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Ciprofloxacin-Induced Thrombocytopenia: A Case Report and Literature Review

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Abstract: Background: Drug induced thrombocytopenia is associated with several usual drugs. It usually presents with stunning, chills, fever, nausea and vomiting followed by the occurrence of petechial hemorrhages and bruising. Fluoroquinolones which are a widely used antibiotics are not recognized to be common offenders. Ciprofloxacin is generally considered a safe and well-tolerated drug. It has a large spectrum and it is one of the most widely prescribed antibiotics in a broad range of infections. Purpose: Only a few cases of fluoroquinolone-induced thrombocytopenia have been reported thus this side effect is largely unknown by clinicians. Case: We report the case of a 55 year old women with a bilateral percutaneous nephrostomy secondary to a radiation-induced cystitis. She was known for chronic kidney disease KDIGO IIIb and arterial hypertension. She suffered severe thrombocytopenia on three different occasions while treated by ciprofloxacin for urinary infections. She remained asymptomatic although her platelet count dropped as low as $6\times10^3/\mu L$. Each time, her platelet count recovered within a few days after ciprofloxacin interruption. Conclusion: Clinicians should be aware of the possible relationship between thrombocytopenia and ciprofloxacin. In depth work-up should be carried out to assess relationship between a newly introduced drug and a serious clinical or biological side effect.

Keywords: Ciprofloxacin, Thrombocytopenia, Drug Induced Toxicity, Antibiotic Toxicity, Hematologic Toxicity

1. Introduction

Thrombocytopenia is a common medical issue, defined as a platelet count less than 150×10^3 per µL. A variety of disease states, disorders, hereditary conditions, environmental toxins, and drugs may cause thrombocytopenia [1]. Drug-induced thrombocytopenia (DITP) is associated with several drugs including heparin, quinidine/quinine, glycoprotein IIb/IIIa receptor inhibitors, salicylates, cimetidine, and digoxin [1-2]. The incidence of DITP varies drastically between therapeutic agents, ranging from less than 1% with most drugs up to 40% with others. Drug-induced thrombocytopenia usually presents with stunning, chills, fever, nausea and vomiting followed by the occurrence of petechial hemorrhages and bruising [3].

Antibiotics, such as sulfamethoxazole / trimethoprim, rifampicin, sulfonamides, linezolid and vancomycin, are also commonly responsible of DITP [4]. Fluoroquinolones, widely used antibiotics, are rarely recognized as drugs causing thrombocytopenia. Until recently only a few cases of fluoroquinolone-related DITP have been reported [2]. However, study has shown a correlation between thrombocytopenia and fluoroquinolone in intensive care unit patients [5]. Some cases of thrombotic thrombocytopenic

purpura (TTP) and hemolytic-uremic syndrome (HUS) associated with fluoroquinolones have been reported [2].

Ciprofloxacin is generally considered a safe and well-tolerated drug. Common side effects include neurological symptoms (dizziness, insomnia, and nervousness), gastrointestinal symptoms (diarrhea, dyspepsia, and nausea), and elevated transaminases [6]. As a fluoroquinolone antibiotic with a large spectrum, it is one of the most widely prescribed antibiotics in a broad range of infections [7] while significant side-effects are estimated to occur in less than 1% of patients [8]. Other adverse reactions associated with ciprofloxacin include interstitial nephritis, tendinitis, and vasculitis [9]. Hematological adverse effects are usually mild and seen in only 0.9–1.8% of cases [10]. The incidence of possible or probable blood disorders related to ciprofloxacin was 0.54/10,000 persons [11].

Here we describe a case of severe thrombocytopenia related to ciprofloxacin occurring on three occasions in the same patient before establishing a cause-effect relationship.

2. Case Presentation

A 55-year-old woman was admitted for acute kidney injury following a bilateral percutaneous nephrostomy, complicated by a urinary tract infection (UTI). The patient had an indwelling urinary catheter for 2 years due to radiation-induced cystitis. She was known for chronic kidney disease KDIGO IIIb and arterial hypertension. The patient had no history of smoking, alcohol, or illicit drug use. Vital signs were within normal limits and physical examination was unremarkable. Urine cultures on both nephrostomy catheters grew *Morganella Morganii*, and ciprofloxacin 500 mg BID, was started. One day later, platelet count dropped from 249×10^3/µL (D0) to 35×10^3 (D1). Ciprofloxacin was switched to Piperacillin/Tazobactam 4 gr/500 mg BID, due to persistent fever. Blood test on D2 showed platelets improvement to 55×10^3/µL, then 155×10^3/µL at D3, then 341×10^3/µL at D4 (figure 1).

