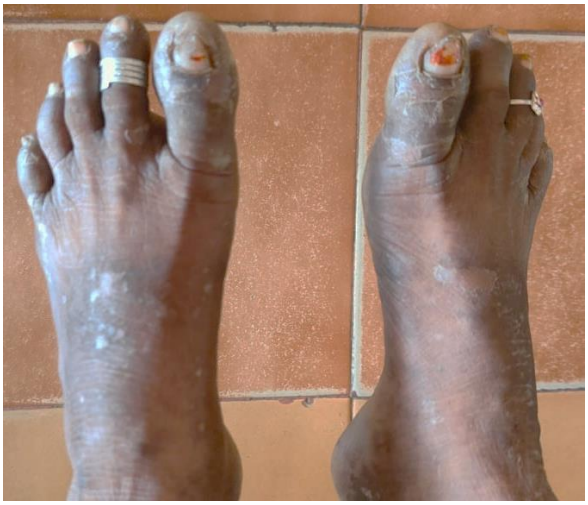

Figure 3: Rashes over limbs.

Medication history

A married female patient who is a known case of hypertension, not currently on any medications. There is no history of smoking, alcohol use, or tobacco consumption. The patient reports no known drug allergies and has no significant family history of medical conditions. Additionally, there is no history of past skin disorders or infections.

As per the history provided by the patient, on 31/05/2024, she developed heat boils over back and limb. For this, she was prescribed with Amoxicillin 500mg tablet twice a day. Post that, on 03/06/2024, patient developed the above-mentioned complaints.

Examination

On examination patient had raised blood pressure of 150/80mmHg, with pulse rate of 86 BPM. There were

multiple hyperpigmented lesions and skin peeling scars over both the hands and legs. Patient was afebrile with no symptoms of cough, breathlessness, vomiting, loose stools and Systemic examination was within normal limits. Patient was suspected for hypersensitivity reaction and was admitted in the hospital.

Relevant blood investigations were done showed raised inflammatory markers with total counts of 14540 cells/mm^3, Erythrocyte sedimentation rate of 77mm/1^{st} hour and Serum C- Reactive Protein of 24.506mg/L. Other laboratory values like complete blood picture, thyroid function test and glycated haemoglobin was found to be normal.

MRI of brain was done in view of weakness of bilateral lower limbs which showed subtle t2/flair hyperintensities in the peri-ventricular white matter of bilateral frontal and parietal lobes which were suggestive of chronic small vessel ischemia, mild cervical and lumbar spondylosis with disc bulges. The patient was planned for nerve conduction study.

Correlating the appropriate medical history and medication history obtained from the patient and her bystanders, we confirmed the diagnosis as Amoxycillin induced hypersensitivity reaction. Patient and patient party was counselled for the prognosis of the condition and patient was managed conservatively as follows.

Table 1: Diagnosis and management.

	Naranjo Adverse Drug Reaction Probability[7]				
Sr. No.	**Questions**	**Yes**	**No**	**Do not know**	**Score**
1.	Are there previous *conclusive* reports on this reactions?	+1✓	0	0	1
2.	Did the adverse event appear after the suspected drug was administered?	+2✓	-1	0	2
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1✓	0	0	1
4.	Did the adverse event reappear when the drug was readministered?	+2	-1	0✓	0
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2✓	0	2
6.	Did the reaction reappear when a placebo was given?	-1	+1	0✓	0
7.	Was the drug detected in blood (or other fluids) in the concentrations known to be toxic?	+1	0	0✓	0
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0✓	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0✓	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0✓	0	0
	Total Score				6

Taking into account of above-mentioned details, we assessed the present data using a causality assessment scale, Naranjo Adverse Reaction Probability Scale (Table 1). The outcome from this assessment was probable, confirming that this reaction has a reasonable time sequence after drug administration, matches a known response to the drug, lacks other explanations, and improves upon withdrawal of the drug.

The patient was diagnosed with a drug reaction of hypersensitivity to Amoxicillin, Newly diagnosed hypertension, subclinical hypothyroidism, prediabetes (HbA1c - 6.3%), and mild cervical and lumbar spondylosis.

The suspected drug was stopped and hypersensitivity was recorded in the patient history. Supportive management was initiated. Dermatological treatment for the drug reaction lesions on the limbs included the application of white soft paraffin and light liquid paraffin lotion (200 ml) locally in the morning and evening, and beclometasone dipropionate lotion (25 ml) also applied locally in the morning and evening. For the management of hypertension, the patient was started on Telmisartan 20 mg, to be taken once daily in the morning. Additionally, the patient received an Optineuron injection (1 ampoule in 100 ml normal saline) administered intravenously.

