66-Year-Old Man With Inarticulate Speech

KELLY K. CURTIS, MD,* AND HOLENARASIPUR R. VIKRAM, MD†

A 66-year-old man presented to our institution with inarticulate speech. The evening before, he had been in his usual state of health when he retired to bed at 10 PM. At approximately 2 AM, when he awoke to use the bathroom, he noticed a headache and returned to bed. At 7 AM his spouse noted that he was awake and alert but that his speech was unintelligible. He was transported to our emergency department for further evaluation.

Medical history was remarkable for coronary artery disease with drug-eluting stents placed 9 months earlier, hypertension, hyperlipidemia, and gastroesophageal reflux disease. The patient had a 20 pack-year history of tobacco use but had not smoked in 40 years. He had lived in Arizona for 5 years. He had no personal or family history of stroke. His medications included aspirin, clopidogrel, ezetimibe, metoprolol, pantoprazole, and telmisartan.

On evaluation in the emergency department, the patient was found to be afebrile, with a blood pressure of 141/63 mm Hg, heart rate of 85 beats/min, and oxygen saturation of 96% while breathing room air. He was able to follow commands; expressive aphasia was noted. Otherwise, findings on examination, including neurologic examination, were unremarkable. A 12-lead electrocardiogram (ECG) showed a normal sinus rhythm and was unchanged when compared with prior ECGs. Computed tomography (CT) of the head revealed no evidence of hemorrhage, infarct, lesion, or mass effect.

1. Which one of the following is the most appropriate next step in the care of this patient?

a. *Administer recombinant tissue plasminogen activator (r-tPA)*
b. *Obtain magnetic resonance imaging/angiography (MRI/MRA) of the brain*
c. *Check electrolyte panel and serum glucose level*
d. *Perform urine drug screen*
e. *Start heparin infusion with concomitant warfarin therapy*

An enzyme that binds to fibrin polymers within a thrombus, r-tPA converts plasminogen to plasmin, leading to subsequent degradation of fibrin polymers and the thrombus. It is indicated for the treatment of acute ischemic stroke with a symptom duration of fewer than 3 hours. In our patient, the time of onset of symptoms was unknown, and a firm diagnosis of ischemic stroke had not been established. Because its risk would outweigh any benefit, r-tPA was not administered to our patient.

The next step in the patient's work-up should be MRI/MRA of the brain, which would allow evaluation of intracranial structures, including the cerebral vasculature, and thus clarify the diagnosis of ischemic stroke. Ordering a serum electrolyte panel and glucose test are important steps in the evaluation because certain electrolyte abnormalities, such as hypernatremia, hyponatremia, hypocalcemia, or hypoglycemia, often present with mental status changes. However, the patient had no history of diabetes mellitus and was not taking oral hypoglycemics. He had no obvious risk factors for the other mentioned electrolyte abnormalities; thus, performing these studies is of secondary importance. The urine drug screen is not warranted because the patient had no history of recreational drug abuse. Finally, without evidence of atrial fibrillation on ECG, heparin or warfarin therapy is not indicated.

The patient's speech improved several hours after his arrival. Magnetic resonance imaging of the brain disclosed no evidence of recent infarct or hemorrhage; mild to moderate small vessel ischemic changes were noted in the white matter. Magnetic resonance angiography of the head and neck showed normal intracranial and cervical vasculature. Transesophageal echocardiography revealed no evidence of mass, thrombus, or atrial shunt.

On the day of admission, the patient developed a fever (temperature, 38.3 C). Further examination disclosed an area of cellulitis with foul-smelling, purulent drainage in the superior aspect of the intergluteal cleft. Adjacent red, palpable nodules on the right buttock were observed (Figure 1). When questioned, the patient reported a "rash" with serosanguineous drainage in this area during the previous week.

2. Which one of the following diagnoses best explains the patient's skin lesion?

a. *Perianal abscess*
b. *Anorectal fistula*
c. *Infected pilonidal cyst*
d. *Herpes zoster eruption with superimposed bacterial infection*
e. *Disseminated coccidioidomycosis*

*Resident in Internal Medicine, Mayo School of Graduate Medical Education, Mayo Clinic, Scottsdale, AZ.
†Adviser to resident and Consultant in Infectious Diseases, Mayo Clinic Hospital, Phoenix, AZ.

See end of article for correct answers to questions.

Individual reprints of this article are not available. Address correspondence to Holenarasipur R. Vikram, MD, Division of Infectious Diseases, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054 (vikram.hr@mayo.edu).

