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Azithromycin-induced severe Thrombocytopenia: A rare entity

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Abstract

An 81-year-old female presented with hematuria, epistaxis and ecchymosis. She was started on azithromycin five days ago for acute pharyngitis. Examination displayed ecchymosis, dark black clots in nostrils and oral cavity, and platelet count of $5x10^9$/L. The diagnosis of azithromycin-induced severe thrombocytopenia was made. Patient received 2 units of platelets, 1g/kg intravenous-immunoglobulin (IVIG), and Intravenous (IV) dexamethasone for 5 days. Her platelet level began increasing to $116x10^9$/L by Day 3. Two days after discharge, the platelet count was 270 $x10^9$/L. During follow-up 1 month later, there was no further episode of thrombocytopenia. Azithromycin-induced severe thrombocytopenia is a very rare adverse effect. Discontinuing the medication usually improves symptoms within 2 days, and platelet count increases to normal range within a week.

Keywords

azithromycin; intravenous-immunoglobulin; drug-induced thrombocytopenia; platelet count; hematology

Abbreviations

IVIG: intravenous-immunoglobulin; DITP: Drug-induced thrombocytopenia; ITP: immune thrombocytopenic purpura; TTP: thrombotic thrombocytopenic purpura; HUS: haemolytic uremic syndrome; DIC: disseminated intravascular coagulation.

Introduction

Drug-induced thrombocytopenia (DITP) is a well-established but underdiagnosed condition. The condition is mostly asymptomatic, but can also cause severe bleeding [1]. Thrombocytopenia is a well-known side effect of treatment with several types of medications. Therapeutic agents, specifically those used for chemotherapy and immunosuppressants, tend to repress hematopoiesis and generate pancytopenia [2]. Azithromycin is a macrolide antibiotic used for bacterial infections (i.e., respiratory, urogenital, dermal), and has immunomodulatory properties to fight chronic inflammatory disorders [3]. This drug is easy to take and has minimal adverse effects including diarrhea, abdominal pain, and mild headache [4]. Although DITP cases are well-known, severe thrombocytopenia caused by azithromycin is very rare. In fact, to our knowledge, there are no previous cases reported on this.

Case Presentation

An 81-year-old female with a history of type II diabetes mellitus presented to emergency department for hematuria, epistaxis and ecchymosis for 3 days. She was started on azithromycin five days ago for acute pharyngitis.

Physical examination displayed generalized ecchymosis of varying sizes ranging from 0.5 to a few centimeters in diameter. There was no lymphadenopathy. She also had dark black clots in nostrils and oral cavity, but no signs of active bleeding. Labs showed platelet count of $5x10^9$/L (Figure 1). Drug-dependent antibody testing was done , antibodies to platelets was negative however the sensitivity and specific of this test is not 100% and there was very high clinical suspicion of medication induced thrombocytopenia. Other differential diagnosis includes hypersplenism, sepsis, autoimmune disorder, immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), and drug-induced thrombocytopenia (DITP).

The patient was only on azithromycin, and the initial step was to stop administering this drug. Patient received 2 units of platelets, 1g/kg intravenous-immunoglobulin (IVIG) once, and IV dexamethasone for 5 days. The next day, platelets count increased to $60x10^9$/L, and to $116 x10^9$/L on day 3 (Figure 1). The blood smear showed normal morphology for both red blood cells (RBC) and platelets. She had normal white blood count, haemoglobin level, and mean corpuscular volume. The activated partial thromboplastin time (PT/APTT), fibrinogen level, and complete metabolic profile were normal, with no schistocytes on blood smear, and negative antithrombocyte antibodies. Blood culture was negative for bacterial infection. Autoimmune workup was negative, including antinuclear antibodies (ANA), rheumatoid factor, anti dsDNA. In addition, tick-borne disease panel for babesiosis, lyme, anaplasmosis, and ehrlichiosis was negative. Hepatitis viral panel was non-reactive for hepatitis A, B, or C., non-treponemal, and Epstein-Barr virus (EBV) antibodies were negative. Furthermore, no splenomegaly was shown in ultrasound abdomen.

