ISMP Adverse Drug Reactions

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MEDWATCH program (800-FDA-1088). If you have reported an interesting, preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MEDWATCH program and Temple University School of Pharmacy. ISMP is an FDA MEDWATCH partner.

ACUTE DISSEMINATED INTRAVASCULAR COAGULATION DUE TO OXALIPLATIN

A 61-year-old male was initiated on a treatment regimen for metastatic colon adenocarcinoma with FOLFOX6 (bevacizumab 5 mg/kg, calcium leucovorin 400 mg/m², oxaliplatin [*Eloxatin*] 85 mg/m², 5-fluorouracil 400 mg/m² bolus followed by 5-fluorouracil 2400 mg/m² infusion). The patient demonstrated improvement in his metastatic disease after cycle 8 of FOLFOX6, and he demonstrated stable disease after cycle 16. On day 1 of the patient's 18th cycle, he received bevacizumab followed by leucovorin with concurrent oxaliplatin. During the leucovorin and oxaliplatin infusions, the patient experienced rigors and a fever of 100.8°F. The patient also exhibited gingival bleeding and a small amount of blood in his ostomy bag. The patient's infusion was discontinued, and he was admitted to the hospital.

Hematologic laboratory tests were drawn. Analysis of a blood sample that was taken immediately after the adverse reaction revealed elevated prothrombin time (PT) 18 seconds (normal range, 9.7–11.7), international normalized ratio (INR) 1.8 (normal range, 0.8–1.2), and partial thromboplastin time (PTT) 33.5 seconds (normal range, 22.8–32 seconds); decreased fibrinogen level less than 70 mg/dL (normal range, 177–460 mg/dL); and an elevated D-dimer level 28.3 mg/mL (normal range, 0.43–2.33 mg/mL). The patient's hemoglobin value subsequently decreased from 8.4 to 7.6 g/dL (normal range, 13.2–17.5g/dL), and his platelet count decreased to 85 × 10⁹/L (normal range, 150–400 × 10⁹/L) from a pretreatment level of 116 × 10⁹/L. The patient's urinalysis was grossly positive for blood with 0 to 1 red blood cells (RBC) visible, which suggested the presence of free hemoglobin. The patient's active bleeding resolved after administration of 10 units of

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cryoprecipitate, and the hemoglobin stabilized after transfusion of 3 units of RBCs. Blood and urine cultures were negative for an infectious cause of the patient's acute disseminated intravascular coagulation (DIC). The patient was discharged after 3 days with normal coagulation parameters and no signs of bleeding. His diagnosis was DIC of unknown cause.

The patient presented to receive cycle 19 of his chemotherapy 2 weeks after his admission. Bevacizumab was held for this cycle, and the patient's oxaliplatin infusion was initiated. After administration of about 40% of the oxaliplatin infusion (approximately 60 mg), the patient complained of chills. He was noted to have profuse gingival bleeding and gross blood in the ostomy bag. His blood pressure decreased to 88/48 (from 114/78), and his oxaliplatin infusion was immediately stopped. The patient then experienced gross hematuria. Blood samples were drawn immediately after the oxaliplatin infusion was stopped, and laboratory analysis revealed significant changes in coagulation parameters and blood counts consistent with acute hemolysis, DIC, and a leukemoid reaction. The patient's hemoglobin had declined to 11g/dL from 12.1 g/dL, with elevated lactate dehydrogenase (LDH) levels of 1,140 IU/L (normal range, 100-190 IU/L). His PT and PTT were elevated (PT, 29.7 from 10.2; PTT, 73.4 from 26.0), fibrinogen levels declined to less than 70 mg/dL, and D-dimer levels were elevated to 41.91 mg/mL from 5.18 mg/mL. The patient's white blood cell (WBC) count increased from 19,200/mL before treatment to 75,000/mL. Over the next 12 hours, the patient's hemoglobin value declined further to 9.5 g/dL and his WBC count increased to 92,400/mL. The following day, the hemoglobin value and platelet count reached their nadirs at 8.6 g/dL and 47,000/mL, respectively.

The patient received 20 units of cryoprecipitate during this admission. His infectious workup was again negative, and he was discharged after being in the hospital for 2 days. Oxaliplatin was omitted from subsequent cycles, and he was treated with additional cycles of bevacizumab, calcium leucovorin, and fluorouracil without incident.

Malkhasyan et al noted that "virtually all cases of oxaliplatin-induced immune-mediated hematologic reactions reported in the literature, including this case, share several features in common. The reaction occurs after repeated exposure to the drug (the earliest described event was during the second cycle), with onset of symptoms within minutes to hours after initiation of the oxaliplatin infusion. Subsequent treatment with oxaliplatin results in earlier onset and

increased severity of symptoms." The authors concluded that these features strongly point to the presence of preformed oxaliplatin-dependent antibodies and that they play a significant role in this adverse reaction. Conversely, Malkhasyan et al postulate, "An alternative mechanism of DIC in this patient could be the presence of oxaliplatin-dependent antiplatelet antibodies, as has been described with quinine. Quinine, like oxaliplatin, is associated with a variety of hematologic immune-mediated side effects, including hemolytic anemia and thrombocytopenia."