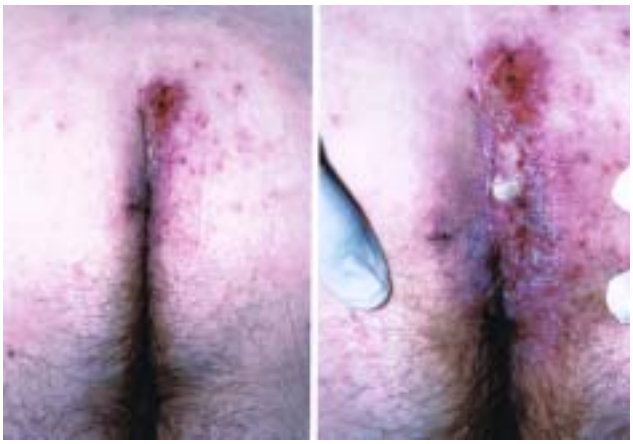

FIGURE 1. Intergluteal cleft of a 66-year-old man presenting with difficulty speaking. The patient noted drainage in this area for approximately 1 week but denied pain or pruritus. Note the satellite red papules on the right buttock.

Although erythema can be a feature of perianal abscess, pain and fluctuation are often observed. The affected area was quite distant from the anal orifice (which itself was normal), making a diagnosis of perianal abscess unlikely. Patients with anorectal fistula typically present with a pustular lesion, drainage, and painful defecation. It is often a complication of inflammatory bowel disease, malignancy, or radiation proctitis. Because the patient had none of these findings, a diagnosis of anorectal fistula was unlikely. An infected pilonidal cyst presents as a painful, inflamed mass at the superior aspect of the intergluteal fold. On the basis of his examination, this is also unlikely. The presence of erythematous papules and crusts confined to the left L2 dermatome with purulent drainage from the intergluteal cleft raises the possibility of a herpes zoster eruption with a superimposed bacterial infection. Finally, although the patient resides in an area where coccidioidomycosis is endemic, he had no pulmonary manifestations and was not immunosuppressed, making disseminated coccidioidomycosis less likely.

The patient continued to be febrile during the next 24 hours. He became confused to place and time but remained oriented to person. He complained of a persistent frontal headache.

3. Given the patient's fever, fluctuating mental status, and headache, which <u>one</u> of the following is the <u>most appropriate</u> next step?

a. *Perform lumbar puncture*
b. *Administer haloperidol*
c. *Repeat CT of the head*
d. *Perform electroencephalography*
e. *Check serum glucose value immediately*

The combination of fever, mental status changes, and frontal headache are suggestive of a central nervous system (CNS) infection. Therefore, a lumbar puncture should be performed to obtain cerebrospinal fluid (CSF) for cell count, glucose and protein values, Gram stain, bacterial culture, fungal serology, fungal stain and culture, *Coccidioides* antibody titers, and herpes simplex and varicella zoster polymerase chain reaction (PCR) studies. Haloperidol, a typical antipsychotic drug, is effective for mental status changes with delusions or hallucinations. The patient was not exhibiting these symptoms and did not require this medication. In the absence of focal neurologic symptoms suggestive of new or progressive stroke, a second CT of the head would be unlikely to provide additional information. An electroencephalogram would not be useful because the patient had experienced no seizure activity. Hypoglycemia can present with altered mental status, but the patient had received no insulin or oral hypoglycemics; his serum glucose level was normal on admission.

A lumbar puncture was performed, yielding clearCSF. Cerebrospinal fluid analysis revealed the following (reference ranges given parenthetically): a glucose level of 56 mg/dL, a total protein concentration of 180 mg/dL (14-48 mg/dL), 23 red blood cells/μL (0-5 cells/μL), and 371 nucleated cells/μL (0-5 cells per μL). Of the nucleated cells, 6% were polymorphonuclear cells, 90% lymphocytes, and 4% monocytes. The simultaneous serum glucose level was 103 mg/dL (70-100 mg/dL). Gram stain of the CSF was negative.

