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Acute Severe Thrombocytopenia Event Associated with Trimethoprim/Sulfamethoxazole Use

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Abstract

Objective: To report a case of life-threatening thrombocytopenia associated with the use of trimethoprim/sulfamethoxazole (TMP/SMX) therapy.

Report of the case: 50-year-old woman with no significant past medical history who presented with one day of petechial rash on her arms, chest and legs. Patient reports that she had just completed a 7- day course of TMP/SMX (1-double strength tablet twice a day) for uncomplicated UTI by her PMD. On admission, the patient was hemodynamically stable, and complete blood cell count revealed a platelet count of 2000/uL. TMP/SMX was believed to be the most likely cause of thrombocytopenia. After discontinuation of TMP/SMX and treatment with 2 units of platelets, 1gm intravenous immunoglobulin (IVIG) and oral dexamethasone, repeat CBC showed a stable platelet count of 90,000/uL. Patient was successfully discharged on hospital day 3 with outpatient follow up with the hematology clinic for further monitoring.

Conclusion and Discussion: Differential diagnosis of severe thrombocytopenia include drug induced thrombocytopenia (DITP), thrombotic thrombocytopenic purpura (TTP), post transfusion purpura (PTP), immune thrombocytopenic purpura (ITP), heparin induced thrombocytopenia (HIT), or catastrophic antiphospholipid antibody syndrome (APS). Drug-dependent antibodies are an unusual class of antibodies that bind firmly to specific epitopes on platelet surface glycoproteins only in the presence of the sensitizing drugs. DITP typically has an abrupt onset of severe thrombocytopenia, usually less than 20,000/uL. Thrombocytopenia usually begins to recover within 1-2 days after the offending drug is discontinued and platelet levels usually normalize within one week as demonstrated in our case report. Pharmacological treatment can include platelet transfusions in case of severe, overt bleeding, corticosteroids or IVIG administration. In most cases, however, discontinuation of the offending drug is sufficient.

Keywords

thrombocytopenia; trimethoprim/sulfamethoxazole; bactrim; adverse drug reaction

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1. Introduction

Drug-induced immune hemolytic anemia (DIIHA) and drug-induced immune thrombocytopenia (DIIT) are rare but serious complications of pharmacotherapy with TMP/SMX. DIIT is often unrecognized; failure to diagnose this condition can result in unintended re-exposure to the drug and increased bleeding risk. [1] TMP/SMX has been available for use in the United States since 1974. TMP/SMX, formerly known as cotrimoxazole is a unique preparation, is specifically formulated to include a combination of agents that are able to inhibit two sequential steps of bacterial metabolism. [2] Side effects of TMP/SMX include pharmacodynamically predictable reactions (type A reactions) such as mild gastrointestinal symptoms, dose related bone marrow effects such as neutropenia, megaloblastic changes and hyperkalemia. Rarely idiosyncratic reactions (type B reactions) can also be seen, including severe liver failure, skin rash, sepsis-like hypersensitivity reaction/hypersensitivity syndrome, and early onset bone marrow changes, such as leukopenia, agranulocytosis, thrombocytopenia and anemia. [2] In this report, we present a case of severe and potentially life-threatening thrombocytopenia possibly associated with TMP/SMX therapy.

2. Case Description

We report a 50-year-old female who presented with one day of petechial rash on her arms, chest and legs. Patient reports that she had just completed a 7-day course of TMP/SMX (1-double strength tablet twice a day) for uncomplicated UTI by her PMD. Of note, the patient was seen 2 weeks prior at her PMD and a complete set of labs were obtained, which were within normal limits per chart review. Two days prior to hospital admission, she had been feeling more fatigued than usual, noticed some itchiness in her chest and took diphenhydramine without relief. The morning of admission she felt that the rash had worsened, which prompted her ED visit. Patient denied any history of bleeding or clotting disorders and there was no family history of hematological conditions. She denied the use of any recent medication aside from diphenhydramine and TMP/SMX. She reports no epistaxis, no hemoptysis, no hematuria, no hematochezia, no menorrhagia and no gingival bleeding. There were no other pertinent findings on review of systems.