A neurology opinion was obtained due to the patient's complaints of weakness in both lower limbs and a history of low back pain. Neurology advised MRI brain and Nerve conduction study. Following the neurology orders, Amitryptiline- methylcobalamine 5 mg was prescribed. To strengthen the lower limb muscles, improve gait, and enhance activities of daily living (ADLs), a physiotherapy plan was advised, including balance training exercises, gait training exercises, and active range of motion (AROM) exercises.

DISCUSSION

Beta-lactam antibiotics encompass a group of drugs such as penicillins, including amoxicillins, cephalosporins, carbapenems, and monobactams. These antibiotics all

share a characteristic beta-lactam ring in their molecular structure. Allergic responses are categorised into four types: Type I (IgE-mediated), Type II (cytotoxic antibodies, which frequently include complement), Type III (antigen-antibody immune complex and complement amplified reaction), and Type IV (cell-mediated hypersensitivity).[5] Previous research indicates that around 10% of the population treated with beta lactams was susceptible to the allergic response that was recorded worldwide.[3] Prescribed medications frequently produce adverse drug responses, which can appear in various forms.[3]

Drug hypersensitivity reactions are immune-mediated responses to medicines that result in hypersensitivity. The World Allergy Organisation recommends categorising hypersensitivity responses as immediate (symptoms develop within one hour of medication administration) or delayed. Reactions might be immediate (within one hour after exposure) or delayed. Hypersensitivity responses can induce life-threatening anaphylaxis, but delayed-onset reactions are less severe. Rashes and skin lesions are the most common manifestations.[7]

Sai sunil P et al., reported similar case in 29-year-old female patient who was admitted to the hospital with complaints of a fall at home 15 days back and unable to chew and swallow. Managing skin reactions induced by amoxicillin involves early detection and discontinuation of the drug. Immediate supportive care, including fluid and electrolyte replacement, is essential. Symptoms can be treated with antihistamines and topical applications such as calamine and liquid paraffin to alleviate itching and rashes.[1] Malpani et al. reported a case of an immediate allergic reaction to amoxicillin in a seven-year-old male child who was prescribed oral syrup amoxicillin/clavulanate at a concentration of 3.3 gm/30 ml, administered at a dose of 2.5 ml twice daily, and syrup paracetamol at a concentration of 125 mg/5 ml, given at a dose of 2.5 ml three times daily. After the second dose of amoxicillin/clavulanate, taken 8 to 10 hours apart, the child developed itching and a maculopapular rash on the trunk within 30 minutes, which subsequently spread to the neck, limbs, and abdomen. Considering the child's condition, the treatment with amoxicillin/clavulanate was discontinued, and he was advised to switch to syrup cetirizine and apply calamine lotion locally to relieve the rashes and control the allergic reaction. The study highlights the importance of careful monitoring and treatment for allergic reactions.[4]

CONCLUSION

This case underscores the importance of recognizing and promptly managing hypersensitivity reactions to beta-lactam antibiotics. Clinicians should use caution in administering Amoxicillin to these patients and do skin testing for betalactams to evaluate tolerance. Reporting this instance contributes to evidence-based practice and encourages effective pharmacovigilance in adverse drug reaction reporting.[1] Patients should be informed of their amoxicillin allergy and given an ADR alert card to carry with them when consulting a doctor. Physicians should always inquire about any prior history of amoxicillin allergy before prescribing medications to ensure patient safety. This helps to prevent adverse drug reactions.[3] Due to the high incidence of adverse drug reactions associated with amoxicillin, it is crucial to closely monitor patients who are prescribed. This case demonstrates the critical role of clinical pharmacists in healthcare, particularly in identifying and managing adverse drug reactions. Their expertise ensures safe medication use and effective patient care, emphasizing their importance in multidisciplinary healthcare teams.[4]

REFERENCES

1. Priyanka C, Navya N, Datrinath V, Prasanthi M. Case Study on Amoxicillin Induced Hypersensitivity Reactions. International Journal of Pharmaceutical Research and Life Sciences, Mar. 11, 2022; 10(1): 5-8.
2. Kaur SP, Rao R, Nanda SA. Amoxicillin: a broad spectrum antibiotic. Int J Pharm Pharm Sci., May 2011; 3(3): 30-7.
3. BP SK. A Case Report on Maculopapular Skin Rash Due to Amoxicillin Hypersensitivity Reaction.
4. Malpani AK, Miya R, Teja P, Reddy BS. Amoxicillin Induced Immediate Allergic Reaction–A Case Report. Indian Journal of Pharmacy Practice, 2020; 13(2).
5. da Fonseca MA. Adverse reaction to amoxicillin: a case report. Pediatric Dentistry, Sep. 1, 2000; 22(5): 401-4.
6. CASTRO SM, SCHWARTZ RH, NAZARIAN LF. Ampicillin and Amoxicillin Delayed Hypersensitivity: Side-Chain—Specific Allergic Reactions in a Child. Pediatric Asthma, Allergy & Immunology, 1996; 10(4): 197-203.
7. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther., Aug. 1981; 30(2): 239-45.