From Blistering to Peeling: A Case Report of Ciprofloxacin-Induced Stevens-Johnson's Syndrome

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Abstract:

This report describes a possible case of Drug induced Stevens-Johnson syndrome (SJS) produced by ciprofloxacin in a 50-year-old woman with a 10-year old history of diabetes mellitus and breast cancer. The patient was diagnosed with a urinary tract infection and treated with Inj. ciprofloxacin 200mg twice daily for two days. But following the fifth dose, the patient experienced swelling in her feet, face, hands, and eyes, as well as hyper pigmentation of her skin. Her skin began to blister and peel the following day, indicating a positive Nicolsky sign. Consequently, the suspected medication, Inj. ciprofloxacin, was stopped. Although SJS is a rare adverse reaction to ciprofloxacin, the exact causes are unknown and require further elucidation. Considering the widespread use of ciprofloxacin in the adult population, close monitoring and caution in its administration are recommended. This case underscores the importance of recognizing the early signs of SJS and promptly discontinuing the suspected medication to prevent serious complications.

Keywords: Ciprofloxacin, Stevens Johnson Syndrome (SJS).

Introduction

Stevens-Johnson syndrome (SJS) is a rare, acute, serious, and potentially fatal skin reaction characterized by sheet-like skin and mucosal loss, accompanied by systemic symptoms. Medications are causative in over 80% of cases. SJS involves detached skin surface areas of less than 10% of the body surface area.[1] The annual incidence of this adverse event is estimated to be 0.045 per 100,000 treated patients, assuming a typical treatment duration of 10 days.[2]

The initial step for SJS may involve the interaction or binding of a drug-associated antigen or metabolite with the Major Histocompatibility Complex (MHC) type 1 or cellular peptide to form an immunogenic compound. This interaction creates an immunogenic compound that triggers an immune response.[3] The exact mechanism of this process is speculative. However, T-cell-mediated CD8+ cells are present in blister fluid and may induce keratinocyte apoptosis, while other cells of the innate immune system, such as CD40 ligand cells, may induce the release of TNF-alpha, nitrous oxide, interleukin 8 (IL-8), and cell adhesion antibodies. TNF-alpha also induces apoptosis, and both Th1 and Th2 cytokines are also involved. Other cells implicated in SJS include macrophages, neutrophils, and natural killer (NK) cells. T-cells and other immune cells play a role in the development of SJS, causing skin cells to die and releasing chemicals that cause inflammation and further damage.

The pharmacologic interaction of drugs with the immune system could result in the binding of the responsible drug to MHC and the T cell receptor. An alternative theory is the pro-hapten concept, in which drug metabolites become immunogenic and stimulate the immune system.[1] Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are severe types of drug hypersensitivity reactions, and antibiotics are among the significant risk factors for their development.[4] Symptoms usually appear within 4 to 28 days of continuous exposure to the triggering drug. The commonly implicated drugs have remained unchanged for the past 30 years and include allopurinol, aromatic anticonvulsants, antibiotics, and non-steroidal anti-inflammatory drugs [5, 6] especially acetaminophen drug which is widely used as antipyretic and analgesic.[7] Antibiotic use was linked to SJS/TEN in 28% of cases worldwide. The sulfonamide

class was linked to 32 percent of cases of antibiotic-associated SJS/TEN, with penicillins accounting for 22 percent, cephalosporins for 11 percent, fluoroquinolones for 4 percent, and macrolides for 2 percent.[4]

Case Report:

A 50-year-old female patient with past history of diabetes mellitus (10 years), Carcinoma (CA) breast and urinary tract infection received with complaints of reduced urine output from the past 4-day. She was prescribed and treated with Inj. ciprofloxacin 200mg and Inj. Ranitidine 50mg/2mlTwice daily (BID) followed by Tab.Metronidazole 200mg thrice daily (TID), Tab. Diazepam 5mg, Tab. B.complex, and Tab. Chlorpheniramine maleate 4mg Once Daily, Tab. Vitamin C 100mg BID, continued for two days. Laboratory findings included haematocrit: 36.3%, total WBC count: 14.7×10^3, neutrophils: 11.7×10^3, random blood sugar (RBS) 405mg/dl, post prandial blood sugar (PPBS): 372mg/dl, fasting blood sugar (FBS): 315 mg/dl were beyond standard normal limits and haemoglobin 10.2g/dl, liver function test, renal function test were normal.(Table1) On the third day after 5^{th} dose of Inj.ciprofloxacin the patient experienced hyperpigmentation on the lower extremities, face, lower arms and mucosal ulceration was observed in the mouth, genital area, and eyes, which were the secondary symptoms that appeared. As a result, the patient experienced difficulty in swallowing and opening her eyes next day. The patient's skin started to peel up with blisters (Figure1, 2). The total percentage of skin involved was 10 percent, Nikolsky's sign is a clinical test where the skin is gently rubbed or pulled to see if it detaches from the underlying layer. It is almost always present in Stevens–Johnson syndrome (SJS).[17]In this case Nicolsky sign was positive, as a result the suspected drug Inj. Ciprofloxacin was stopped. C-reactive protein (CRP) was measured using a turbidimetric immunoassay, and values below 5ng were considered normal.

On the first day of ciprofloxacin administration, the patient's CRP levels were normal. However, on the 4th day, the CRP levels were elevated, indicating an increase in inflammatory response. Subsequently, the CRP levels progressively decreased. It's important to note that typical cases of Stevens-Johnson Syndrome (SJS) are characterized by increase in serum values of lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and other inflammatory parameters, including CRP. However, the provided laboratory data only mentions CRP levels,

and there is no information on LDH, CPK, or other inflammatory parameters. Without a comprehensive set of laboratory results, it may be difficult to clarify all discrepancies and conclusively confirm or exclude SJS based solely on the data provided. Additional laboratory investigations are often necessary for a comprehensive evaluation of the patient's condition but clinical examination and dermatological picture allowed physician to make an initial diagnosis of SJS, likely triggered by the administration of ciprofloxacin. The management strategy for SJS in this case was determined by taking into accounts the patient's increased blood sugar levels and prior medical history of diabetes. High doses of corticosteroids are typically a part of the treatment regimen for SJS; however, in this particular case, it was decided not to administer corticosteroids due to the patient's uncontrolled diabetes. Given the concern of exacerbating the patient's diabetes with corticosteroid use, an alternative treatment approach was adopted. Supportive care was initiated as the initial step, focusing on hydration with continuous slow intravenous fluid administration. Additionally, for the management of mucosal ulceration in the eye, ophthalmic beclomethasone, a corticosteroid with localized action, was administered to address the specific area of concern while minimizing systemic effects. She was treated as a burn patient with massive cutaneous injuries and the concomitant systemic effects with Continuous IV fluids of normal saline at a rate 100ml/hr for hydration, Zinc cream for skin care were given.

The chosen treatment approach aimed to provide supportive care while cautiously managing the patient's diabetes and potential adverse effects associated with corticosteroid use. The decision to exclude high doses of corticosteroids was based on the consideration of the patient's medical history and the need to balance the benefits and risks of treatment. The patient's condition and response to treatment was closely monitored to ensure appropriate management throughout the course of the illness. The patient was reviewed on daily basis and by the end of 3 weeks there was a significant healing of hyper pigmentation and the exfoliated skin, the patient fully recovered without any sequelae, as shown in Figure 3 (Figure 3) and discharged home in good condition after 10 days of intravenous antibiotics. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale indicated a possible association (score = 4) between ciprofloxacin and the adverse reaction; however, the presence of multiple concomitant medications and the absence of rechallenge limit definitive causality attribution (Table 2 & 3).[8]

Discussion:

Adverse drug reactions (ADRs) remain a significant cause of morbidity and mortality, accounting for approximately 2.9–5.6% of hospital admissions. Among these, Stevens–Johnson syndrome (SJS) represents a rare but severe delayed hypersensitivity reaction, most commonly drug-induced. SJS is a type 4 delayed hypersensitivity reaction. In the present case, the temporal association between drug exposure and onset of symptoms raises suspicion of a drug-induced etiology. The onset of symptoms occurred on the third day of therapy (following the fifth dose of ciprofloxacin), with progression to blistering and epidermal detachment by the fourth day.[9] Although histopathological confirmation via skin biopsy was not performed, the diagnosis was made based on characteristic clinical features, including mucosal involvement, epidermal detachment, and a positive Nikolsky sign. In resource-limited or acute clinical settings, SJS is often diagnosed clinically to facilitate prompt management. Additionally, while laboratory markers such as LDH and CPK were not assessed, elevated CRP and the clinical presentation supported an inflammatory process consistent with SJS. The patient was concurrently receiving multiple medications, including metronidazole, which has also been reported in association with SJS. Therefore, a definitive attribution to a single drug is challenging. However, the temporal relationship observed in this case, with symptom onset following the fifth dose of ciprofloxacin, along with clinical improvement after its withdrawal, suggests a stronger association with ciprofloxacin compared to other concomitant medications. Nevertheless, the possibility of contribution from other drugs cannot be completely excluded.