A follow-up of complete blood count was completed 2 days after discharge, showing a platelet count of 270×10^9/L (Figure 1). During interval follow-up 1 month and 6months later, there was no further episode of thrombocytopenia.

Discussion

Azithromycin can induce thrombocytopenia but severe thrombocytopenia is a rarely reported, with an estimated 10 per million affected by DITP annually[5-7].

Thrombocytopenia becomes clinically evident when patients are exposed to the sensitizing medication. Once an antibody is made, exposure to the sensitizing drug may produce symptoms such as faintness, chills, fever, nausea, hypotension, and even syncope in patients with high titer antibodies[6]. Typical symptoms in DITP range from asymptomatic thrombocytopenia to life-threatening hemorrhage, and thrombotic thrombocytopenia purpura and haemolytic-uremic syndrome have been associated in severe cases. The onset is often rapid, and the platelet count is usually below 20×10^9/L [1,2].

The etiology of DITP is complex and can be either low platelet production or high platelet

destruction. Most medications hasten platelet destruction through immune or less commonly non-immune mediated reaction. At least 100 types of medications were suggested as possible causes of drug-dependent, immune thrombocytopenia, including: cinchona alkaloids, non-steroidal anti-inflammatory agents, various antibiotics including sulfamethoxazole and vancomycin, anticonvulsants and sedatives, and the platelet inhibitors [6]. Table 1 includes a list of agents commonly suspected to cause thrombocytopenia [8]. DITP must only be reviewed in patients with acute thrombocytopenia of unknown cause. A comprehensive review of drug exposure history should be taken [6].

The diagnosis of DITP is made after other causes are excluded in the patient, or by finding an antibody that reacts with normal platelets in the presence of a drug taken by the patient. Level of evidence 2 (criteria 1-3) was fulfilled in evaluating causative relationship in DITP, since: therapy with azithromycin occurred before thrombocytopenia (Criteria 1); platelet count rapidly recovered after discontinuing azithromycin (Criteria 2); azithromycin was the only drug taken before having thrombocytopenia (Criteria 2); and other causes were ruled out (Criteria 3). Thus, this is a probable case of DITP [6,8]. Mycoplasma infection was not suspected because of patient's history and clinical signs/symptoms.

This case reported rapid normalization of platelet count in 3 days after discontinuation of azithromycin. The quick recovery for this patient is unusual with this medication since the half life of azithromycin is 68-72 hours, or even longer for older patients like this. For normal cases at that time, half of the drug would still be in the body. Gradual normalization of platelet count would be more in line with DITP caused by this long-acting medicine. If thrombocytopenia is caused by a drug dependent antibody, drug would be maintained in the patient for several days follow cessation of the drug leading to prolonged thrombocytopenia.

Initial treatment for immune-mediated DITP is to discontinue the medication, causing symptoms to be improved within 2 days and platelet count increases to normal range within a week [1,2]. Our patient's platelets count began increasing on day 2, and became normal in 3 days by after discontinuing antibiotics and receiving IVIG and steroids. The patient was advised to avoid azithromycin in the future for antimicrobial treatment. With myelo-suppressive medications, thrombocytopenia is also managed with platelet transfusion [1,9]. In patients with life-threatening bleeding, second-line treatment, such as IVIG and/or steroids and plasmapheresis, can be administered. Platelet transfusion is used when thrombocytopenia is severe with high risk of spontaneous hemorrhage, or when the patient is showing signs of intracranial hemorrhage [1,8,9].

Conclusion

In conclusion, DITP is well-documented but often unrecognized by clinicians. DITP caused by azithromycin is very rare. There are no previous cases reported on this. Initial treatment for immune-mediated DITP is to discontinue the medication. In cases of life-threatening bleeding, second-line treatment, such as IVIG and/or steroids, plasmapheresis, or platelet transfusion can be administered.

