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Minocycline-Induced Drug Fever Without Skin Rash

A 24-year-old female had been receiving minocycline 100 mg daily for 6 days for the treatment of acne. The patient reported a fever of 39.2°C (102.6°F), dizziness, chest tightness, and eye pain. Her physician diagnosed her with a cold and she was treated. Minocycline therapy was stopped at this time. The patient's fever and malaise lasted 5 days. Three days later, the patient was restarted on minocycline for her acne. Within 3 hours of minocycline administration, she again developed a high fever of 39.2°C with dizziness, chest tightness, and eye pain.

The patient was initiated on 30 mg of prednisone. She was examined and her blood pressure, respiratory rate, and heart rate were normal. She did not exhibit any throat swelling, enlarged lymph nodes, or rash. Magnetic resonance imaging of the brain revealed no abnormalities and a computed tomographic scan of the chest also was negative. The patient did have an eosinophilia with a white blood cell count (WBC) of $7.5 \times 10^9/L$ (normal range, $4.5\text{--}11 \times 10^9/L$) and eosinophils of $1.2 \times 10^9/L$ (normal range, $0.1\text{--}0.6 \times 10^9/L$). Her renal and liver function tests were normal as well as blood cultures for bacteria and testing for the anti-human herpes virus-6 IgG were also negative.

The authors¹ note that there have been rare reports of minocycline-induced drug fever and the consequences can be serious. In prior cases, minocycline has been overlooked as a potential cause because the patient did not have a skin rash. The authors state,

“The diagnosis of drug fever is often difficult, and a careful review of the clinical presentation and medication history can confirm the diagnosis. Although this patient had severe symptoms, the diagnostic criteria for drug reaction with eosinophilia and systemic symptoms (DRESS) were not fulfilled because of the absence of skin rash and other systemic features.”

The authors warn that clinicians should be alert for unusual drug-induced fever, especially in patients without apparent skin rashes.

Lupus Erythematosus–Like Eruption Induced by Hydroxyurea

A 14-year-old female had been receiving hydroxyurea 1500 mg daily for the past 5 years for the management of her sickle cell anemia. The patient developed a hyperpigmented rash and plaques on her bilateral upper arms, back, and right conical bowl as well as pruritus. She also exhibited scattered discrete erythematous, hypopigmented, hyperkeratotic papules across her back, left malar cheek, and bilateral upper extremities. The patient had tried to self-treat the condition with clotrimazole cream with no effect.

The patient had biopsy specimens taken from the lesions and the results pointed to a possible collagen vascular disorder-like eruption and hydroxyurea dermatopathy. The patient was subsequently started on fluocinonide 0.05% cream for the lesions; however, she did not experience significant improvement. Additional testing pointed to a possible discoid lupus with a positive antinuclear antibody (ANA) titer of 1:160 and a high antihistone immunoglobulin G (IgG) level of 4.5 U (reference range, <1 U).

The patient's hydroxyurea was then stopped, and treatment with fluocinonide cream was continued. The patient began to experience significant improvement in her rash, and her antihistone IgG level fell gradually. One year after stopping the hydroxyurea, the patient noted minimal hyperpigmentation with no new lesions.

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The authors² point out that hydroxyurea is a cytotoxic chemotherapeutic drug that acts on an enzyme ribonucleotide reductase to inhibit DNA synthesis and promote cell death. While hydroxyurea is generally well tolerated, occasional dermatologic adverse effects have been reported.

The authors explain that hydroxyurea is a cytotoxic chemotherapeutic drug that acts on the enzyme ribonucleotide reductase to inhibit DNA synthesis and promote cell death. Hydroxyurea is generally well tolerated; however, cases of hydroxyurea dermatopathy have occurred in patients receiving hydroxyurea therapy after an average of 5 years. The exact mechanism of this dermatopathy is unknown; however, the proposed mechanism is the cumulative toxicity of hydroxyurea in the proliferating cells of the stratum basale, the deepest layer of the 5 layers of the epidermis. Based on the patient's laboratory test results and positive ANA, the authors suspect hydroxyurea-induced chronic cutaneous lupus erythematosus. In conclusion, the authors' state, "This patient's autoimmune profile and clinical appearance suggest that drug-induced lupus is a distinct, albeit rare side effect of hydroxyurea, separate from hydroxyurea dermatopathy."

