ISMP Adverse Drug Reactions

Delayed Anaphylaxis with Methimazole

Nicolau Syndrome After Oxytocin Intramuscular Administration

Anastrozole-Induced Autoimmune Hepatitis

Amoxicillin- and Cephalexin-Induced Eosinophilic Colitis

Docetaxel-Induced Supravenous Erythematous Eruption

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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.

DELAYED ANAPHYLAXIS WITH METHIMAZOLE

An 18-year-old female who had been treated for 5 years with methimazole for her Graves disease was admitted to the hospital with a complaint of 3 days of feeling that her throat was closing. She also reported tongue, lip, and facial swelling; urticaria; shortness of breath; and recurrent vomiting. One day earlier, she had presented to another facility and was given prednisone, but this did not relieve her symptoms. Her medication history included atenolol and methimazole for which she had been variably adherent. She had a 5-year history of Graves disease and had received various doses of methimazole over that time. One month ago, her methimazole dosage was increased to 25 mg twice daily.

Based on the patient's physical exam, anaphylaxis was suspected. She was given intramuscular epinephrine, intravenous diphenhydramine, and methylprednisolone. Her symptoms resolved within 2 hours. Lab tests revealed a normal complete blood count with no peripheral eosinophilia and a normal tryptase level. Her free thyroxine level was elevated at 2.67 ng/dL (reference range, 0.8–1.7 ng/dL), and she had a low thyrotropin level of less than 0.005 μ U/mL (reference range, 0.400–4.60 μ U/mL). The patient was then admitted to the hospital and continued to have recurrent symptoms less than 24 hours apart. Her recurrent symptoms only responded to epinephrine. A detailed allergy analysis did not reveal a food, insect, or infectious trigger for the patient's symptoms. Since

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the dosage of methimazole was recently increased, it was suggested to hold her methimazole and initiate propylthiouracil 150 mg every 8 hours for her Graves disease. The patient's atenolol was continued, and she remained asymptomatic while taking propylthiouracil. The patient was discharged from the hospital with an epinephrine autoinjector in case symptoms recurred.

The authors analyzed the patient's reaction and were satisfied that the patient experienced anaphylaxis. They point out that the time of reaction was atypical, because her reactions were not immediate and occurred approximately 4 to 7 hours after the methimazole dose was administered in the hospital. The authors also conducted skin prick and intradermal testing on the patient. The patient had negative skin prick and intradermal tests with methimazole, however the patient developed pruritus, erythema, and induration at the test site approximately 8 hours after testing. The authors concluded that the patient began to develop symptoms secondary to an increase in methimazole to 25 mg twice daily. They concluded that anaphylactic reactions to methimazole may be atypical with delayed onset and a normal tryptase level. They recommend that skin tests that are not immediately positive should be followed for 8 to 10 hours for a possible delayed response.

Shtessel M, Toh J, Gavrilova T. Anaphylaxis as a delayed reaction of methimazole therapy. *Ann Allergy Asthma Immunol.* 2015;115:245-247.

NICOLAU SYNDROME AFTER OXYTOCIN INTRAMUSCULAR ADMINISTRATION

The authors report 2 cases of Nicolau syndrome after the administration of intramuscular oxytocin. The first patient was a 34-year-old female who received oxytocin to prevent postpartum hemorrhage following a vaginal delivery a week prior to her presentation. The patient reported that she had immediate pain on injection of the oxytocin and developed a lesion. Two weeks later, the lesions developed into a cutaneous ulceration approximately 5 inches by 4 inches. A culture of the ulcer was negative, and the patient was successfully treated with surgical wound debridement. The second patient was a 26-year-old female who had also received oxytocin to prevent postpartum hemorrhage after vaginal delivery. Two weeks after oxytocin administration, she presented with a painful necrotic cutaneous ulcer on her left buttock. She reported that a painful erythematous skin reaction developed on her buttock within a few minutes of oxytocin intramuscular administration.

The patient's lesion was necrotic, crusted, and approximately 2 x .75 inches. A culture of the lesion was negative, and she was treated successfully with surgical wound debridement.

Nicolau syndrome is also known as embolia cutis medicamentosa and is a very rare complication occurring after intramuscular drug injection. The condition is characterized by local intense pain and immediate blanching of the skin at the site of injection. A red macule develops and evolves into ulceration, which eventually heals with an atrophic scar. The authors point out that there are 2 possible mechanisms for this adverse reaction. It may be due to sympathetic nerve stimulation and vasospasm leading to ischemia and cutaneous necrosis, or it may be due to thrombosis of small arteries. Many drugs have been associated with Nicolau syndrome such as phenylbutazone, local anesthetics, antihistamines, corticosteroids, vitamin K, vitamin B complexes, sulfonamides, benzathine penicillin, procaine penicillin G, pyrazolone, chlorpromazine, interferon alfa, interferon beta, vaccines, and etanercept.

The authors state that "oxytocin is a potent vasoactive drug and is reported to have mild constrictive effects in skeletal muscle arteries." They believe it is likely that this vasoactive effect contributed to the cause of Nicolau syndrome in both patients. They warn, "Clinicians should be aware of this complication and intramuscular injection should be performed very slowly and only after having aspirated with the syringe to ensure extravascular injection of the drug."

