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TOXIC EPIDERMAL NECROLYSIS INDUCED BY METRONIDAZOLE: A CASE REPORT

Medical Education

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ABSTRACT

The term adverse drug reaction (ADR) is a response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy." Drug-induced skin reactions account for 60 to 70% of the documented ADRs. Antibiotic class of medications account for about 40.9% of all the documented ADRs, some of which are associated with severe outcomes. Stevens-Johnson syndrome (SJS) is a hypersensitivity reaction to various medications or illnesses, which affects less than 10% of the entire body surface area, and toxic epidermal necrolysis (TEN), which affects more than 30% of the total body surface. The skin and mucosal surfaces of the conjunctiva, oral cavity, urethra, or genitalia are affected by these disorders to varying degrees. They are also associated with high morbidity and mortality. We report a case of metronidazole-induced TEN in a geriatric female diabetic patient. The patient was managed symptomatically, and the causality assessment of the adverse drug reaction was a "certain" reaction as per the WHO-UMC causality assessment system and Naranjo's algorithm. Hartwig's severity assessment scale categorized the reaction as "severe" in nature. Our case highlights the importance of the judicious use of antibiotics and contributes to the existing literature about this uncommon clinical presentation.

KEYWORDS

Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Drug reaction, Adverse drug reactions (ADRs).

INTRODUCTION:

World Health Organization (WHO) defined adverse drug reactions as "A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." [1]. In many countries, ADRs rank among the top ten leading causes of mortality [2]. Life-threatening conditions like Stevens-Johnson syndrome are a disease process that lies on a spectrum with one end as erythema multiforme, which can be caused by either medicines or sometimes infections, with increased severity getting to toxic epidermal necrolysis. Rapid progression of disease within a few days to weeks from erythematous macules to erythroderma to a skinny layer walled bullae formation and starts showing positive Nikolsky's sign, wherein the formed bullae are very likely to rupture, even with a touch [3]. In 90% of the cases, mucosal involvement affects oral mucosa, lips, conjunctiva, urethra, or genitalia. This condition involves an extensive skin and mucosal membrane area with systemic symptoms. It has high morbidity and mortality associated with it. A criterion used to diagnose the SJS or the TEN divides patients into groups based on the severity of skin detachment. The afflicted body surface area (BSA) parameter is used for the international classification; SJS affects less than 10% of the BSA, whereas when 10% to 30% of the body's surface area is involved, it is called SJS/TEN overlap. TEN affects more than 30% of the BSA [4]. These are similar to severe burns. The widespread epidermal loss can lead to systemic issues such as significant heat losses, electrolyte imbalance, hypovolemia, and an increased risk of infection because of the weakened functioning of the primary skin barrier.

Case Presentation:

A 75-year-old female with a known past medical history of ischemic heart disease and hypertension for the last 15 years and type two diabetes mellitus for the last 11 years. The patient presented to the emergency department of a teaching hospital with complaints of reddish skin peeling all over the body [Fig. 1, 2, and 3] suggest toxic epidermal necrolysis.

The detailed history revealed that her left great toe was infected 15 days before this presentation. Empirically, she was prescribed oral tablets of Metronidazole 400 mg three times daily, tablets of Ciprofloxacin 500 mg twice daily, and tablets of Paracetamol SOS for five days. However, on the fourth day, she noticed itching and rashes on her upper limbs and chest. The same day, she re-consulted the same doctor and was advised to continue the medications with some additional nutritional supplements. However, the patient voluntarily stopped all the medications. Within a span of another five days, these symptoms progressed to an abrupt appearance of maculopapular rash involving the torso and both the lower extremities, prompting her to visit the nearby primary government hospital, where she received treatment for three days with injections of Dexamethasone, Meropenem, Pantoprazole, and injection of Metronidazole. After receiving the treatment for three days, her condition worsened. This prompted her to visit the emergency department of a tertiary care hospital. On triage in the emergency room, she reported no allergies to any medicines before this. Her skin examination showed that her symptoms had progressed to skin lesions with pain and involvement of 80% of her body surface area in the form of dusky macules. There was epidermal detachment and a positive Nikolsky's sign of more than 50% of the body surface area, involving the back, trunk, upper limbs, and lower limbs. The patient was diagnosed with TEN based on the medical history and typical clinical features; thus, the biopsy was not required. A review of other systems was unremarkable. On examination, she had a low-grade fever of 100.4°F, blood pressure of 110/70 mm Hg, pulse rate of 122 beats per minute, and respiration rate of 20 breaths per minute. Lungs were clear on bilateral auscultation. The central nervous system showed an oriented, conscious with no abnormalities. The kidney function tests were standard. The patient was obviously in physical distress due to pain. Scaling and crushing were seen in both eyelids with no erythema or edema. The oral cavity showed multiple lesions associated with difficulty opening the mouth and pain in swallowing. She was started on supportive therapy with aggressive intravenous fluids for volume replacement. All the prescribed drugs were stopped, and intravenous Dexamethasone was started along with empirical broad-spectrum antibiotics with topical steroids and emollients. Her clinical condition improved with all the multidisciplinary treatment received at the hospital. She recovered and was discharged after the treatment.

