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CIPROFLOXACIN INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

This is a case report of 13 year old female patient, who was on Ciprofloxacin and Piroxicam tablets for the treatment of fever. Purpuric rash were developed all over the body on the 5th day from drug administration. The patient was then admitted to intensive care unit at a hospital, where her condition was diagnosed as Idiopathic Thrombocytic Purpura (ITP) or vasculitis. Later it was found that, the patient was suffering from "Drug Induced Lupus (DIL)", and the drug behind the reaction was suspected to be Ciprofloxacin. The patient was experiencing purpura rash all over the body and pustular rash all around the mouth with low levels of platelets. Ciprofloxacin induced lupus is very rarely observed, the present ADR has scored 5 on naranjo scale and is severe according to Hartwig and Siegel scale of causality assessment.

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INTRODUCTION

Among the numerous idiopathic immune-mediated diseases that can be drug-induced, such as pemphigus, psoriasis, lichen, etc, drug-induced lupus is the most widely commented upon and investigated. The first report to link lupus with a medication-sulfadiazin dates back to 1945. Morrow et al in 1953 were the first to describe a definite association between hydralazine and lupus.[1] It has been estimated that 15,000–30,000 cases of drug-induced lupus (DIL) occur in the United States every year.[2]

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations.[3] Its cause is still unknown and genetic, immunologic, hormonal and environmental factors have been implicated in its pathogenesis. The disease is more prevalent amongst women of childbearing age.

SLE is one of the two sub types of Lupus Erythematosus (LE), the other being Cutaneous Lupus Erythematosus (CLE).Oral lesions are present in 9–45% of SLE patients and in 3–20% of patients suffering from CLE. [4]

Over 80 drugs have been implicated in DIL, and the number is increasing constantly. The drugs that have been associated with DIL differ widely in their pharmacological and chemical characteristics and therapeutic indications, as indicated by their belonging to at least 10 major categories of drugs: antiarrhythmics, antihypertensives, antipsychotics, antibiotics, anticonvulsants, antithyroidals, antiinflammatories, diuretics, cholesterol-lowering (statins), biologicals, and miscellaneous. [2]

DIL is probably under-reported since most cases are mild and self-limiting once the off ending drug is discontinued. [5]

Over the past five decades, it has been recognized that certain drugs may exacerbate underlying systemic lupus erythematosus (SLE) or induce a lupus-like illness known as drug-induced lupus erythematosus (DIL) in patients with no prior history.[11]

Ciprofloxacin is a second generation fluoroquinolone, commonly used to prevent or cure bacterial infections. In the event of biological warfare, ciprofloxacin may also be used to treat and prevent dangerous illnesses that are deliberately spread such as anthrax, plague, tularemia, and anthrax of the skin or mouth.[6]

Ciprofloxacin is not recommended in pediatric population on account of its possible adverse effect on growing cartilage, however It is being commonly used for treatment of variety of infections in children very little information is available on the risks involved in its use.[6]

Although quinolones are well tolerated and relatively safe, certain adverse effects are common with all agents in this antibiotic class. Gastrointestinal and central nervous system (CNS) effects are the most frequent adverse events, occurring in 2 to 20 percent of patients treated with quinolones.[7] Ciprofloxacin is one of the drugs associated with Tendinopathy.[8] Rash, photosensitivity and pruritus are the commonly observed adverse effects in dermatologic category.[7] Ciprofloxacin is a drug suggested to induce lupus.[1] Musculoskeletal toxicity is the most frequently reported AE following the administration of ciprofloxacin.[10]

Quinolones rapidly suppress DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid lysis of bacteria. As a general rule, gram-negative bacterial activity corresponds with inhibition of DNA gyrase, and gram-positive bacterial activity correlates with inhibition of DNA type IV topoisomerase.[7]

The absolute bioavailability of Ciprofloxacin is around 70% with no significant loss by first pass metabolism. Maximum serum concentrations are achieved in 1 to 2 hours post oral dosing. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. 20 to 40% binding of Ciprofloxacin to serum proteins is seen, which is not likely to be high enough to cause significant protein binding interactions with other drugs.[6]

Although there are currently no formal classification criteria for the diagnosis of DIL, it is widely accepted that DIL is defined as the development of lupus-like symptoms (commonly fever, musculoskeletal involvement and serositis) that is temporally related to continuous drug exposure (>1 month) which resolves with cessation of the offending drug. It is usually accompanied by serologic findings of a positive antinuclear antibody (ANA) as well as anti-histone antibodies. Unlike idiopathic SLE, antibodies to dsDNA are rare. [11]

Clinical signs and symptoms

The clinical abnormalities in DIL are usually milder than those seen in idiopathic SLE, although very severe cases, some with fatal outcome, have been described (e.g., after statin therapy). Onset of symptoms can be abrupt, but more typically there are only a few mild symptoms initially, with gradual worsening over a period of weeks or even months.