Table

Table: List of Drugs that Cause Thrombocytopenia

LIST OF DRUGS THAT CAUSES THROMBOCYTOPENIA (WITHOUT ANTI-NEOPLASTIC DRUGS)	EXAMPLES
QUININE/QUINIDINE GROUP	Quinine, Quinidine
HEPARIN	Regular unfractionated heparin, Low molecular weight heparin
ANTIMICROBIALS	Cephalosporins (Cephamandazole, Cefotetan, Ceftazidime, Ciprofloxacin), Clarithromycin, Fluconazole, Fusidic acid, Gentamicin, Nilidixic acid, Penicillins, Pentamidine, Rifampin, Sulpha group (Sulfamethoxazole), Suramin, Vancomycin
ANTI-INFLAMMATORY DRUGS	Acetaminophen, Salicylates (Aspiring, Diflunisal, Sodium amiosalicylate, Sulfasalazine), Diclofenac, Fenoprofen, Ibuprofen, Indomethacin
CARDIAC MEDICATIONS AND DIURETICS	Digoxin, Digitoxin, Amiodarone, Procainamide, Alprenolol, Captopril
ANTI-EPILEPTIC DRUGS	Carbamazepine, Phenytoin, Valproic Acid
H2-ANTAGONISTS	Cimetidine, Ranitidine
SULFONYLUREA DRUGS	Chlorpropamid, Glibenclamide
RETINOIDS	Isotretinoin
ANTIDEPRESSANTS	Amitriptyline, Desipramine, Doxepin, Imipramine
MISCELLANEOUS DRUGS	Tamoxifen, Actinomycin-D, Aminoglutethimide, Danazole, Desferrioxamine, Ticlopidine

Figure

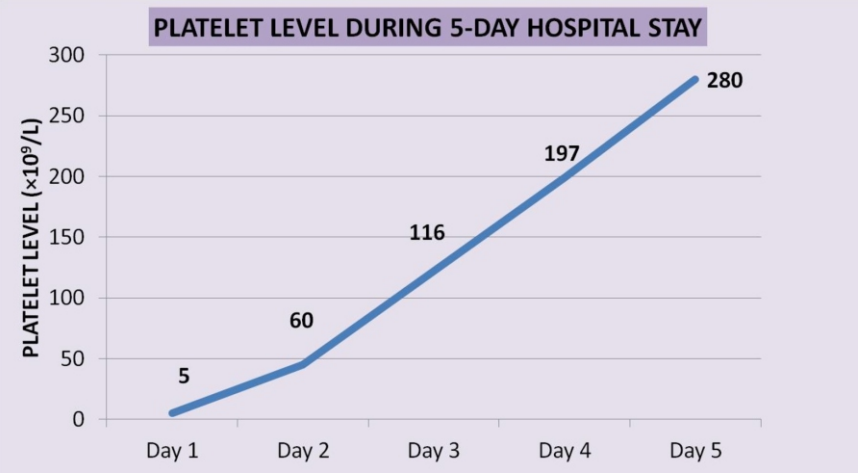

Figure: Platelet Level During Patient's 5-Day Hospital Stay

Initial labs showed platelet count of $5x10^9$/L. The next day, platelets count increased to 60,000, and to 116,000 on day 3. A follow-up of complete blood count was completed 2 days after discharge, showing a platelet count of $270×10^9$/L.

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References

1. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med. 2007;357:580-7.

2. Arnold, DM, Nazi I, Warkentin TE, Smith JW, Toltl LJ, George JN, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfus Med Rev. 2013;27:137-45.

3. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther. 2014; 43: 225-45.

4. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med. 1991; 91: S40-5.

5. Kaufman DW, Kelly JP, Johannes CB, Sandler A, Harmon D, Stolley PD, et al. Acute thrombocytopenic purpura in relation to the use of drugs. Blood. 1993;82:2714-8.

6. Reese JA, Li X, Hauben M, Aster RH, Bougie DW, Curtis BR, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood. 2010; 116:2127-33.

7. Polprasert C, Prayongratana K. Levofloxacin-induced severe thrombocytopenia. J Med Assoc Thai. 2009; 92: S69-71.

8. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7:911-8.

9. Visentin GP, Liu CY. Drug-induced thrombocytopenia. Hematol Oncol Clin North Am. 2007;21:685-96.

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