Cardiotoxicity and Fever Induced by Clozapine

A 31-year-old Caucasian male with a 9-year history of schizophrenia had received a number of atypical antipsychotics without success. The patient's symptoms including hallucinations, delusional ideas of persecution and reference, as well as apathy continued to recur. The patient was admitted to an inpatient facility and initiated on clozapine. On day 1, the patient received clozapine 25 mg and was titrated up to 100 mg daily over a period of 10 days. The clozapine titration was a gradual increase of 25 mg daily every 3 days up to the 100 mg daily dosage and the patient's white blood cell count was evaluated after each dosage increase.

On day 11 of clozapine therapy, the patient experienced a significant elevation in leukocytes 13,660 cells/ μ L (normal value, 4500-11,000 μ L) and neutrophils 75% of WBC (normal value, 40%-60% of WBC). This increase in leukocytes and neutrophils indicated a potential immune stimulation. On day 13, the patient developed fever, rigors, and sweating with a maximum temperature of 39.6°C (103.3°F) with a slight tachycardia of 140 bpm and a blood pressure of 130/85 mm Hg. The patient's clozapine was immediately discontinued, and he was treated with acetaminophen and received rehydration with intravenous normal saline. An electrocardiogram (EKG) revealed sinus tachycardia with a normal QTc interval and a chest x-ray and urinalysis produced unremarkable findings. Blood tests were also within the normal range except for the white blood cell count, which revealed a leukocytosis of 13,100 cells/ μ L and a corresponding increase in neutrophils to 85% of white blood cells. At this time, the patient's high sensitivity troponin (Hs-troponin) was normal at 11.7 pg/mL (gray zone 14-53 pg/mL, pathological > 53 pg/mL).

On day 14, the patient was feeling better with a resolution of his leukocytosis; however, his Hs-troponin was elevated to 28.7 pg/mL. A subsequent creatinine kinase-MB level was normal as well as a procalcitonin level; however, the patient's C-reactive protein (CRP) level was elevated to 88.6 mg/L (normal range, 0.00-6.00 mg/L). Additional CRP levels drawn on days 15 and 17 of his hospital stay decreased to 76.5 mg/L and 28.4 mg/L, respectively, with a Hs-troponin of 20 pg/mL. By day 32, the patient was in good medical condition, and his blood tests were within normal range.

The authors³ mention that clozapine-induced fever is a common adverse effect with an incidence as high as 55% of patients. They note that there seems to be a correlation between the fever and the days after initiation of clozapine. Prior research demonstrates the development of fever on day 5 to 20 after clozapine initiation. The authors state, "Recent reports suggest that clozapine stimulates the production of pro-inflammatory cytokines including TNF α , interleukin 1, and interleukin 6. These have also been implicated in causing myocardial depression by direct actions on the myocytes."

The Naranjo scale was utilized by the authors to evaluate the causality of this adverse reaction relative to clozapine administration and the scale revealed the causality as probable. They surmise that the case hints at the presence of initially subclinical cardiotoxicity as an underlying factor in patients developing fever. The increase in troponin observed 1 day after resolution of fever, probably, is a late reaction of cardiotoxicity. The authors state, "More case-control studies are needed in order to clarify the putative model arising from our clinical observations; specifically, a larger sample of patients who develop clozapine-induced fever versus patients commencing clozapine without developing fever."

Denosumab-Induced Hepatotoxicity

A 72-year-old female was evaluated for an increase in liver enzymes around 5 times the upper limit of normal (ULN). Her medication history included amlodipine, bisoprolol, and occasional nonsteroidal anti-inflammatory drugs (NSAIDs). Approximately 1 month prior to her increase in liver enzymes, she had received a subcutaneous injection of denosumab (Prolia) 60 mg for osteoporosis. The patient had no evidence of chronic liver disease with negative results for hepatitis B and C. Additional autoimmune testing was conducted and the results were unremarkable. During the following 6 weeks, the patient's serum transaminases increased to 12 times the ULN and then subsequently an elevation to 1500 IU/mL (aspartate transaminase [AST] normal range, 10-30 U/L; alanine transaminase [ALT] normal range, 10-40 U/L). The patient's gamma-glutamyl transferase (GGT) was also elevated to 755 U/L (GGT normal range, 2-30 U/L). The patient became icteric with a bilirubin of 10 mg/dL (bilirubin, total normal range, 0.3-1.2 mg/dL) which increased to 13.8 mg/dL. The patient's international normalized ratio (INR) increased to 1.79 and would not correct with intravenous

administration of vitamin K. The patient's serum albumin also decreased to 2.8 g/L (normal range, 3.5-5.5 g/dL).

