74-Year-Old Woman With Dysarthria and Left Lower Extremity Weakness

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A 74-year-old woman with a history of rheumatoid arthritis who was receiving long-term immunosuppression with prednisone and methotrexate was seen in the pulmonology clinic and complained of acute-onset dysarthria and left lower extremity weakness. At the time, she was being evaluated for follow-up of a recent left upper lobe cavitary pneumonia, which had been diagnosed 6 weeks previously when she had presented with productive cough and weakness. She had been treated with an extended course of empirical levofloxacin and metronidazole and had returned to the clinic for repeated computed tomography (CT) of the chest. The CT documented resolution of the prior left upper lobe cavitary consolidation, but during her visit, she noted these new neurologic symptoms and was referred to the emergency department for further evaluation.

On arrival at the emergency department, her vital signs were stable, with a temperature of 36.5°C, blood pressure of 121/76 mm Hg, pulse rate of 85 beats/min, respiratory rate of 14 breaths/min, and oxygen saturation of 95% while she breathed room air. The only abnormalities on physical examination were in the neurologic evaluation, which revealed mild hypokinetic dysarthria and difficulties with attention, calculation, and recall. Cranial nerve examination revealed poor extraocular tracking to the left. Although she noted subjective left lower extremity weakness, objective neuromuscular examination was limited by her severe rheumatoid arthritis. Findings on evaluation of cerebellar function, deep tendon reflexes, and sensory examination were unremarkable. Laboratory studies yielded the following findings (reference ranges provided parenthetically): leukocytes, 6.8 × 10^9/L (3.5-10.5 × 10^9/L); hemoglobin, 10.5 g/dL (12.0-15.5 g/dL); platelet count, 254 × 10^9/L (150-450 × 10^9/L); creatinine, 1.0 mg/dL (0.6-1.1 mg/dL); and international normalized ratio, 1.2 (0.8-1.2).

1. Which *one* of the following would be the *best* initial imaging study for evaluation of this patient's symptoms?

a. Contrast CT of the head
b. Noncontrast CT of the head
c. Noncontrast magnetic resonance imaging (MRI) of the head
d. Cerebral angiography
e. Transcranial Doppler ultrasonography

For patients presenting with sudden development of neurologic symptoms, the initial concern is for acute ischemic stroke. The American Heart Association/American Stroke Association guidelines for management of acute ischemic stroke recommend emergent brain imaging before initiation of any specific therapy.[1] The use of contrast with CT does not add any sensitivity and has additional risks including nephropathy. Noncontrast-enhanced CT of the brain is the recommended imaging modality because it excludes hemorrhage and can also reveal nonvascular causes of neurologic symptoms such as a mass or tumor.

Although MRI has superior sensitivity and specificity for acute infarction[2] and angiography stands as the criterion standard for diagnosing most types of cerebrovascular disease given its superior sensitivity, specificity, and resolution, the limited availability of these imaging modalities may delay imaging in the emergent setting. Doppler ultrasonography can detect stenoses in extracranial vessels, although either CT or magnetic resonance angiography would be superior for diagnosing intracranial stenosis. Doppler ultrasonography also does not capture the posterior circulation and does not rule out hemorrhage, so some other modality of imaging would still be recommended before initiating therapy.

See end of article for correct answers to questions.

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In this patient, the noncontrast CT findings were unremarkable, with no evidence of intracranial hemorrhage or mass effect. Carotid ultrasonography was also performed and did not reveal any flow-limiting stenoses. The patient was admitted for further evaluation because of concern for stroke. The next morning, the patient's family clarified that her deficits had arisen over the course of at least a week. For further evaluation, noncontrast MRI of the head was performed, which revealed symmetric restricted diffusion of the splenium of the corpus callosum and the bilateral dentate nuclei of the cerebellum, with associated T2 hyperintensity. There was no evidence of severe edema or hypodensities suggestive of microhemorrhage.

2. Given our patient's history and imaging findings, which *one* of the following is the *most likely* etiology of her neurologic symptoms?

a. Stroke/transient ischemic attack
b. Central nervous system (CNS) vasculitis
c. Multiple sclerosis
d. Lymphoproliferative disorder
e. Toxic/metabolic insult

The differential diagnosis for CNS lesions is wide and includes metabolic disorders, vascular diseases, degenerative disease, inflammatory diseases including infection, and neoplasms. This patient's MRI findings do not fit within a single vascular territory, which limits the differential diagnosis and makes a cerebrovascular event such as stroke unlikely. Unfortunately, MRI was performed without the use of gadolinium contrast medium, which did limit its utility in excluding other diagnoses, but other clinical findings were used in conjunction with the imaging.