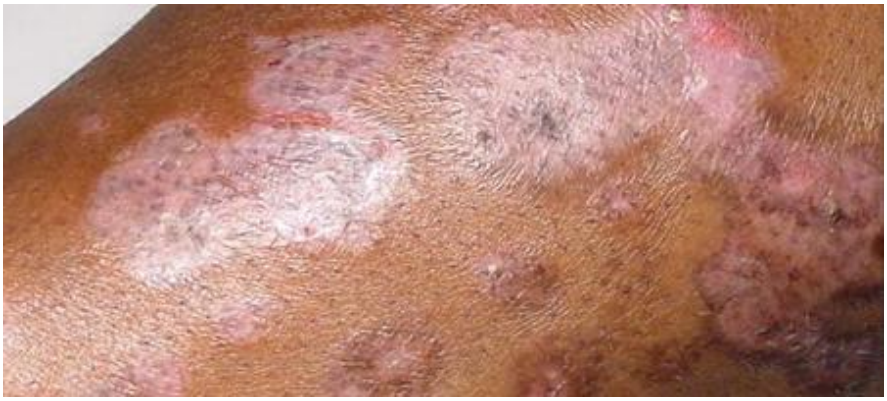
The most frequent clinical signs and symptoms of DIL are arthralgia, myalgia, arthritis, fever, malaise, anorexia, and weight loss. Cutaneous manifestations, particularly the typical butterfly rash, are much less common than in SLE, with rash (erythematosus, macular, maculopapular, urticarial, or vasculitic) being seen in5–40% of DIL patients depending on the inducing agent. Other manifestations include pleuritis/pleural effusion, pericarditis, and hepatosplenomegaly.[2]

One of the most common laboratory findings in DIL is an elevated erythrocyte sedimentation rate (ESR), occurring in up to 80% of patients. C-reactive protein (CRP) is often normal, but is markedly increased in a vast majority (89%) of patients with minocycline-induced lupus. Hematological involvement, in particular leukopenia and cytopenia, is present in 5–25% of DIL cases. Thrombocytopenia is rare in DIL in general, but has been reported in 47% (9/19) of patients with quinidine-induced lupus17 and in 4 of 12 RA patients with anti TNF-α associated lupus. Like idiopathic SLE, DIL is characterized by the presence of antinuclear antibodies (ANA), and ANA positivity has been suggested as a prerequisite for the diagnosis of DIL.[2]

The estimation of the probability that a drug caused an adverse clinical event is usually based on clinical judgment. Lack of a method for establishing causality generates large between-raters and within-raters variability in assessment.[12] There are several methods to assess causality, which includes WHO probability scale, Naranjo's scale, Karch & Lasagna scale, Spanish quantitative imputation scale, Kramer's scale, Jones scale, European ABO system and Bayesian system. The Naranjo's scale and the WHO scale of assessment are the most commonly used scales.[13]

Oral consent was taken from the patient, prior to the study.

Figure 1: Rash on the limbs



CASE REPORT

A thirteen year old female patient was on Ciprofloxacin and Piroxicam tablets for the treatment of fever. On the fifth day from drug administration, purpuric rash were developed all over the body, which were accompanied by 5 episodes of loose motions and 1 episode of vomiting. No similar history was observed in the past and the child was immunized as per schedule.

Before admission to the hospital, patient was receiving the following medications:

Tab. Cipmac 500mg (Ciprofloxacin)

Tab. Piroxicam 20mg – dispersible

Tab. Voveled SR (Multi vitamin)

The patient was admitted to Pediatric Intensive Care Unit (PICU) at Princess Esra Hospital, Hyderabad with chief complaints of purpuric rash, loose motions, vomiting, lower limbs pain and mild fever.

Vitals at the time of admission were:

Pulse rate -120/min

Respiratory rate - 30/min

Temperature - 99˚F

GRBS: 141mg/dL

On the first day, the patient was advised for CBP, CUE, ESR. and Serum electrolytes. On examination, per abdomen was found to be soft, both heart sounds were heard, bilateral airway entry was observed and central nervous system was conscious/coherent. The list of medications on the first day are depicted in table 1.

Table 2: Medications on day one

Sl. no.	Drug	Generic Name	Dose	Route	Frequency
1	IVF RL	Ringer lactate	500ml	iv	TID
2	Inj. Taxim	Cefotaxime	1gm	iv	BD
3	Inj. Amikacin	Amikacin	240mg	iv	BD
4	Inj. Zofer	Ondansetron	2cc	iv	BD
5	Tab. Sporolac	Lactic acid	1tab	po	TID
6	Rebalanz sachets	ORS	1sachet	po	BD
7	Tab P_{500}	Paracetamol	500mg	po	TID/SOS
8	Inj. Pantop	Pantoprazole	40mg	iv	OD

Complain of Hematochezia was observed on the second day. CVS, CNS and abdomen were found to be normal on examination with bilateral airway entry. The CUE, serum electrolytes and CBP reports for the first day were received, which are represented in table 2, 3 and 4 respectively. Same therapy was continued on day 2 and the patient was advised for CT, BT, PT and PTT.