On the second episode, the patient was admitted for acute pyelonephritis and treated again by ciprofloxacin 500 mg BID. After 24 hours (D1), platelet count dropped from 249×10^3/µL (D0) to 6×10^3/µL. Ciprofloxacin was switched to flucloxacillin 2 gr, 4 times per day, for 2 days, then sulfamethoxazole/trimethoprim 400/80 mg, two times a day for 10 days. Blood tests during hospitalization showed progressive increase in platelets to 29×10^3/µL at D3, 129×10^3/µL at D5 and reached their normal rate with 260×10^3/µL at D7 (figure 1) when the patient was discharged.

Causal relationship between ciprofloxacin and severe thrombocytopenia was missed on these two occasions.

The last episode occurred while the patient was admitted to the emergency department for gross hematuria. Laboratory findings revealed a chronic anemia with hemoglobin at 10,9 g/dl, a normal platelet count at 251×10^3/µL and normal leucocyte count of 7×10^3/µL. C-reactive protein level of 2 mg/L, stable renal function with a creatinine of 2,9 mg/dl. Urinalysis showed hematuria (>8000/µL), and leukocyturia (>11000/µL). A urinary tract infection was diagnosed and the patient was discharged on empirical ciprofloxacin 500 mg OD adapted to the GFR.

Four days later, the patient presented for follow up at the outpatient re-evaluation. She had no more hematuria but complained from nausea. Laboratory findings showed a drop in platelets count to 7×10^3/µL. Her physical examination was unremarkable. There was no hemorrhagic diathesis. Her urine culture grew *Staphylococcus Aureus* sensitive to ciprofloxacin and Sulfamethoxazole/trimethoprim. The patient received immunoglobulin IV 1 gr/Kg, ciprofloxacin was shifted to sulfamethoxazole/trimethoprim 400 mg/80 mg two times daily, then the patient was referred to the hematology department. Blood test on Day 5 showed platelets at 25×10^3/µL, 53×10^3/µL (D)6) and 83×10^3/µL at D8 (Figure 1). Antiplatelet IgG antibodies were unfortunately not obtained.

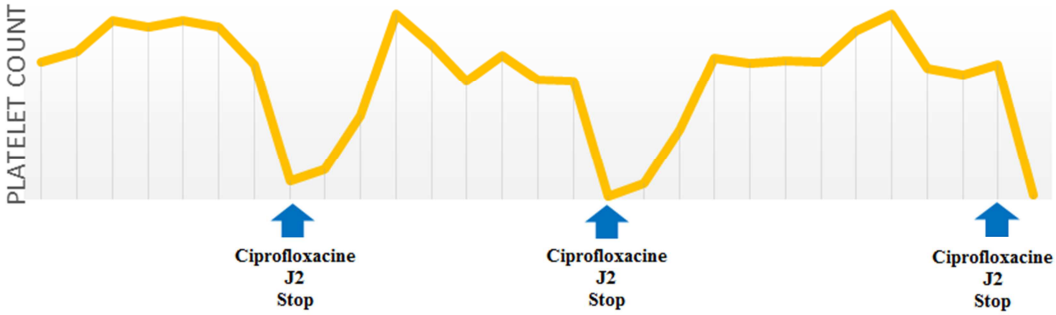

Figure 1. *First two episodes of thrombocytopenia related to Ciprofloxacin treatment.*