Risk factors for SJS development include high doses of medication and slow metabolism. Several case reports have documented SJS induced by ciprofloxacin in the literature.[10,11] First case reported in Bangladesh in a 28-year-old female patient,[12] while some suggest a possible link to grapefruit consumption[13] there is no clear evidence to support this. Ciprofloxacin is primarily metabolized by CYP1A2 with partial CYP3A4 metabolism, while grapefruit juice strictly inhibits enterocyte CYP3A4.[14] In this particular case, a patient with a history of CA developed SJS, likely due to unnecessary antibiotic use during a routine procedure.[15]As of 2018, the top five classes of antibiotics widely used worldwide were penicillins, macrolides, tetracyclines, other β-lactams, and fluoroquinolones. These antibiotics are essential for treating various infections, but it is crucial to be aware of their potential association with severe drug

hypersensitivity reactions like SJS/TEN.[16] Systematic review examining the relationship between Amoxicillin usage and the development of Stevens-Johnson syndrome or toxic epidermal necrolysis has been published in the Journal of Chemotherapy, based in Florence, Italy, on March 14, 2022.[17] This highlights the potential risks associated with prescribing antibiotics and the importance of careful consideration before prescribing them. The primary drawback of this case report is the absence of any subsequent follow-up examinations or assessments. A limitation of this report is the absence of confirmatory skin biopsy and incomplete inflammatory marker evaluation, which restricts definitive diagnostic confirmation. This case highlights the diagnostic and causality challenges in polypharmacy settings, emphasizing the importance of structured causality assessment and cautious interpretation when multiple potential offending agents are involved.

Conclusion:

To prevent allergic reactions to drugs like ciprofloxacin or other fluoroquinolones, it's crucial to conduct extensive post-marketing surveillance to identify potential risk factors and severe cutaneous reactions. We recommend providing patients with a medical allergic card listing their known drug allergies, which should be reviewed by healthcare providers while prescribing medication. It's important to educate patients about the card's importance and to carry it with them for future hospital visits.

Informed Consent

Written informed consent was obtained from the patient’s legally authorized representative for publication of this case report and accompanying clinical images.

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Table 1: Laboratory Investigation

S.No SI.NO	PARAMETER QUESTIONS	OBSERVED VALUE YES	NO	DON'T KNOW	REFERNCE VALUE SCORE
1.	Total counts	14.7×103 cells/µL			11.0 × 10^3 cells/µL
2.	Neutrophiles	11.7× 103			40% to 75%
3.	Lymphocytes	35%			20% to 40%
4.	Eosinophiles	4%			0% to 5%
5.	Hematocrit	36.3%			37% to 47%
6.	Serum Creatinine	0.7mg/dL			0.6 to 1.2 mg/dL
7.	Blood Urea	20mg/dL			6to 21mg/dL
8.	SGOT (Serum Glutamic Oxaloacetic Transaminase):	38U/L			5 to 40 U/L
9.	SGPT (Serum Glutamic Pyruvic Transaminase)	32U/L			7 to 56 U/L

Table 2 Naranjo Scale (Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239245)

1	Are there previous conclusive reports on this reaction?	+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 re-administered?	+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	-1
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 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	+1
TOTAL = 4					

Table.3. Interpretation of score

Score	Interpretation of Scores
Total Score ≥9	Definite. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	Probable. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	Possible. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	Doubtful. The reaction was likely related to factors other than a drug.