Central nervous system vasculitis could be a concern, particularly given the patient's known autoimmune disease and higher risk for additional autoimmune processes. Central nervous system vasculitis often presents in multiple vascular territories, and although the imaging study performed has low sensitivity for the diagnosis, it did not reveal any vessel irregularities or segmental narrowing to suggest vasculitis.[3] Further testing could be pursued such as angiography (CT, magnetic resonance, or conventional angiography) or a biopsy, but these options were deferred at the time given high suspicion for an alternative diagnosis. Multiple sclerosis can also present with demyelinating lesions in multiple territories of the nervous system including the basal ganglia, but this patient had no previous neurologic episodes to document dissemination through time.

The patient's clinical history would lead to concern for a lymphoproliferative disorder given her long-term immunosuppression with methotrexate,[4] but this disease typically presents as a mass lesion rather than the described findings. A lumbar puncture can help to further evaluate some of these etiologies including inflammatory conditions such as multiple sclerosis, lymphoproliferative disorder, and infection. However, given the subacute onset of symptoms and lack of fever or leukocytosis, there was low suspicion for these conditions, and therefore a lumbar puncture was not performed.

Overall, given the patient's clinical presentation, subacute onset of symptoms, lack of mass lesion or vascular abnormalities on imaging, and lesions in multiple vascular territories, her findings were most consistent with a toxic/metabolic insult. Wernicke encephalopathy was considered because of the distribution of the lesions, mental status changes, and ataxia, but she lacked consistent risk factors such as alcohol abuse or severe malnutrition. In view of her recent hospitalization and treatment for pneumonia, her recent exposures and medications were reviewed for a most likely toxic cause.

3. In addition to supportive care and physical, occupation, and speech therapy, which *one* of the following would be the *best* treatment option for this patient?

a. Discontinue her outpatient antibiotics
b. Plasmapheresis
c. Dialysis
d. Escalate her antibiotic therapy
e. Decrease her immunosuppression

With any toxic insult, the first step should be to remove the offending agent, which in this case was metronidazole. Metronidazole-induced encephalopathy is a rare adverse effect that typically presents with subacute cognitive impairment, cerebellar ataxia, and

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dysarthria. Characteristic MRI findings are symmetric lesions in the bilateral dentate nuclei and corpus callosum and less commonly in the midbrain, basal ganglia, and subcortical white matter.[5,6] Although toxic metronidazole levels may be documented at the time of diagnosis of metronidazole-induced encephalopathy, there is no evidence for the role of plasmapheresis or hemodialysis for attempted drug clearance. Discontinuing the medication would be the most appropriate step. Escalation of antibiotic therapy would be appropriate in the case of untreated CNS infection causing her symptoms, but her imaging findings are inconsistent with CNS infection. Decreasing immunosuppressive medications would be indicated if a lymphoproliferative disorder was suspected.

Given the evidence of resolution of her cavitary pneumonia on outpatient chest CT, antibiotics had been discontinued on hospital admission. Speech pathology was consulted for her dysarthria, and physical and occupational therapy were consulted for her severe debility.

4. Which one of the following would be the *most accurate* description of the patient's reaction to metronidazole when documenting this event in her medical record?

a. Side effect
b. Toxicity
c. Allergic reaction
d. Adverse reaction
e. Medication error

All of these terms can be used to describe various events that occur after medication administration, but although they are often used interchangeably, this usage is imprecise.

Side effects are events "related to the pharmacologic properties of the drug"[7] and may even be intended effects of the medication. For example, a side effect of first-generation antihistamines is drowsiness, and some individuals may take the medication specifically for this effect. Toxicities are "exaggerations of the desired therapeutic effect"[8] and are rare with normal therapeutic doses, although they may occur at normal doses in the setting of impaired excretion. When measurable, supratherapeutic drug levels are expected in cases of toxicity. Although supratherapeutic levels of metronidazole have been documented in cases of metronidazole-induced encephalopathy, it is not requisite to the diagnosis, and this reaction is unrelated to the therapeutic effect of metronidazole. Allergic reactions are immunologically mediated hypersensitivity reactions that are characterized by specificity of antibodies and recurrence with repeated exposures. Metronidazole-induced encephalopathy is not an immunologically mediated reaction.