The authors warn that since oxaliplatin is widely used, clinicians should be aware of this potentially life-threatening reaction. Close attention to the typical signs of hypersensitivity can help in early recognition of this drug-related adverse event.

Malkhasyan K, Halene S, Lacy Jill. Oxaliplatin-related acute disseminated intravascular coagulation syndrome in a patient with metastatic colon cancer. *Clin Colorectal Cancer*. 2015;14(1):e9-e12.

AZITHROMYCIN-INDUCED STEVENS-JOHNSON SYNDROME

A 58-year-old male complained of malaise, fever, and oral discomfort with oral swelling. He said he had completed a 5-day course of azithromycin and that he had experienced oral discomfort and swelling followed by a painful and itchy rash on his trunk, abdomen, neck, and bilateral upper and lower extremities one day after the completion of a 5-day course of azithromycin. He sought treatment at a local emergency department and was treated with antihistamines and steroids for a presumed allergic reaction to azithromycin.

Seven days later, he presented to a second emergency department complaining of a worsening rash for the preceding 7 days that had started one day after completion of a 5-day course of azithromycin. His rash was predominantly described as atypical target-like lesions on his trunk, neck, abdomen, axillae, groin, and palmar and dorsal surfaces of his wrists and hands as well on his oral mucosa and scrotum. The authors noted that the patient displayed blistering and mild skin detachment and oozing of serous fluid. He also displayed mild skin sloughing and his presentation was indicative of Stevens-Johnson syndrome (SJS). A medication history revealed the patient had chronically received atenolol, atorvastatin, and famotidine with the recent addition of prednisone and hydroxyzine. His lab tests were unremarkable. Because his presentation was clinically consistent with SJS, the patient was then admitted to the burn unit for care.

Nappe et al point out that azithromycin is not commonly thought of as being associated with causing SJS, erythema multiforme, toxic epidermal necrolysis, or many of the severe cutaneous adverse reactions. They also mention that SJS is less commonly associated with several infections including *Mycoplasma pneumonia* and viral infections. The patient had not been exposed to any other new medication or medication associated with causing SJS. Also since the patient was treated with azithromycin, the likelihood of a *Mycoplasma*-induced SJS is remote.

Nappe et al remind us that when SJS is suspected, any offending medication should first be discontinued, followed by supportive care and management at a burn unit for further specialized treatment as there can be severe morbidity and mortality associated with this condition. In closing, the authors state, "The case reminds us that despite significant pressures to prescribe antibiotics when the necessity is in question, we should consider the potential adverse effects of such antibiotics. More specifically, we should begin to actively consider azithromycin as an associated risk factor for SJS."

Nappe TM, Goren-Garcia SL, Jacoby JL. Stevens-Johnson syndrome after treatment with azithromycin: An uncommon culprit. *Am J Emerg Med*. 2016;34:676.e1-676.e3.

ACUTE JUGULAR VEIN THROMBOSIS WITH RITUXIMAB

A 22-year-old female with stage III B diffuse large B cell non-Hodgkin lymphoma began combination immune-chemotherapy consisting of rituximab (*Rituxan*), cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). The patient received premedication with acetaminophen 650 mg orally and diphenhydramine 50 mg orally 30 minutes before the first rituximab administration. The rituximab infusion was initiated at a rate of 50 mg/h to be increased to 100 mg/h after 30 minutes. Within 45 minutes of initiating the first rituximab infusion, she developed generalized seizures. The rituximab infusion was immediately discontinued, and the patient was given a benzodiazepine that successfully terminated the seizure. The patient then rapidly regained her normal level of consciousness.

An MRI with contrast was immediately conducted and no abnormality and no evidence of acute infarction was discovered. All intracerebral major blood vessels exhibited normal activity, however a filling defect within the right jugular vein was detected. This filling defect was due to a jugular vein thrombosis that had not been present during the patient's staging imaging. A transcranial Doppler ultrasound of

the cerebral and jugular vessels confirmed an extensive thrombosis of the right internal jugular vein. The patient was then initiated on enoxaparin 80 mg subcutaneously twice per day for treatment of the thrombosis. Further anticoagulation studies revealed a normal protein C, protein S, and fibrinogen level with an elevated d-dimer, which was anticipated with the patient's thrombosis.

Rituximab was removed from subsequent chemotherapy cycles, and treatment continued using CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) combination chemotherapy. Anticoagulation and antiepileptic drug therapies were stopped after the fourth cycle. The patient received a total of 8 cycles and achieved positron emission tomography-negative complete remission. The patient remains in remission 18 months after completing chemotherapy.