Seremet S, Turan E, Erdemir AT. Nicolau syndrome following intramuscular injection of oxytocin in pregnant women: A report of two cases. *Derm Online J.* 2015;21(8). Permalink: <http://escholarship.org/uc/item/8q81z5mh>.

ANASTRAZOLE-INDUCED AUTOIMMUNE HEPATITIS

A 66-year-old Caucasian female had been receiving anastrozole (*Arimidex*) for the past 6 months for postsurgical treatment of estrogen receptor positive breast cancer. After 6 months of treatment, the patient had significantly elevated liver function tests (LFTs) that lead to her hospital admission. Her LFTs were alanine aminotransferase (ALT) 621 IU/L (reference range, 10-35 IU/L), aspartate aminotransferase (AST) 438 IU/L (reference range, <35 IU/L), gamma-glutamyl transferase (GGT) 624 IU/L (reference range, 7-51 IU/L), alkaline phosphatase (ALP) 185 IU/L (reference range, 44-147 IU/L), and albumin 30 g/L (reference range, 3.5-5.5 g/L); the international normalized ratio (INR) was 1.4.

On admission to the hospital, the patient's anastrozole was discontinued. She received 10 mg of intravenous vitamin K daily for 3 days and acetylcysteine 150 mg/kg intravenously as a loading dose followed by 100 mg/kg intravenous infusion over the next 2 days as part of the hospital's acute liver injury protocol. The patient's liver ultrasound was normal as well as hepatitis A, B, and C; herpes simplex virus (HSV); cytomegalovirus (CMV); and Epstein-Barr virus (EBV) serology. Metabolic screening was also negative. Autoimmune screening was positive with an antinuclear antibody (ANA) (1:160) and weakly positive for antismooth muscle antibody (1:80). A liver biopsy was performed; it revealed heavy portal tract inflammation and mixed inflammatory cells. The hospital pathologist concluded that the histological results reflected drug-induced liver injury, although there was a possibility of autoimmune hepatitis. Over the next 10 days, the patient's LFTs markedly improved but did not completely normalize. She was discharged after a 2-week hospital stay with ursodeoxycholic acid 250 mg 3 times daily. However her ursodeoxycholic acid was stopped after 1 month due to significant nausea. Over the next 3 months, the patient's LFTs experienced a gradual normalization.

Twelve months later, the patient had a second asymptomatic increase in LFTs with peak ALT of 970 IU/L, ALP 223 IU/L, ANA titers (1:800), and an elevated IgG level of 2,106 g/L (reference range, 5.5-16.5 g/L). The patient had no history of hepatotoxic medication and was still not receiving anastrozole. The patient was then treated for possible autoimmune hepatitis with a tapering dose of prednisone 40 mg once daily. The patient's LFTs eventually normalized 3 months later; she remains asymptomatic and is no longer receiving prednisone.

The authors state, "The exact mechanism of liver injury from anastrozole is not very clear, but metabolic and immune-mediated damage and individual susceptibility are likely involved in what are often idiosyncratic reactions." They also mention that prior reports of anastrozole-induced liver injury have been predominantly cholestatic hepatitis that quickly improved after drug withdrawal. However one other case report identified ANA in the serum and suggests there may be an autoimmune response to anastrozole. They state that this case was associated with late-onset progression to acute liver failure evident by hypoalbuminemia and coagulopathy. This case also revealed ANA positivity and resolution after withdrawal of anastrozole, indicating that

anastrozole may have induced hepatitis with autoimmune features rather than exposing underlying autoimmune liver disease.

Islam MS, Wright G, Tanner P, et al. A case of anastrozole-related drug-induced autoimmune hepatitis. *Clin J Gastroenterol*. 2014;7:414-417.

AMOXICILLIN- AND CEPHALEXIN-INDUCED EOSINOPHILIC COLITIS

A 42-year-old male came to the emergency department with a 2-week history of non-bloody diarrhea and dehydration. His stools were small volume, green, and contained mucus. The patient reported that 2 weeks prior, his stools became soft and he experienced episodes of chills. He reported that 1 week prior to his emergency room presentation, his stool frequency increased to 15 bowel movements daily. The patient reported his last travel abroad was 5 years earlier. His stool examination and culture were negative on 3 occasions for bacteria, *Clostridium difficile* toxin and ova, cysts, and parasites. *Strongyloides* and *Toxocara* serology and autoimmune studies were all negative. The patient's absolute neutrophil count (ANC) was 9.7×10^3 cells/ μ L when he arrived at the emergency department; his ANC peaked 7 days later at 29.9×10^3 cells/ μ L. A medication history revealed that 3 weeks prior the patient had received a 1-week course of cephalexin for the treatment of an upper respiratory infection.