Fig.1; haemorrhagic necrosis and detachment of the skin on face, neck, shoulder and upper chest.

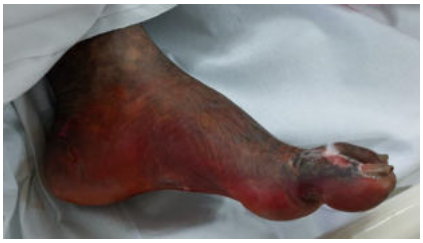

Fig.2; haemorrhagic necrosis of the skin in the patient's foot.

Fig.3; Detachment of the top layer of skin of the upper extremity (Right)

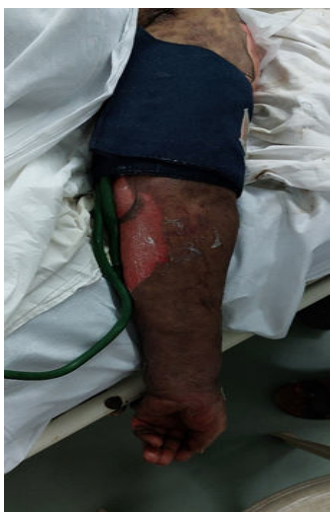

Fig.4; Detachment of the top layer of skin of the upper extremity (Left)

DISCUSSION:

Potentially fatal mucocutaneous drug hypersensitivity syndrome like SJS and TEN are characterized by blistering and epidermal sloughing. With the apparent clinical presentation and absence of upper respiratory tract infection, viral infection, or malignancy, this case can be assessed as TEN. Metronidazole kills parasites and anaerobic bacteria by damaging their DNA. Ciprofloxacin's mechanism of action is by preventing the bacterial cells from dividing and repairing, thus killing the bacteria. ADRs with metronidazole are infrequent and primarily limited to side effects such as feeling or being sick, stomach pain, hot flashes, difficulty breathing, palpitations, and headaches. On analyzing the available literature data, metronidazole was found to be the most suspected drug. There have been reported cases of severe ADRs like TEN caused by metronidazole [9, 10]. The patient was non-allergic to paracetamol as per the case history. Ciprofloxacin can also cause TEN [11], but in the above case, the metronidazole drug was unintentionally re-introduced (that is, the rechallenge was carried out). The results of the rechallenge came out as “a positive rechallenge.” There are preparations of ciprofloxacin (500 mg) and metronidazole (300 mg) available in the market with minor common side effects like nausea, vomiting, metallic taste, and headaches. There is no reported literature on ADRs of TEN due to drug-drug interaction between metronidazole and ciprofloxacin so far.

The causality assessment was done for each administered drug separately using standard systems such as the WHO-UMC causality assessment system [5] and Naranjo's algorithm [6]. The reported ADR for the drug metronidazole was found to be a “certain” category ADR. For the drug ciprofloxacin, it was categorized as a “possible” ADR. Further severity assessment was made using the Modified Hartwig and Siegel severity scale [7], which showed the ADR as a “severe” reaction. The preventability assessment was done using the Schmock and Thorton scale [8], which showed that the ADR was non-preventable. The outcome of the event was reported as recovered.

CONCLUSION:

The above case study is a TEN induced by the drug metronidazole. Metronidazole is a frequently used antibiotic and antiprotozoal medication, and its empirical use is predominant, especially in developing countries. This antibiotic can lead to severe hypersensitivity reactions such as SJS and TEN, even at therapeutic dosages. Extensive post-marketing surveillance has been done with metronidazole, as it has been an approved medication for a long time. The authors believe such ADR reporting will contribute to the post-marketing surveillance data, a continuous process throughout the drug life. Such surveillance needs to be performed continuously to determine the other risk factors for its development to establish the incidence of toxic epidemic losses and other severe cutaneous reactions and increased awareness, which can reduce the incidence of suspected drug re-administrations. Clinicians should judiciously use these drugs and discuss their potential side effects with patients before use. The ADR reporting monitoring should be encouraged and practiced from the remote primary care center to the tertiary care center.

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