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Case Study

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CIPROFLOXACIN INDUCED LYELL'S SYNDROME: A CASE REPORT

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ABSTRACT

Lyell's syndrome, also known as Toxic epidermal necrolysis (TEN), is a severe cutaneous drug reaction with a high mortality. Drugs are the most common trigger which accounts for around 65%-80% of the cases. The immune response is the possible cause in its pathomechanism. Serious adverse reactions with ciprofloxacin are rare with 0.6 percent occurrence. There is very little published information regarding ciprofloxacin-induced toxic epidermal necrolysis. We describe here a patient with TEN induced by ingestion of oral ciprofloxacin.

KEYWORDS: Toxic epidermal necrolysis, Ciprofloxacin, Nikolsky sign, emergency.

INTRODUCTION

In 1956, a Scottish dermatologist Lyell first described this syndrome. He observed that in 4 patients with skin peeling due to epidermal necrolysis of toxic origin, presented with a clinical picture of burns, and that the causes for SJS and TEN were the same.[1] Toxic epidermal necrolysis, or Lyell's syndrome, is an idiopathic, idiosyncratic, exfoliative disease of the skin and mucous membranes associated with a mortality rate between 25 and 70 percent.[2] The risk of TEN has been estimated to reach 2–3 cases per million per year.[3] TEN can occur at any age and is more common in women and the elderly.[4]

Lyell's syndrome is usually regarded as a drug-induced reaction rather than a skin disorder. The most commonly responsible agents are sulphonamides, allopurinol, antiepileptic and non-steroidal anti-inflammatory drugs.[5] In contrast, fluoroquinolones, broad-spectrum bactericidal agents, rarely cause severe cutaneous adverse reactions (SCAR) such as Lyell's syndrome and Stevens-Johnson syndrome. The management of this reaction is mainly symptomatic.

Fluoroquinolones are the most widely used drugs that have wide coverage and low profile for adverse effects. Ciprofloxacin is an antibiotic active against a broad range of bacteria. It is a relatively safer drug.[6] Only a handful of cases have been reported in the medical literature, where ciprofloxacin has been implicated. We present a case of TEN probably caused by ciprofloxacin.

CASE REPORT

A 45 year old man presented with the complaints of burning sensation, skin rash and itching of skin. A targetoid erythematous maculopapular skin rash with bulla was observed on his bilateral hands and abdominal region. It is also associated with fever. An excess peeling of skin along with intense inflammation of lips, genitalia, groins and oral cavity also occurred. Prior to admission he had been prescribed with 14 day course of ciprofloxacin therapy for cellulitis in his left leg. His symptoms started appearing after taking 4 doses of ciprofloxacin. During this time he did not take any other herbal or over the counter medications. Patient had no personal and family history of skin diseases. He is a chronic smoker and he is allergic to tree nuts and fish.

On physical examination, the patient presented with a temperature of 39.2□ C and blood pressure of 110/75mm Hg and all other vitals were in normal limits. Cutaneous examination revealed that many lesions had annular patterns with a targetoid appearance. Approximately 30% of the patient's body surface was involved with this rash. The Patient's chest X-ray was normal. Laboratory workout was performed and the results are as per Table.1.

Table 1: Laboratory data of the patient on the day of admission.

Parameter	Observed Value	Reference value
Haemoglobin	12.3g/dl	11-14g/dl
Red cells	4.7 m/mcL	4.7-6.2 m/mcL
White blood cells	11,000 c/ mcL	4500-10800 c/ mcL
Platelets	6,70,000 / mm^3	150,00-450,00 /mm^3
Neutrophils	80%	40-75%
ESR	60mm per 1st hour	1-15mm per 1st hour
C-Reactive Protein	26mg/dl	0.5-10 mg/dl
Sodium Bicarbonate	18mmol/l	20-26mmol/l
Direct bilirubin	3.52mg/dl	0-0.3mg/dl
Indirect bilirubin	0.9mg/dl	< 0.8 mg/dl
Total bilirubin	3.05mg/dl	0.3 - 1.0mg/dl
AST	34 IU/L	0-38 IU/L
ALT	37 IU/L	0-41 IU/L
GGT	28 IU/L	5-36 IU/L
Serum creatinine	0.9 mg/dl	0.5-1.2mg/dl
Serum Urea	13.7mmol/L	1.8 to 7.1mmol/L

A Skin biopsy was taken from the left hand. Skin biopsy demonstrated full thickness necrosis of epidermis and focal separation of epidermis from the dermis beneath the basal layer and mild perivascular lymphocytic infiltrate were seen in upper dermis. Pemphigoid and pemphigus could be ruled out based on negative immunofluorescence on skin biopsy.