The patient underwent a colonoscopy that revealed patchy colitis in the descending and sigmoid colon. Multiple biopsies were taken during the procedure, and histopathological results revealed similar changes from the rectum to the caecum. Increased eosinophils were also present, however no parasitic infection, inflammatory bowel, or connective tissue disease were noted. The patient did not receive any doses of corticosteroids or antihelminthic medication, and his symptoms subsided with supportive care after a 1-week hospital stay. The patient was seen for a follow-up visit 4 weeks after his discharge. He reported his bowel movements had returned to once or twice daily and he had not lost any weight or experienced abdominal pain. His peripheral eosinophil count had decreased to 1.1×10^3 cells/ μ L.

Two months later, the patient received a course of amoxicillin that caused similar symptoms to his prior hospital admission. His peripheral eosinophilia also recurred. The patient was diagnosed with eosinophilic colitis secondary to exposure to beta-lactam antibiotics. This diagnosis was based on the

patient's prior spontaneous clinical and hematologic recovery, timing of drug exposure, and symptom onset. Other possible causes were also ruled out.

The authors explain that eosinophilic colitis is an exceptionally rare condition and its pathogenesis is incompletely understood. It is thought that this condition is due to a combination of genetic predisposition to the condition or an environmental trigger. Eosinophilia occurs when a large number of eosinophils are recruited to a specific site in the body or the bone marrow produces too many eosinophils. This can be caused by a variety of conditions, diseases, and factors, including parasitic and fungal diseases, allergies (including to medications or food), adrenal conditions, skin disorders, toxins, autoimmune diseases, endocrine disorders, and tumors. Eosinophilic colitis is an exceptionally rare condition, and drug-induced eosinophilic gastroenteritis has only been reported in a small number of case reports that have implicated tacrolimus, clozapine, carbamazepine, rifampicin, gold, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Mogilevski T, Nickless D, Hume S. Beta-lactam-associated eosinophilic colitis. *BMJ Case Rep.* 2015 June 23; 2015. doi:10.1136/bcr-2014-206964.

DOCETAXEL-INDUCED SUPRAVENOUS ERYTHEMATOUS ERUPTION

The authors report 2 cases of docetaxel-induced supravenuous erythematous eruptions. The first case occurred in a 68-year-old female with breast cancer who had been treated with 4 cycles of doxorubicin and cyclophosphamide and 4 cycles of docetaxel (*Taxotere*) and trastuzumab. The patient reported that she developed an erythematous macule on her left forearm a few days after her second course of chemotherapy with docetaxel and trastuzumab. On examination it was noted that the patient had a supravenuous brownish macule that followed the venous pathway on her left upper arm. The patient also had detachment of her fingernails from the nailbeds and alopecia. It was concluded that the patient had a persistent erythematous eruption that followed the venous pathway secondary to docetaxel administration. The patient received methylprednisolone daily for 1 week, and her rash progressed with residual hyperpigmentation.

The second case occurred in a 65-year-old female who had been diagnosed with grade 4 ductal breast cancer with metastases who was receiving palliative chemotherapy with docetaxel and filgrastim. After

the third cycle of chemotherapy with docetaxel, the patient reported a pruriginous erythematous macule on her left forearm and hyperpigmentation of the fingernail plate after the sixth cycle of chemotherapy. On examination the patient had erythematous-brownish macules on the back of her hand following the venous pathway on the left upper arm and discoloration of the fingernails and the underlying tissue. The patient was treated with methylprednisolone daily for 7 days, and she experienced complete remission of lesions 3 months after the end of chemotherapy.

Docetaxel acts by stabilizing the microtubules, preventing breakdown, and leading to cell death. Docetaxel is an irritating drug that can cause tissue damage that does not progress to necrosis, but it may cause erythema, pain, inflammation at the venous puncture site and venous pathway and a burning sensation. The skin, the mucus membranes, and skin appendages are tissues that have rapid cellular proliferation and are therefore susceptible to adverse reactions resulting from systemic anticancer treatment.

Docetaxel may cause a variety of adverse effects such as alopecia, acral erythrodysesthesia (also known as hand-foot syndrome, which is reddening, swelling, numbness, and skin sloughing or peeling on palms of the hands and soles of the feet and occasionally on the knees or elbows), detachment of the nail from the nail bed, hyperpigmentation of the nail plate, urticaria, angioedema, and persistent erythematous rash that follows the venous pathway. An erythematous eruption that follows the venous pathway is characterized by macules at the site of infusion, which at times can progress to residual hyperpigmentation. Lesions may appear between 24 hours and 15 days after infusion of the cytotoxic drug and disappear spontaneously in weeks or months.

The authors elaborate, "The etiology of this adverse effect is not well defined. It is believed that a chemotherapy agent generates direct cytotoxicity in the vascula endothelium, increasing its permeability and contributing to the leakage of the medication out of the vessel, producing a direct toxic effect on keratinocytes and melanocytes." They recommend that prevention of the adverse effect can be achieved by administering a saline infusion before and after chemotherapy. In patients with long chemotherapy sessions, it is advisable to attain central access to prevent this adverse effect.

Fernandes KAP, Felix PAO. Persistent docetaxel-induced supravenuous erythematous eruption. *An Bras Dermatol.* 2015;90(5):728-730. ■