Table 3: CUE on day one

Parameter	Lab value	Normal range
Epithelial cells	2-3	0
Pus cells	5-6	0
RBC	2-3	0
Crystals	nil	nil
Albumin	+	0
Sugar	nil	nil

Table 4: Serum Electrolytes

Parameter	Lab value	Normal range
Sodium	133 meq/L	130-150
Potassium	4 meq/L	3.5-5.5

Table 4: CBP

Parameter	Lab values					Normal range
	Day 1	Day 2	Day 3	Day 4	Day 5	
WBC	15.3	16.9	23.4	20	17.7	$4x10^3/mm^3$ to $10x10^3/mm^3$
RBC	4.23	3.6	3.61	3.83	3.87	$3.8x10^6/mm^3$ to $5.8\ x10^6/mm^3$
Hemoglobin	12	10	10.3	10.8	10.9	11.5 g/dL to 16.0 g/dL
Hematocrit	34.6	29.2	30.1	31.2	31.4	37 L% to 47 L%
Platelets	114	62	87	127	148	$150x10^3/mm^3$ to $500x10^3/mm^3$

On the third day, pustular rash all around the mouth were reported with pain notable to opening of mouth. The color of stool was found to be dark green. No fresh Rash were observed on the body, patient was afebrile on examination. Diffuse tenderness in abdomen and bilateral airway entry was seen with normal CVS and CNS functions. Plantars were 4/5 4/5, where as DTRS were 2+ 2+.
Reports of BT, CT, PT and PTT were received, which are depicted in table 5.

Table 5: Lab value and normal range.

Parameter	Lab value	Normal range
Bleeding Time	2:30 min	2-9 min
Clotting Time	4:15 min	5-8 min
Prothrombin Time	17.1 sec	10-20
Partial Thromboplastin Time	39 sec	20-34

Patient was referred to the Dermatologist, who has provisionally diagnosed the condition as "Ciprofloxacin induced purpura" after observing multiple petechiae and lesions all over the body. The following drugs were added to the treatment by the Dermatologist:
Tab. Hicope 10mg/OD (Hydroxyzine Hydrochloride)
Aloekin lotion BD (Aloe Vera)
Mucopain oral gel TID (Benzocaine)
150ml of Fresh Frozen Plasma (FFP) was infused to cope up with the platelet count and CBP investigation was repeated.

On the fourth day, purpuric rash on extremeties were decreased and no fresh complains were observed. On examination, patient was afebrile and both heart sounds were heard.

Patient was shifted to Pediatrics general ward (PGW) and the medications prescribed are given in table 6.

Table 6: Medications on day four

Sl. no.	Drug	Generic Name	Dose	Route	Frequency
1	IVF RL	Ringer lactate	500ml	iv	TID
2	Inj. Taxim	Cefotaxime	1gm	iv	BD
3	Inj. Amikacin	Amikacin	240mg	iv	BD
4	Inj. Zofer	Ondansetron	2cc	iv	BD
5	Tab. Sporolac	Lactic acid	1tab	po	TID
6	Rebalanz sachets	ORS	1sachet	po	BD
7	Tab P_{500}	Paracetamol	500mg	po	TID/SOS
8	Inj. Pantop	Pantoprazole	40mg	iv	OD
9	Zovelax Cream	Acyclovir	-	dermal	BD
10	Tab. Hicope	Hydroxyzine Hcl	10mg	po	OD
11	Aloekin lotion	Aloe Vera	-	dermal	BD
12	Mucopain gel	Benzocaine	-	mucous	TID

CBP reports are in table 4 and it was again repeated.

Table 7: Medications on day seven

Sl. no.	Drug	Generic Name	Dose	Route	Frequency
1	Inj. Taxim	Cefotaxime	1gm	iv	BD
2	Inj. Amikacin	Amikacin	240mg	iv	BD
3	Inj. Zofer	Ondansetron	2cc	iv	BD
4	Tab. Sporolac	Lactic acid	1tab	po	TID
5	Rebalanz sachets	ORS	1sachet	po	BD
6	Tab P_{500}	Paracetamol	500mg	po	TID/SOS
7	Inj. Pantop	Pantoprazole	40mg	iv	OD
8	Zovelax Cream	Acyclovir	-	dermal	BD
9	Tab. Polaramine	Dexchlorpheniramine	2mg	po	BD
10	Flutibact cream	Mupirocin	-	dermal	BD
11	Mucopain gel	Benzocaine	-	mucous	TID

