Clinical Reasoning:

A young woman with respiratory failure, hearing loss, and paraplegia

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SECTION 1

A 35-year-old woman with bipolar disorder presented to the emergency room (ER) obtunded with hypercapnic respiratory failure. Neurology was consulted because the patient had acute hearing loss and paraparesis. She was last seen normal the prior night by her ex-husband. Paramedics found her on the couch, obtunded, bradypneic, and hypoxic to 82% SpO₂, blood pressure 116/79 mm Hg, heart rate 98 beats per minute, and normothermic. She awakened after 0.4 mg of naloxone administration. Home medications included oxycodone/acetaminophen for chronic pain and venlafaxine, alprazolam, and lamotrigine for bipolar disorder. Of note, 34 pills were missing from the oxycodone/acetaminophen bottle.

Examination revealed supple neck, nontender and atraumatic back, reduced tone, and no withdrawal to

noxious stimuli in the legs. Strength was normal in the arms. Reflexes were 2+ throughout but crossed knee adduction was noted. Babinski and Hoffman signs were absent. Pinprick and temperature were decreased bilaterally to a T2-3 level. Vibration and proprioception were intact; rectal tone was normal. The patient reported that she could not hear finger rub in either ear.

Bloodwork was remarkable for mild leukocytosis and mild transaminitis. Salicylate and acetaminophen levels were unremarkable. Urine toxicology was positive for benzodiazepines but negative for opioids.

Questions for consideration:

1. What is your localization and differential diagnosis?
2. How does the pattern of sensory involvement narrow the differential?

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SECTION 2

The patient's paraplegia along with a T2-3 spinal cord level suggested an upper thoracic spinal cord lesion. Her hearing loss and tinnitus were difficult to colocalize with the paraplegia. Although a brainstem lesion could tie together both deficits, the absence of cranial nerve deficits and normal motor-sensory examination in the arms made this unlikely. Diffuse coagulopathy involving the anterior spinal artery and bilateral anterior inferior cerebellar arteries that supply the cochlea was also less likely given absence of cerebellar symptoms. A toxic/metabolic insult such as drug toxicity or hypoxic injury to cochlea was thought to be more likely.

The acute onset of symptoms together with the dissociated sensory loss between spinothalamic tracts and dorsal columns point towards an acute anterior spinal cord syndrome, which is typically caused by ischemia/infarction from a vascular or hypoxemic insult. Other etiologies for acute spinal cord dysfunction include epidural abscess or hematoma, vascular malformation, ischemia, vasculitis, infectious or autoimmune myelitis, spinal mass apoplexy, and cervical flexion myelopathy.

Question for consideration:

1. What tests can be ordered to confirm the diagnosis?

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SECTION 3

An emergent CT spine excluded a fracture or epidural hematoma. Subsequent spine MRI showed increased T2 signal from C5 to T5 and was more prominent in the anterior portion of the spinal cord; this region also showed positive diffusion restriction. No spinal canal stenosis was identified (figure). MRI findings were compatible with an anterior spinal cord infarction in the watershed territory. Brain MRI showed symmetric T2 fluid-attenuated inversion recovery hyperintensities with diffusion restriction in the globus pallidus consistent with hypoxic ischemic injury (figure).

CT angiogram of the head, neck, and aortic arch did not reveal any vascular pathology or dissection that could predispose the patient to a spinal cord

infarction. Conventional angiogram of the spine to look for a vascular malformation was considered; however, the patient declined the test. Spinal fluid analysis ruled out any potential infectious, autoimmune, or vasculitic process. Extensive serum workup was also unrevealing (table).

After this workup, it was concluded that prolonged global hypoxia caused an anterior spinal cord infarction in the watershed territory, as well as hypoxic infarctions in the highly metabolic regions of the basal ganglia. The hearing loss was also thought to be due to hypoxic cochlear injury. Given the improved respiratory status after naloxone administration, her hypercapnic respiratory failure was the cause and not the consequence of her spinal cord infarction.

Figure MRI of the brain and cervical spine

(A) Sagittal short tau inversion recovery image of the cervical spinal cord reveals T2 hyperintensity at C5 extending to the thoracic spine with diffusion restriction on sagittal focus diffusion-weighted imaging (DWI) (B). (C) Axial cervical spinal cord T2 sequence demonstrates the preferential involvement of the anterior cord. (D) Axial brain T2 fluid-attenuated inversion recovery sequence shows bilateral hyperintensities in globus pallidus. (E) Brain DWI sequence demonstrates diffusion restriction within the highly metabolic regions of the basal ganglia.

Table Laboratory tests from the day of admission	
Laboratory tests	Results
Serum leukocytes, 10 ³ /μL	16.8 (4.5-11)
Neutrophils, %	90.3 (40-78)
Arterial blood gas, pH/pCO ₂ /pO ₂	7.14/68/58
Aspartate aminotransferase, U/L	117 (1-50)
Alanine aminotransferase, U/L	37 (1-53)
Bilirubin direct, mg/dL	1 (0-0.8)
Alkaline phosphatase, U/L	88 (30-110)
Salicylate, mg/dL	1 (2-29)
Acetaminophen, μg/mL	12 (10-25)
Ethanol, mg/dL	<10 (0-50)
Urine drug screen	
Amphetamine	Negative
Benzodiazepine	Positive
Cocaine	Negative
Opiate	Negative
Methadone	Negative
Opiate urine assay, ng/mL	
Hydrocodone	<20
Oxycodone	>4,000
Oxymorphone	381
Hydromorphone	<20
HIV	Nonreactive
Hepatitis panel	Negative for HAV, HBV, HCV
ANA, ANCA, SSA, SSB	Negative
Methemoglobin, %	0.9 (0-1)
Carboxyhemoglobin, %	0.6 (0-4)
Serum glucose	132
CSF studies	
Leukocytes/μL	1 (0-5)
Erythrocytes/μL	6 (0)
Protein, mg/dL	38 (15-45)
Glucose, mg/dL	90 (40-80)

Abbreviations: ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; SSA = anti-SS-A/Ro antibodies; SSB = anti-SS-B/La antibodies.