A liver biopsy was performed which revealed inflammation of hepatic tissue, submassive hepatic necrosis, and bile duct proliferation consistent with drug-induced liver disease (DILI). The patient was initiated on oral prednisone 40 mg once daily. Over the next 3 weeks, the INR decreased to 1.3 and the albumin initially rose to 3 g/dL, but then declined to 2.7 g/dL while the bilirubin decreased to 7.8 mg/dL. At this time, ursodeoxycholic acid 300 mg twice daily was initiated. Over the following months, there was a slow decline in the levels of both the transaminases and the GGT with a concomitant increase in serum albumin. The patient's prednisone was slowly tapered, and her ursodeoxycholic acid was discontinued and 1 month later there was a large increase in her transaminase levels and a decrease in serum albumin from 3.2 to 2.9 mg/dL. The patient's prednisone was increased to 25 mg daily, and her ursodeoxycholic acid was reinitiated. Over the next 3-month period, there was a decrease in transaminases with a slow tapering off of the patient's prednisone. The patient remains healthy on maintenance therapy of prednisone 5 mg and ursodeoxycholic acid 600 mg daily.

The authors⁴ set out to identify the correlation between denosumab and the patient's liver toxicity. They examined the temporal relationship, the amount of drug administered, and the duration of use. They also investigated the possibility of exposure to over-the-counter medications, as well as herbal and dietary supplements; however, there was no evidence of exposure to these agents. To determine if the liver injury was due to biologic therapy, they performed a lymphocyte toxicity assay (LTA) to denosumab because reexposure to denosumab would be unethical. The LTA to denosumab demonstrated a hypersensitivity reaction to denosumab resulting in 31% toxicity while the control patient showed toxicity to denosumab.

The authors suggested a possible mechanism by which denosumab could cause this severe liver toxicity. In reviewing denosumab's mechanism of action, it is noted that it blocks receptor activator of nuclear factor- κ B (NF κ B) ligand (RANKL). Initially, it was suggested that denosumab by actively reducing RANKL might produce a cholestatic reaction. Denosumab may also induce an elevation of other members of the tumor necrosis factor family, as well as other inflammatory cytokines and chemokines. The authors state,

"Due to the prolonged half-life of denosumab (25.4 days), this immune activation is a long-lasting event. Interestingly there is a report in mice of RANKL protecting against hepatic ischemia and reperfusion. In addition to prolonged immune activation, there is concomitant loss of RANKL due to direct effect of the denosumab, which deprived the liver of a means of defense."

Severe Cardiotoxicity Induced by Bevacizumab

A 62-year-old female with stable colorectal cancer had received combination chemotherapy with S-1 (tegafur/

gimeracil/oteracil) with oxaliplatin and bevacizumab (Avastin) 7.5 mg/kg for 4 months. Partial remission was documented and then the patient received 17 courses of S-1 and bevacizumab until her disease was stable. The next month, the patient was admitted to the hospital complaining of wheezing, dizziness, and edema of the legs. Her blood pressure was 200/130 mm Hg with a heart rate of 116 bpm. A color Doppler echocardiogram revealed tricuspid regurgitation, pulmonary hypertension, left ventricular diastolic dysfunction, and a pericardial effusion. Additional significant laboratory data were an AST of 38 U/L, creatinine kinase (CK) of 154 U/L (normal range, 26-192 U/L), creatinine kinase-MB (CK-MB) of 4.96 ng/mL (normal range, 0-2.88 ng/mL), and lactate dehydrogenase (LDH) of 511 U/L (normal range, 81-234 U/L). A thoracic puncture was initiated in the area of the hydrothorax. The hydrothorax reached 19,660 mL in total. The patient was forced to withdraw from the original chemotherapy regimen due to severe cardiotoxicity.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Inhibition of VEGF, an initiator of tumor angiogenesis, inhibits tumor growth and invasion of surrounding tissue. The anti-cancer efficacy of bevacizumab has been established however adverse effects such as hypertension, congestive heart failure, and decreased left ventricular ejection fraction can occur. The authors⁵ state, "Anti-angiogenesis drugs often cause reversible cardiac damage by either a "target effect" or "missed target effect." The former hypothesis means bevacizumab inhibits VEGF which is indispensable for cardiac function. Therefore, VEGF is crucial for normal cardiac function, and its inhibition by bevacizumab can lead to cardiotoxicity. The authors then pose the next question, "How long does the latency of severe cardiotoxicity last before manifesting syndromes?" In their case, the patient had a latency period of 20 months after the first bevacizumab administration. The authors call for an optimal recommended time course for patients using bevacizumab to be evaluated to assure patients have the most advantageous clinical efficacy.

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