Causality assessment was done using Naranjo's causality assessment scale [total score=8] suggest a causal relationship between the ciprofloxacin and reaction is probable and SCORTEN score was 4, indicating a high risk of mortality (58.3%).

Based on the cutaneous examination and skin biopsy, the patient was diagnosed with TEN induced by Ciprofloxacin. Ciprofloxacin was discontinued immediately. Patient was treated like a burn victim with plenty of oral fluids and a high protein diet. He was given intravenous dexamethasone and parenteral antibiotics linezolid and piperacillin + tazobactam combination. Local soframycin and topical steroids were added along with fluid and electrolyte replacement therapy.

The patient was made to lie on the sterile banana leaf in order to prevent skin from sticking to the bed. Steroids were gradually tapered off and the patient exhibited an uneventful recovery over the next 3 weeks. He was given appropriate and aggressive physiotherapy and mobilization. After 1 month, the progression of the skin lesions halted, and the general condition of the patient improved significantly.

DISCUSSION

TEN is a rare disease generally followed by exposure to drugs. It is predominantly induced by medications such as allopurinol, anticonvulsants, quinolones and non-steroidal anti-inflammatory drugs.[5] By definition, SJS and TEN involve <10% and >30% of BSA, respectively. It is a life-threatening disease that typically begins with prodromal flu-like symptoms, accompanied by the onset of a muco-cutaneous morbilliform rash, initially localized in acral areas then spreading rapidly across the body. Flaccid blisters may develop as the condition progresses, bursting rapidly and causing large areas of denudation. The skin is extremely fragile, with formation of denudations or blisters at pressure sites (Nikolsky sign). The severity depends on the extent of involvement of the skin and mucous membranes. It is usually associated with multi system involvement and a high mortality between 20% and 66% in the acute phase.[7] Females appear to have a greater predilection for developing toxic epidermal necrolysis than males.[8] SCORTEN is a tool which helps predict the risk of death by the parameters listed in Table 2.[9]

Table 2: SCORTEN severity-of-illness score	
SCORTEN parameters	**Score**
Age > 40 years	1
Malignancy	1
Tachycardia (>120/min)	1
Initial surface of epidermal detachment >10%	1
Serum urea >10 mmol/l	1
Serum glucose >14 mmol/l	1
Bicarbonate >20 mmol/l	1
SCORTEN Score	**Predicted mortality (%)**

0-1	3.2
2	12.1
3	35.8
4	58.3
≥5	90

The precise SJS / TEN mechanism is still largely unknown. Immunological mechanisms, reactive drug metabolites or interactions between these two are proposed. Interactions between CD95 L and Fas (CD 95) are directly involved in the epidermal necrolysis. Granulysin is also considered as a key mediator for disseminated keratinocyte death in SJS/TEN.[10] The histological findings of full-thickness epidermal necrosis imply that the epidermis is directly or indirectly the target of the disease process and most likely a T-cell mediated immune reaction.

The interval between drug initiation and SJS/TEN is usually 5 to 28 days.[11] The temporal relationship between ciprofloxacin administration in our patient and the onset of TEN strongly suggests ciprofloxacin's causative role. The time course was approximately four days, which is within the time frame noted to be associated with causality. Diagnosis relies primarily on clinical signs of skin lesions and histopathology.

Early withdrawal of the suspected drug is essential. TEN is an acute emergency and is potentially life-threatening unless promptly treated. Currently, there are no specific treatments that are established. Current treatments are mainly supportive with short-term pulsed corticosteroids, cyclosporine and anti-TNF as first line agents.[11-14] In severe cases or in corticosteroid unresponsive patients, intravenous immunoglobulin (IVIG) or cyclosporine may also be considered.[14] Parenteral nutrition is often seen required in patients with oral lesions. We need to administer a high protein diet as this is a hypercatabolic state. TEN patients should receive special intensive wound care to prevent further detachment, to avoid systemic complications such as secondary infections and to protect the exposed dermis.[15]

CONCLUSION

Lyell's syndrome is a severe, devastating and potentially life-threatening mucocutaneous reaction associated with the use of some medications such as ciprofloxacin. The cessation of the causative drug is a key step in the treatment of the disease. The importance of early management of patients with TEN in an intensive care unit is clearly understood as in our case. Although TEN rarely occurs with ciprofloxacin, comprehensive post-marketing surveillance is required to determine other risk factors for TEN development and to determine the occurrence of this and other serious skin reactions triggered by ciprofloxacin or other fluoroquinolones. Clinicians and clinical pharmacists prescribing fluoroquinolones should consider the possibility of SCAR and explain to their patients the risks of hypersensitivity to these agents.

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