Normal ranges are shown in parentheses.

Questions for consideration:

1. What drug caused the hypercapnic respiratory failure and hypoxemia?
2. Why was the assay negative for opioids?

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SECTION 4

The initial screening urine toxicology assay was positive for benzodiazepines, but negative for opiates, which cannot explain the patient's missing oxycodone tablets. The screening assay for opioids in the ER measures the presence of morphine, which is a metabolite of both heroin and codeine. Substances such as fentanyl, which lacks metabolites, and oxycodone, which is not metabolized to a morphine derivative, are typically undetected by urine drug

screening. A specialized opioid assay detected >4,000 ng/mL of oxycodone in the urine of our patient, thus confirming oxycodone overdose as the cause of hypoxemia and hypercapnic respiratory failure. This led to a global hypoxic state with end organ damage in highly susceptible neurologic tissues.

Question for consideration:

1. What would be the next step in management?

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SECTION 5

Acute management was focused on reversing the hypoxemic respiratory failure. The patient was immediately placed on bilevel positive airway pressure in the ER and the effects of oxycodone were reversed with naloxone. Measures to increase spinal perfusion were considered but ultimately not done because the mechanism of spinal cord infarction was thought to be due to reduced blood oxygen content and not compromised blood flow. Furthermore, the patient's blood pressures were normotensive to slightly hypertensive.

Psychiatry was consulted to assess the patient's depression and determined that her overdose was recreational and not a suicide attempt. Within days, the patient exhibited improved hearing, but her neurologic examination was otherwise unchanged. After 2 months of rehabilitation, she was still paraplegic with impaired pinprick sensation below T3 but could produce some trace non-anti-gravity muscle movements on the left leg. She developed spasticity in her lower extremities requiring a baclofen pump insertion and a neurogenic bladder necessitating frequent self-catheterizations.

DISCUSSION Opioid overdose is a major cause of morbidity and mortality.¹ Opioids can affect the spinal cord via multiple mechanisms and a unified clinical syndrome is lacking. A myelopathy on awakening from opioid overdose or naloxone reversal has been described in the literature, although most cases were associated with heroin overdose and not oxycodone. The mechanism of injury could be either vascular, mediated by hypotension and hypoxemia leading to a watershed infarction in the spinal cord,²⁻⁴ or mechanical, secondary to prolonged flexion of the cervical spine in patients with preexistent spinal stenosis.^{5,6} IV use of opiates can be associated with spinal cord embolism by particulate matter or infectious complications such as intramedullary or epidural abscess causing compression.

Although spinal cord infarction is an uncommon presentation of opioid overdose, clinicians should have a high index of suspicion to achieve an accurate diagnosis and prompt management. There are at least 3 different types of watershed infarctions in the spinal cord. The first and most common location is between the anterior spinal artery supplying the anterior two-thirds of the cord and the paired posterior spinal arteries that supply the rest of the posterior one-third of the cord; second, the watershed between the highly variable aortic feeders coming in along the length of the spinal cord, i.e., between the artery of the cervical enlargement, diverse thoracic feeders, and artery of Adamkiewicz; and finally, the watershed between the central anterior spinal artery supply and the pial supply to the superficial surface of the cord circumferentially.^{7,8} Our patient's clinical and radiographic presentation was consistent

with the most common form of spinal cord infarction, anterior spinal artery syndrome. Management of spinal cord infarction in the setting of opiate overdose should focus on reversal of the effects of the toxic agent, augmentation of oxygenation and circulation, and prevention of complications. In acute ischemic infarctions of the spinal cord complicating aortic surgeries, acute management also involves measures to increase perfusion of the spine by raising the blood pressure and placing a lumbar drain to decrease intraspinal pressure and resistance, thus increasing microcirculatory flow.⁹ However, their role has not been established for nonoperative hypoxic spinal cord infarctions, where the aortic feeders and spinal circulation are intact. In addition, in our case and likely in other cases of spinal cord infarctions due to opiate overdose, patients are most likely to present outside the window for an acute intervention. Finally, tissue plasminogen activator or endovascular thrombolysis are not well-supported by data for use in spinal cord infarctions.

The prognosis of spinal cord infarction is variable and is dependent on the type and severity of the neurologic deficits. Near complete sensorimotor deficits, as well as bladder dysfunction or impaired proprioception at onset, signify poor prognosis, whereas a positive Babinski sign predicts a more favorable outcome.⁹ In a follow-up study of 115 patients with spinal cord infarctions, the 3-year mortality rate was 23%, but it was not uncommon for patients to show substantial functional improvement.^{9,10} Forty-one percent of patients who were discharged in a wheelchair were walking at 3 years and 33% of those requiring bladder catheterizations at discharge were catheter-free at 3 years.^{9,10}

This case demonstrates the unique constellation of a spinal cord infarction combined with bilateral globus pallidus infarctions and a possible hypoxic cochlear injury that were all caused by oxycodone overdose. It also demonstrates the utility of more specialized urine toxicology assays to accurately diagnose drug overdose when there is a high clinical suspicion and rapid urine toxicology screens are negative.

AUTHOR CONTRIBUTIONS

Achilles Ntranos: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Hazem Shoirah: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision. Mandip Singh Dhamoon: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. David Hahn: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Thomas Naidich: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Susan Shin: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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