3. Discussion

Thrombocytopenia may be induced by exposure to certain substances (plants, food, vaccines, drugs...) [12]. While heparin is the best-known cause of DITP, there are several other drugs that can induce a severe thrombocytopenia, as quinine, sulfonamides, penicillin, cimetidine, and digoxin. The frequency of drug-induced thrombocytopenia varies drastically between therapeutic agents, ranging from less than 1% with most drugs up to 40% with others [1]. DITP can have either central or peripheral origin. Many drugs may cause an inhibition of platelet production, by direct bone marrow toxicity, as with antineoplastic agents. The most common

origin of DITP is peripheral, by platelet destruction, whether immune mediated or not. There are four different mechanisms that lead to platelet destruction; drug-protein-hapten complex formation as for heparin-induced thrombocytopenia (HIT), induction of autoantibodies that bind to specific receptors on platelet membranes, which is the mechanism of Quinine-related DITP. The two other mechanisms of DITP are exposure to new antigenic sites on a major platelet glycoproteins (GPIIb-IIIa and Ib-IX) and finally, induction of structural changes on Glycoprotein IIb-IIIa receptors, which is then recognized by antibodies [1].

Fluoroquinolones, as a class effect, can induce drug-dependent platelet-reactive antibodies causing complement-mediated destruction of platelets. The mechanism of fluoroquinolone-induced thrombocytopenia might be explained by the chemical similarities shared with quinine, which is well known to cause platelet-reactive antibody-mediated immune thrombocytopenia, HUS and TTP [4], by induction of autoantibodies that bind to specific receptors on platelet membranes. The pre-existence of these auto-antibodies, before any further exposure to the drug, is probably responsible of the fast onset of fluoroquinolones DITP, which is similar to what we observed with our patient since the first episode of thrombocytopenia.

Several studies did not mention any hemostatic or platelets dysfunction when ciprofloxacin is used at therapeutic doses [13, 14]. To our knowledge, no study has reported platelet dysfunction or more generally any other kind of hemostatic disorders under ciprofloxacin at a therapeutic dose, platelet disorders reported in the literature are mainly quantitative. A follow-up study of ciprofloxacin users has reported one single case of thrombocytopenia over 37 233 patients. In addition, an international trial data post of 8861 patients [15] reported four cases of thrombocytopenia in the UK. We proceeded to a review of reported cases of DITP associated with Ciprofloxacin, using MEDLINE (Table 1), and found six cases [1, 2, 4, 12, 15, 16] of isolated thrombocytopenia induced by ciprofloxacin, have been reported, including 4 women and 2 men, with a time to onset of thrombocytopenia varying between 1 to 5 days after starting ciprofloxacin. No patient died. Eight other cases have been reported, including three cases of pancytopenia, and five cases of HUS/ PTT.

Table 1. *Review of the reported cases of drug-induced thrombocytopenia associated with Ciprofloxacin.*

Case report	Sex	Age	Adverse effect
Erdemli Ö, et al. Ciprofloxacin-induced severe thrombocytopenia. Kaohsiung J Med Sci. 2015	W	61	Isolated DITP
Starr JA, et alk. Thrombocytopenia associated with intravenous ciprofloxacin. Pharmacotherapy. 2005	W	72	Isolated DITP
Cheah CY, et al. Fluoroquinolone-induced immune thrombocytopenia: a report and review. Intern Med J. 2009	M	76	Isolated DITP
Santucci R, et al. Thrombocytopénie induite par la ciprofloxacine. Med Mal Infect. 2012	M	63	Isolated DITP
Sim DW, et al. Ciprofloxacin-induced immune-mediated thrombocytopenia: No cross-reactivity with Gemifloxacin. J Clin Pharm Ther. 2018	W	77	Isolated DITP
Teh C, McKendrick M. Ciprofloxacin-induced thrombocytopenia. J Infect. 1993	W	80	Isolated DITP
Tuccori M, et al. Severe thrombocytopenia and haemolytic anaemia associated with ciprofloxacin: a case report with fatal outcome. Platelets. 2008	M	30	PTT/ Fatal
Allan DS, et al. Ciprofloxacin-associated hemolytic-uremic syndrome. Ann Pharmacother. 2002	M	53	SHU
Aydogdu I, et al. Autoimmune haemolytic anaemia and thrombocytopenia associated with ciprofloxacin. Clin Lab Haematol. 1997	M	42	AHAI + DITP
Hashmi HR, et al. Ciprofloxacin-Induced Thrombotic Thrombocytopenic Purpura: A Case of Successful Treatment and Review of the Literature. Case Rep Crit Care. 2015	W	49	PTT
Mouraux A, et al. Purpura thrombotique thrombocytopenique fulminant au décours d'un traitement par ciprofloxacine. Rev Neurol (Paris). 2002	W	43	PTT/ Fatal
Chaudhry M, et al. Bone marrow suppression: a side effect of ciprofloxacin therapy. Am J Ther. 2010	W	50	Agranulocytose
Dutta TK, Badhe BA. Ciprofloxacin-induced bone marrow depression. Postgrad Med J. 1999	M	24	Pancytopénie
Dutta TK, Badhe BA. Ciprofloxacin-induced bone marrow depression. Postgrad Med J. 1999	M	25	Pancytopénie / Fatal