The World Health Organization defines an adverse drug reaction as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function."[8] Adverse reactions differ from side effects in that they are inherently unintended and detrimental, as in the case of metronidazole-induced encephalopathy. This event would not qualify as a medication error because the medication was prescribed with an appropriate dosage and route, it was taken as prescribed, and the event did not involve mistakes in medication dispensing or administration.

Metronidazole-induced encephalopathy is most accurately described as an adverse effect given its injurious nature at a recommended dose. In view of the patient's critical presentation, a reaction to metronidazole was noted in her electronic medical record so that prescribers would be aware of this reaction before prescribing metronidazole in the future.

5. Which *one* of the following is a late side effect of metronidazole?

a. Metronidazole-induced encephalopathy
b. Peripheral neuropathy
c. Metallic taste
d. Gastrointestinal upset
e. Disulfiram-like reaction to alcohol

Although metronidazole can cause all of these side effects, most side effects will resolve with discontinuation of the drug.[9] Metronidazole-induced encephalopathy should resolve after discontinuation of the drug, with symptoms improving rapidly. The MRI findings reverse as well but may require a period of weeks to months.[5,10] Peripheral neuropathy, while also a dose-related neurologic side effect, is often a

longer-lasting effect and may persist for years despite drug cessation.[11] The metallic taste, gastrointestinal upset, and disulfiram-like reaction to alcohol, the most common side effects of metronidazole, should resolve nearly immediately once the drug is discontinued.

Our patient's inattention and poor extraocular tracking improved, and her speech returned to baseline within 72 hours of discontinuation of her metronidazole. A repeated brain MRI 6 weeks later revealed resolution of the previously seen dentate nuclei abnormalities. However, she had persistent painful paresthesias in her bilateral lower extremities. She had not experienced neuropathy before her exposure to metronidazole. Given the persistence of symptoms, gabapentin was initiated with some benefit.

DISCUSSION

In an elderly patient presenting with new neurologic symptoms, the immediate concern is often for ischemic stroke. For initial work-up, noncontrast CT is the most common modality because of its widespread availability and speed of acquisition. Magnetic resonance imaging, particularly the diffusion-weighted imaging sequence, is superior to CT in specificity and sensitivity,[2] but cost, limited availability. longer duration of the test, and patient contraindications including pacemakers and inability to remain motionless are major limitations. Thus, in the case of a patient with acute neurologic symptoms concerning for ischemic stroke, noncontrast CT should typically be the first imaging modality used.

As further work-up of acute neurologic symptoms, brain MRI is often pursued. The pattern and distribution of any lesions, including whether the lesions fall within a consistent vascular territory, whether the lesions appear to be mass-like, and whether there is vascular involvement, can be used to narrow the differential diagnosis for lesions.[3,4] Clinical features such as comorbid conditions, medication exposures, markers of infection, and time course are all key to further categorizing CNS lesions.

In patients with suspected toxic or metabolic insults causing neurologic symptoms, metabolic laboratory work-up should be pursued, and exposure history must be evaluated thoroughly. Myriad medications may cause neurologic symptoms. Clinicians should suspect metronidazole-induced encephalopathy in patients who have received a prolonged course of metronidazole and experience new neurologic symptoms, particularly cerebellar ataxia, nystagmus, and dysarthria.[5,10] There may be increased risk in the setting of hepatic dysfunction, in which clearance of metronidazole may be impaired.[5,6]

Although the mechanism of metronidazole-induced encephalopathy is not fully understood, proposed mechanisms based on animal models include metronidazole binding to RNA in neurons, inhibiting protein synthesis and causing axonal degradation, and antagonism of thiamine, causing encephalopathy in a mechanism similar to that of Wernicke encephalopathy. Another possible mechanism involves metronidazole-dependent oxidation of catecholamines to form free radicals that reduce tissue oxygenation.[9]

When any adverse drug reaction, including metronidazole-induced encephalopathy, presents, the offending agent should be discontinued immediately.[8] Fortunately, the effects of metronidazole-induced encephalopathy have been found to be reversible with medication withdrawal, similar to most side effects of metronidazole.[5,6,9]

Although metronidazole offers many benefits over other antibiotics in its oral bioavailability and low cost,[9] the potential for this serious neurotoxicity should be considered when prescribing a prolonged course of empirical antibiotics. Clinicians must maintain a high index of suspicion for metronidazole-induced encephalopathy, and if suspected, the practitioner should discontinue the medication to achieve resolution of symptoms.

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CORRECT ANSWERS: 1. b. 2. e. 3. a. 4. d. 5. b.