Reyad et al completed an extensive search in the English literature and found 2 publications that reported thrombosis during rituximab treatment. Feuring-Buske et al reported 1 out of 38 patients who developed a venous thrombosis after treatment with rituximab. Suzuki et al reported 2 patients who developed thrombotic events after rituximab retreatment. Both cases were positive tested for antiphospholipid syndrome (APS). The timing of these thrombosis events in relation to rituximab therapy was not clear in the report.

Dada et al stated, "The discussed literature may not provide a final explanation for a possible causal relationship between rituximab and venous thrombosis in our case. However, timing of symptoms, documentation of the event in relation to rituximab infusion, lack of recurrence of thrombosis after omitting rituximab, and absence of preexisting classic pro-thrombotic high risk factors such as pregnancy, oral contraceptives, immobility, central venous catheter, or deranged coagulation laboratory results make a causal relationship plausible." The authors recommend that close monitoring be conducted on all patients receiving rituximab during and shortly thereafter administration. If the clinical suspicion of thrombosis is suspected then detailed clinical, laboratory, and radiological studies should be conducted.

Dada R, Zekri J, Ramal B, et al. Acute jugular vein thrombosis during rituximab administration: Review of the literature. *J Oncol Pharm Pract*. 2016;22(1):165-169.

Feuring-Buske M, Kneba M, Unterhalt M, et al. IDEC-C2B8 (Rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: Results of a phase-II study of the German Low-Grade Lymphoma Study Group. *Ann Hematol*. 2000;79:493-500.

Suzuki K, Nagaswa H, Kameda H, et al. Severe acute thrombotic exacerbation in two cases with anti-phospholipid syndrome after retreatment with rituximab in phase I/II clinical trial for refractory systemic lupus erythematosus. *Rheumatology*. 2009;48:198-199.

HEMORRHAGIC BULLAE OF THE FINGERS INDUCED BY FUROSEMIDE

A 79-year-old male had an elective coronary bypass surgery that was uneventful. One week after the surgery, the patient reported lethargy, orthopnea, and chest discomfort as well as a 3 kg weight gain over the previous week with lower leg pitting edema. Furosemide was initiated, and the patient improved and was discharged. The patient's current medication regimen in addition to the furosemide included aspirin, digoxin, perindopril, simvastatin, carvedilol, and warfarin.

One week later, the patient reported with hemorrhagic bullous lesions on the second to fifth digits on the dorsum of his right hand and on the dorsum of the left little finger. The patient reported that the lesions were painless and non-pruritic and that they had developed over the course of 3 to 4 days, after which they began to ulcerate and bleed on contact. The following labs were obtained: anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, extractable nuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, complement C3 and C4, creatine kinase, cryoglobulins, hand and chest x-rays, and culture from fluid from the lesions on the patient's hands. All laboratory analyses were normal.

The patient was initially treated with ciprofloxacin and topical steroids, however the lesions worsened over the next 3 days. A skin reaction due to furosemide was suspected, and then biopsies were performed which suggested a drug reaction. Furosemide

was discontinued. After 4 days, the lesions dried up. Spironolactone was added to the patient's medication regimen, and his hands remained normal.

Sladden et al report that several dermatological reactions have been reported with furosemide, including acute generalized exanthematic pustulosis, erythema multiforme, cutaneous necrotizing, vasculitis, Sweet's syndrome, and acute febrile neutrophilic dermatosis. Sladden et al state, "Some dermatological reactions may be a result of the chlorine in the chemical structure exhibiting photochemical activity which causes free radical reactions with lipids, DNA and proteins, leading to photosensitive skin eruptions." They noted that the lesions in this patient were not typical of erythema multiforme in their appearance and were non-pruritic.

Sladden et al state, "Bullous hemorrhagic eruptions secondary to furosemide follow a similar distribution as this patient's case. They have also been described in other members of the sulfonamide class of drugs, including antibacterial sulfonamides, thiazide and loop diuretics, acetazolamide, sulfonylurea hypoglycemic agents some COX-2 inhibitors and sulfasalazine, although distribution of lesions may vary." The dermatological side effects of sulfonamides like furosemide are estimated at 2.5% to 3.5%, while rare recognition is important in this commonly utilized diuretic.

The authors state that "there is little evidence about alternative diuretic therapy should the patient be diuretic dependent. Other loop diuretics should be avoided, as should thiazide diuretics because of a crossover effect. Spironolactone or ethacrynic acid, a loop diuretic without a sulfa group may be an alternative."

Sladden D, Mizzi S, Casha AR, et al. Furosemide-induced eruption of haemorrhagic bullae on the fingers. *Br J Hosp Med*. 2016;77(7):428-429. ■