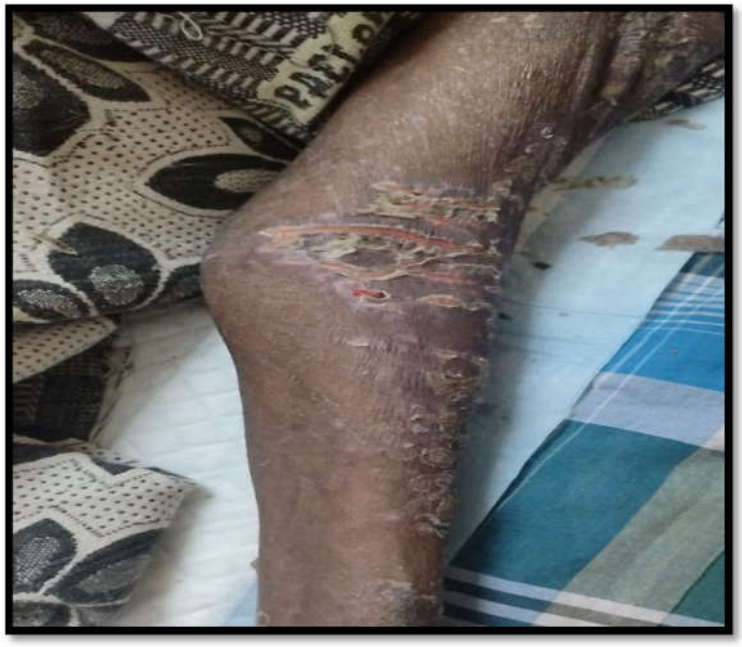

Figure 1: Blistering Skin on 4th day therapy

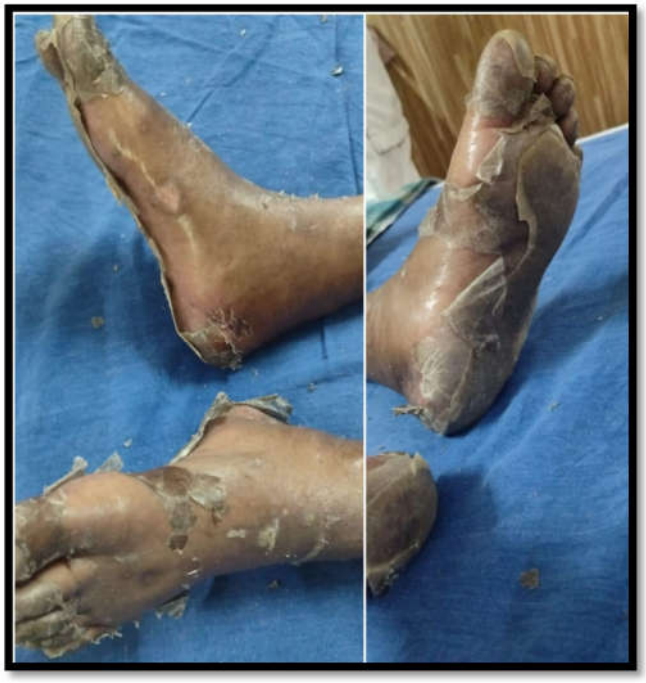

Figure 2: Peeling of Skin on Day 4 & 5

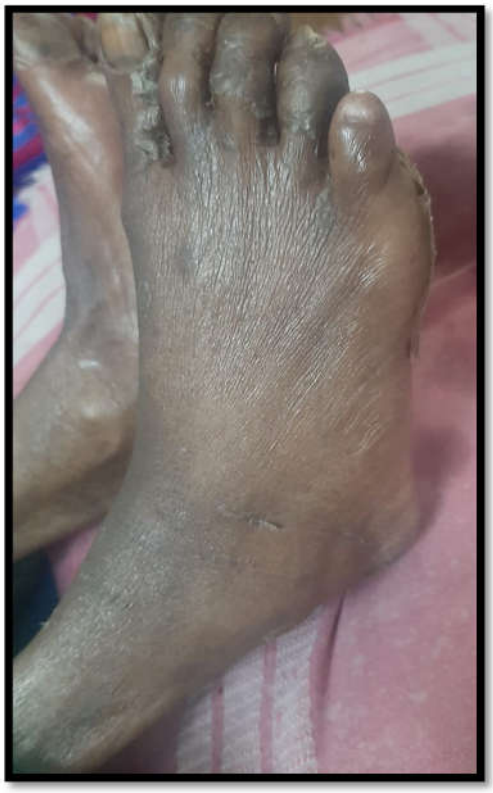

Figure 3: Condition Resolved