4. Which <u>one</u> of the following <u>best</u> explains the CSF findings?

a. *Subarachnoid hemorrhage*
b. *Bacterial meningitis*
c. *CNS involvement with varicella zoster virus (VZV)*
d. *Coccidioidal meningitis*
e. *Tuberculous meningitis*

Analysis of the CSF revealed substantial lymphocytosis and elevated total protein concentration. These findings, in combination with absence of hemorrhage on brain CT and MRI, essentially exclude subarachnoid hemorrhage. The values are not consistent with bacterial meningitis (in which the white blood cell count is often >1000 cells/μL with polymorphonuclear cell predominance, the CSF–serum glucose ratio is <0.5, the protein concentration is ≥500 mg/dL, and the Gram stain is often positive for organisms). Findings on analysis of this patient's CSF are most compatible with pleocytosis and elevated protein concentration secondary to CNS involvement with VZV.[1,2] Coccidioidal meningitis often manifests with lymphocyte predominance and elevated CSF protein concentration. However, our patient's normal CSF–serum glucose ratio makes this choice less likely. Finally, tuberculous meningitis would be characterized by mononuclear pleocytosis, low CSF

glucose levels, and elevated protein values. Although part of the differential diagnosis, it is unlikely in this case.

We were able to detect VZV DNA in the CSF by PCR. Cerebrospinal fluid PCR studies for herpes simplex virus, Epstein-Barr virus, or cytomegalovirus were negative. No growth was observed on bacterial, fungal, mycobacterial, or viral cultures at 6 weeks. Serum and CSF fungal serologies showed no evidence of coccidioidomycosis, histoplasmosis, or blastomycosis.

Dermatology consultation was subsequently requested. Bacterial cultures were obtained from the purulent drainage, revealing *Haemophilus parainfluenzae* and group G streptococcus. A punch biopsy specimen of the gluteal lesions showed an intraepidermal spongiotic vesicle, multinucleate giant cells, and perivascular lymphocytic infiltrates—all features consistent with herpes virus infection. Viral culture of the biopsy specimen was negative, likely because of the superimposed bacterial infection and healing phase of the lesions. Fungal, bacterial, and mycobacterial stains of the biopsy specimen were all negative.

5. Which one of the following is the most appropriate treatment for this patient?

a. *No treatment indicated; disease process will spontaneously remit*
b. *Antiviral agent with corticosteroids*
c. *Antiviral agent with an anticonvulsant*
d. *Antibiotic alone*
e. *Antiviral agent combined with antibiotic therapy*

Results of the gluteal skin biopsy and swab cultures suggest herpes zoster eruption with bacterial superinfection. The presence of fever and gross purulence necessitates the administration of antimicrobial therapy. The use of antiviral agents with corticosteroids vs antiviral agents alone has been shown to improve healing of herpes zoster lesions and hasten the resolution of pain.[3,4] However, this choice does not include antibiotic therapy, which is clearly indicated in this case. Antiviral agents with an anticonvulsant are not appropriate for the same reason. Treating the secondary bacterial infection with antibiotics alone might be considered a reasonable option because the patient's herpes zoster rash had been present for longer than 72 hours, and antiviral agents are effective for shortening the duration of zoster rash and lessening pain only if started within 72 hours of the appearance of rash.[5] However, this patient had signs that aroused concern for CNS involvement with herpes zoster, making treatment with antibiotics alone inadequate. The therapy of choice was an antiviral agent in combination with an antibiotic. We initiated treatment with intravenous acyclovir and ampicillin-sulbactam because the patient clearly had CNS manifestations on admission, abnormal CSF findings indicating either herpes zoster meningitis or early encephalitis, and a secondary bacterial infection of the involved dermal area.

The patient improved during the next 3 days of hospitalization; his fever abated within 24 hours of initiating antibiotic therapy. His mental status rapidly returned to normal, and he experienced no further episodes of inarticulate speech. The patient was discharged on the fifth hospital day, with plans to complete a 14-day course of oral amoxicillin-clavulanate and intravenous acyclovir. Given the lack of findings on MRI/MRA or transesophageal echocardiography to suggest cerebrovascular accident, the presenting symptoms of aphasia were thought to represent CNS manifestations from reactivation of VZV. The episodes of delirium during hospitalization could have been due to fever, bacterial infection, or herpes zoster.