Initial vitals, BP 138/97, HR 101, RR 19, S_pO₂100% RA (room air), Temp. 98.8F. Physical exam was notable for petechiae most prominently on the lower legs bilaterally. Laboratory findings were as follows: CBC (complete blood count) Hb 13.1 g/dL; Htc, 41.1%; WBC (white blood cell count) 2710/uL; Plt (platelet) 2000/uL; CMP (comprehensive metabolic panel) wnl; Absolute Reticulocyte Count .0364 M/uL; aPTT wnl; INR wnl; LDH 237 u/L; Haptoglobin wnl, D-Dimer 864 ng/mL; UA wnl; ESR wnl; CRP wnl; SARS-COV-2-PCR negative; HIV negative; HCV negative; Peripheral Smear RBC: normocytic normochromic cells, no schistocytes, no NRBCs, no tear drop cells; WBC: decreased in number, granular lymphocytes and plasmacytoid lymphocytes seen, no other immune cells seen; Platelets: barely visible, no clumps, no large platelets. CTH (computed tomography head) scan performed to rule out intracranial bleed, showed no acute findings. Hematology was consulted, and the patient was admitted to internal medicine for further workup of thrombocytopenia of unknown etiology.

During hospital admission stay, the patient was given 2 units of platelets and 1gm IVIG for 2 days. Repeat CBC showed adequate platelet recovery to 90,000 without any further decrease in platelets after therapy and removal of the offending agent. Patient denied further symptoms of spontaneous bleeding or bruising. Patient was hemodynamically stable and was discharged on hospital day 3 and was to continue dexamethasone 40mg daily for an additional 4 days. She was instructed to return to the hematology clinic for a 2-week follow-up. CBC results from her clinic follow-up (2 weeks from discharge) revealed continual of platelet count recovery to 227,000.

3. Discussion

DITP is an idiosyncratic immune-mediated reaction. Drug-dependent antibodies are an unusual class of antibodies that bind firmly to specific epitopes on platelet surface glycoproteins only in the presence of the sensitizing drugs. DITP can result from three different processes: a) direct injury to the bone marrow consequently affecting its thrombopoietic function, b) immune-mediated process with the antibody production, and c) formation of haptens. [3] It has been proposed that the sensitizing drugs typically contain structural elements that enable them to bind to both the antibody and platelet surface proteins. Studies have shown that the drugs bind noncovalently and reversibly to platelets, commonly to sites on GP IIb-IIIa and/or GP Ib-V-IX, and also to the antibody. This forms a tight bond between the antibody and platelet epitope. Upon exposure to the sensitizing drugs, antibodies are induced and are selected on the basis of the ability of their Fab domains to recognize the drug bound to the platelet epitope. These antibodies can be IgG or IgM in nature. These antibodies occur after exposure to a new drug for 1-2 weeks or even after intermittent use for a long time. These antibodies can also target red cells and neutrophils, but for unknown reasons, platelets are more affected. It has been indicated that overall 0.22% of blood dyscrasias (including thrombocytopenia) are associated with TMP/SMX therapy. [4] Mortality rates of 30% in adults have been observed in previous small retrospective studies. DIIHA from treatment with TMP/SMX is a rare entity. There are seven reported cases in the English literature. Thrombocytopenia due to TMP/SMX occurs more frequently than DIIHA, with 50 cases reported in the literature and seven reported cases of DIIHA. Severe thrombocytopenia can point to a limited number of diagnoses including DITP, TTP, PTP, ITP, HIT, or catastrophic APS. In previously asymptomatic patients, DITP is often misdiagnosed as ITP with resulting inappropriate treatment. In addition, some patients will not report self-administered medications, beverages or foods because they do not think these are relevant to their bleeding symptoms. [3] Usually, the patient in question has a history of drug exposure of at least five to seven days. The following clinical criteria are used to evaluate such patients:

1.	Therapy with the suspected drug was instituted prior to the development of thrombocytopenia and the resolution of thrombocytopenia occurred after the discontinuation of the suspected drug
2.	Only the suspected drug was used before the onset of thrombocytopenia and the platelet count was normal or continued to rise toward normal range with continuation or reinstitution of other drugs after the suspected drug was discontinued

3.	Other causes for thrombocytopenia were excluded
4.	The suspected drug resulted in the recurrent thrombocytopenia on re-challenge or re-exposure

Level of evidence	Criteria met	Comments
I	1, 2, 3 and 4	Suspected drug is a definite cause
II	1, 2 and 3	Suspected drug is a probable cause
III	1 only	Suspected drug is a possible cause
IV	1 is absent	Suspected drug is unlikely to be a cause

(adapted from www.ouhsc.edu/platelets).

Our patient meets the level of evidence II, and thus TMP/SMX was suspected as a probable cause for thrombocytopenia. In terms of detection of the offending antibodies, serological assays that test a patient's serum against normal platelets in the presence and absence of the drug can be used. The test shows the presence of drug-dependent antibodies and may help to confirm the etiology of thrombocytopenia. However, these tests have low sensitivities and are not available at all medical centers.

DITP typically has an abrupt onset of severe thrombocytopenia, usually less than 20,000/uL. As is seen historically, the recovery of thrombocytopenia begins within 1-2 days after the drug is discontinued. Platelet levels usually normalize within one week. Pharmacological treatments include platelet transfusions in case of severe, overt bleeding and corticosteroids. In most cases, discontinuation of the offending drug is sufficient. When corticosteroids are required, they are effective in up to 90% of cases due to anti-inflammatory and thrombopoietic effects. IVIG is usually the second line of therapy due to its high cost, and is used when corticosteroids have failed. It is thought to act by saturating platelet receptors which in turn prevents binding of drug-induced antiplatelet antibodies, consequently decreasing the platelet destruction. [5] The estimated frequencies of drug induced immune hemolytic anemia and drug induced immune thrombocytopenia are 1 and 10 per million, respectively.

Thrombocytopenia has also been reported with piperacillin-tazobactam, due to antibody mediated platelet destruction and reversible myelosuppression. In a mechanism similar to that explained above with TMP/SMX, piperacillin-tazobactam acts as a hapten by binding itself to the platelet membrane and forming a drug-platelet complex. At least 100 drugs have been implicated in DITP; convincing data for a causal relationship between medications and immune mediated thrombocytopenia exists for a more selective group of drugs, which include quinine and quinidine (cinchona alkaloid derivatives), penicillin, vancomycin, abciximab, ranitidine, sulfonamides, gold salts, thiazide diuretics (which can also mediate megakaryocyte suppression), and antirheumatic and oral antidiabetic drugs. [6]

Serotonin release assay and 4T's score can rule out the possibility of HIT. [7] In a patient with unexpected thrombocytopenia, the possibility of DITP must always be considered. It is

important to be reminded of this possibility of DITP, and to initiate appropriate management and monitoring to prevent adverse events like death.

4. Conclusion

Thrombocytopenia of any etiology can be serious or life threatening because it may result in significant bleeding complications including intracerebral bleeding. A platelet count as low as 2,000/uL as in this patient, is certainly alarming to many physician, and with such a wide differential, even more so. Any rash should prompt a clinician to suspect some kind of drug reaction. With a systematic approach that includes evaluation for pharmaceutical agents in the original assessment of the patient, clinicians can quickly navigate through an intricate array of causes for thrombocytopenia. Clinicians would do well to keep in mind that TMP/SMX can have serious hematologic complications, further encouraging the community of clinicians to be mindful of antibiotic stewardship.

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Figure 1.
Petechiae of the lower extremities