In a review of fluoroquinolone-induced thrombocytopenia, ciprofloxacin represented 8/29 cases. Thrombocytopenia reached its nadir at a mean time of 9.6 days. [4]

Reports of DITP are common. It is difficult in many cases to confirm the causality between the suspected drug and thrombocytopenia. Re-challenging a patient with a suspected causative agent solely to confirm the diagnosis could be risky and usually not recommended [1]. Our patient received ciprofloxacin on two additional occasions after the first episode of thrombocytopenia. A causal relationship between the drug and thrombocytopenia has escaped our vigilance. The Adverse Drug Reaction (ADR) Probability Scale [17], developed in 1991, is a method by which to assess whether there is a causal relationship between an identified untoward clinical event and a drug [18] using a simple questionnaire to assign probability scores. The scores assigned are as follows: definite ≥ 9, probable 5 to 8, possible 1 to 4, doubtful ≤ 0 [17]. According to the ADR probability score, a definite relationship existed between the thrombocytopenia observed and the use of ciprofloxacin in our patient with a score of 10.

In a systematic review of published case reports of DITP [19], George JN et al developed and used standard criteria to evaluate causality (definite, probable, possible or unlikely) and did not find any evidence for ciprofloxacin as a definite or probable cause of the thrombocytopenia in most of the cases. Among 515 cases reports related a definite or probable causal role for the drug in only 48 % of cases. Women were found to be at higher risk (59 %) than men, in accordance with their systematic review [19]. Again, the application of the George JN criteria in our case supports the existence of a definite causality effect between the thrombocytopenia observed and the use of ciprofloxacin in our patient.

This observation underlines the fact that in the event of an explained severe thrombocytopenia in a polymedicated patient, the responsible drug should be identified as quickly as possible and replaced by an alternative medication. Tools such as ADR can help in this process. The first action is to discontinue the offending drug, which allows, in most cases, platelets count recovery [1]. Platelets' transfusion could be indicated in persistent severe thrombocytopenia ($\leq 2\times10^3/\mu L$) [20], due to high risk of complications such as cerebral hemorrhage. Intravenous immunoglobulin, plasma exchange and administration of corticosteroids have been reported in a few severe cases, with uncertain benefit [12]. A retrospective analysis of the use of corticosteroids in 309 cases of DITP, didn't show any beneficial effect on the recovery time between the patients receiving corticosteroids and those who didn't [20].

4. Conclusion

Thrombocytopenia may result from various causes. Fluoroquinolones as ciprofloxacin emerge as a cause to be aware of.

In this case, we reported occurrences of thrombocytopenia in a female patient exposed to ciprofloxacin on three occasions. A definite relationship between the thrombocytopenia and the use of ciprofloxacin in our patient was made according to the ADR score.

Our review suggest that ciprofloxacin induced acute thrombocytopenia remains a rare occurrence.

This shows the need for practitioners and patients to be aware of this risk. Complete work-up to exclude drug toxicity associated with the introduction of new drugs in case of clinical or biological (serious) adverse effect should be carried out.

Declaration of Interest

The authors have no relevant financial or nonfinancial interests to disclose.

Ethical Approval and Consent

The patient gave his written informed consent for this publication. Document available on request.

Disclosures

The authors have no relevant financial or nonfinancial interests to disclose.

Data Availability Statement

All data are available upon request from the corresponding author.

Author Contributions

Conception and design, acquisition of data or analysis and interpretation of data: AO, MTS and PC

Drafting the article: AO, MTS and PC

Final approval of the version published: AD, JC, VCP, AE

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