DISCUSSION

Primary infection with VZV usually occurs in childhood, resulting in the clinical syndrome of varicella or "chickenpox."[6] The virus then becomes latent in the sensory dorsal root ganglia. With reactivation, a distinct rash localized to a single dermatome ensues. This rash, known as herpes zoster or "shingles," is preceded by itching or pain in the affected area. Vesicular lesions then appear within 3 to 5 days and progress through pustular and ulcerated phases to crusting within 7 to 10 days. Healing is usually complete within 4 weeks, and recurrence in immunocompetent hosts is uncommon.[6]

At least 90% of US adults have been exposed to VZV.[7] The incidence of herpes zoster is estimated to be between 1.5 and 3.0 cases per 1000 individuals, or approximately 500,000 cases per year in the United States.[6] Advancing age increases the risk of VZV reactivation.[7] Other risk factors for herpes zoster include immunosuppression (eg, patients receiving corticosteroid or tumor necrosis factor inhibitor therapy, those taking immunosuppressive drugs, those with human immunodeficiency virus infection, and those with underlying malignancies).[6]

Complications of herpes zoster include postherpetic neuralgia (PHN) (characterized by persistent pain lasting longer than 30 days after the onset of herpes zoster rash), secondary bacterial infections; herpes zoster ophthalmicus (a sight-threatening condition caused by herpes zoster eruption along the first division of the fifth cranial nerve), acute retinal necrosis, Ramsay Hunt syndrome (a polycranial neuropathy characterized by facial paralysis, ear pain, and vesicles in the auditory canal), and meningoencephalitis. One study identified a 12% risk of developing at least 1 complication by day 60.[8]

Central nervous system involvement with VZV is well described. In a study of 50 immunocompetent patients with herpes zoster and without signs of meningoencephalitis or myelitis, 61% of patients were found to have abnormal CSF; 46% had pleocytosis; and VZV DNA was detected in 22%.[2] With a sensitivity and specificity greater than 95%, PCR testing of CSF for herpes viruses is now considered the criterion standard for diagnosing herpes virus meningitis/encephalitis.[9] Viral cultures are negative in most cases.[9] Our patient's transient expressive aphasia and CSF findings of lymphocytosis, elevated protein concentration, and detectable VZV DNA on PCR suggest the possibility of CNS involvement with VZV.

Small and large vessel encephalitis have been described previously with VZV CNS involvement.[10,11] Whereas large vessel encephalitis typically manifests with contralateral hemiplegia due to infarction, small vessel encephalitis can present with motor deficits, aphasia, and/or vision changes. Commonly seen in immunosuppressed patients, small vessel encephalitis is the most common CNS complication of VZV infection. Magnetic resonance imaging of the brain shows evidence of small vessel ischemia and/or hemorrhage in both gray and white matter.[11] In our patient, MRI of the brain did not reveal abnormalities consistent with encephalitis.

Three antiviral drugs are available for the treatment of herpes zoster: acyclovir, famciclovir, and valacyclovir. They are most effective if prescribed within 48 to 72 hours of the onset of rash. Acyclovir has been shown to reduce pain, accelerate healing, and decrease the incidence of PHN.[12] Compared with acyclovir, famciclovir and valacyclovir have better oral bioavailability and more convenient dosing schedules.[6] The addition of corticosteroid therapy to acyclovir in patients with herpes zoster has been evaluated in at least 2 randomized controlled trials.[3,4] Patients treated with corticosteroids and acyclovir experienced faster healing of lesions and resolution of pain, but the incidence of PHN was not diminished. Currently, corticosteroids are given only to patients with severe symptoms in the absence of risk factors for corticosteroid-induced toxicity.[6]

Given the substantial morbidity and potential mortality associated with herpes zoster, preventive strategies are important. A vaccine for VZV has recently been approved in the United States for use in adults older than 60 years; it is administered in a single dose via subcutaneous injection. A randomized, double-blind, placebo-controlled trial of the VZV vaccine showed a 51% reduction in the incidence of herpes zoster during a 3-year period with a shorter duration of pain and a 67% reduction in the incidence of PHN.[13] This vaccine is contraindicated in immunocompromised and pregnant patients and is not useful for treatment of active herpes zoster or prevention of PHN. It is unknown if the vaccine is helpful for patients younger than 60 years or patients with a history of herpes zoster.[14]

In summary, our patient's illness began as a simple case of gluteal herpes zoster. Central nervous system manifestations that mimicked acute stroke led clinicians on a tangential diagnostic work-up. The patient's inability to provide accurate history about his gluteal rash in the face of speech difficulty and superimposed bacterial infection contributed to a missed diagnosis of herpes zoster. This case illustrates the potential for CNS involvement with VZV and draws attention to some of the atypical manifestations of herpes zoster.

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Correct answers: 1. *b*, 2. *d*, 3. *a*, 4. *c*, 5. *e*