On the fifth day, lethargy, decreased appetite and myalgia were observed. CBP reports were received, as shown in table 7. Same therapy was continued as that of day 4. On the sixth day, fever spikes, body pains and purpuric rash all over the body were observed. Both heart sounds were heard, lungs were clear, abdomen was soft and no FND was observed. Same therapy was continued on day 6. On the seventh day, vesicles over the lips and mouth were observed with pustular rash all over the body. Fever on/off with decreased appetite and lethargy was reported. Dermatologist opinion was taken for the second time. It was suspected as "Drug Induced Vasculitis". Patient was advised to undergo ANA and dsDNA tests. Therapy on day seven is depicted in table 7.

On the next day, patient appeared dull with rashes, vesicular lesions and decreased appetite.
Same therapy was continued as that of day 7.

ANA and dsDNA reports were received on the ninth day, which were positive confirming the condition as Systemic Lupous Erythematosus (SLE). The patient was then discharged and referred to a Rheumatologist for further treatment.

DISCUSSION

Ciprofloxacin is generally considered to be a safe and well-tolerated drug with mild side effects, but this is not the case in the present report. Ciprofloxacin has caused a very severe reaction upon administration to this 13 year old patient. Drug induced Lupus (DIL) is an ADR which can be experienced with drugs such as hydralazine, procainamide, isoniazid, etc. but ciprofloxacin induced lupus erythematosus is a rare case, about which there may be hardly any reports. In this case, SLE was experienced by the patient after the administration of ciprofloxacin. Earlier, this condition was diagnosed as Idiopathic thrombocytic purpura (ITP) and Drug induced vasulitis, ultimately it was after ten days Drug induced Lupus was confirmed. Although the clinical manifestations of the case were indicating SLE, but ANA and dsDNA played a vital role in confirming the condition as DIL. Even though the patient was recovering slowly with discontinuance of ciprofloxacin, re-challenge with the drug was not performed for ethical reasons.

Hartwig and Siegel scale: On this scale, the present ADR is of level 5 or 'severe'.
Naranjo's Algorithm: The present ADR has scored 5, which indicates the reaction as Probable.

Moderate: Level 4 (b): The ADR is the reason for admission.
Severe: Level 5: Any level 4 ADR that requires intensive medical care.
Score in the range of 5 to 8: Probable

Treatment

Generally, symptoms resolve within several days to weeks after ceasing the medication that caused the symptoms. NSAIDs are used to treat pleurisy and arthritis.

Corticosteroid creams are used to treat skin rashes. Antimalarial drugs (hydroxychloroquine) are occasionally used for skin and arthritis symptoms. Sensitivity to light is treated by protective clothing, sun-glasses, and sunscreen. Routine eye check-up is recommended to detect eye complications in early stages.

Sometimes, the steroid prednisone is used to treat more severe cases, especially if the heart is involved. Very rarely, high doses of steroids and strong medications that suppress the immune system, such as azathioprine or cyclophosphamide are used in severe drug-induced lupus with cardiac involvement or significant kidney or neurologic disease. It is essential not to restart the culprit medication at a later time, as symptoms will usually recur. [14]

Non-pharmacological methods should be identified for diseases, for instance dark chocolate appear to reduce risk factors for cardiovascular diseases[9]. By this way, drug induced diseases can be minimized.

CONCLUSION

Data on Ciprofloxacin induced systemic lupus erythematosus is not reported in considerable studies. The findings of this case report is new, which may help in the future for further studies to be carried out. Careful selection of drug and dose calculation should be done before prescribing a drug to a pediatric patient to avoid any untoward reaction.

CONFLICT OF INTEREST

Authors state that there is no conflict of interest.

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LIST OF ABBREVIATIONS

Abbreviation	**Full Form**	**Abbreviation**	**Full Form**
ANA	Anti Nuclear Antibodies	gm	Gram
BD	Twice a day	GRBS	Gross Random Blood Sugar
BT	Bleeding time	iv	Intravenous
CBP	Complete Blood Picture	mg	Milligram
CNS	Central Nervous System	O/E	On Examination
CT	Clotting time	OD	Once a day
CUE	Complete Urine Examination	ORS	Oral Rehydration Salt
CVS	Cardio Vascular System	po	Per oral
DIL	Drug Induced Lupus	PT	Prothrombin time
dL	Decilitre	PTT	Partial Thromboplastin Time
dsDNA	Double stranded DNA	RBC	Red Blood Cell
DTRS	Deep Tendon Reflexes Scoring	RS	Respiratory System
ESR	Erythrocyte Sedimentation Rate	SR	Sustained Release
FND	Focal Neurological Deficits	TID	Thrice a day

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