57-Year-Old Man With Headache, Vomiting, and Gait Instability

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A 57-year-old man, originally from Burma, presented to the emergency department with headache, nausea, vomiting, and unsteadiness in December 2020. He had no significant medical history and was not taking any medication.

He reported worsening headaches associated with nausea and vomiting for the preceding 2 to 3 months. His headache was characterized as bifrontal and unchanged with positioning, coughing, or sneezing. His gait worsened, and he had 1 fall. The patient also had intractable hiccups for the preceding 2 months. Additionally, his family noted he was more forgetful, although the patient remained independent with his activities of daily living. He was born in Burma and lived there until 2008, when he moved to Thailand where he worked as a farmer. He moved to Minnesota in 2013 and worked at a meat processing factory. He endorsed regular cooked beef, pork, and poultry ingestion. He denied sick contacts, fevers, chills, pain, cough, diarrhea, or constipation. He reported no changes in his strength, sensation, vision, or hearing. He did not endorse other significant infectious exposure history or social history.

On presentation, temperature was 36.1°C, heart rate 54 beats/min, blood pressure 127/109 mm Hg, and oxygen saturation 97% on room air. On physical examination, he was not in acute distress and had intermittent hiccups. Eyes were anicteric, and mucous membranes were moist. Cardiac examination revealed no murmurs, rubs, or gallops; rate and rhythm were regular. His extremities exhibited no edema. Lung fields were clear to auscultation. Abdominal examination was benign with no palpable organomegaly, and skin examination was unremarkable. On neurological examination, he was alert and oriented. He was able to follow 1- and 2-step commands, but unable to follow crossbody commands. Assessment of strength, sensation, coordination, and reflexes was normal. His gait was abnormal with a forward lean, short stride length, and reduced ground clearance.

The initial laboratory results revealed a white blood cell count of 10.0×10^9/L (normal range, $[3.4\text{-}9.6]\times10^9$/L). Head computed tomography (CT) revealed marked ventriculomegaly with widespread multifocal calcifications and cysts.

1. **Which *one* of the following is the *next best* step in management?**
   a. Discharge home with anti-nausea medications and outpatient follow-up
   b. Electroencephalogram
   c. Lumbar puncture (LP)
   d. Magnetic resonance imaging (MRI) of the brain and spine
   e. Brain biopsy

Conservative management with anti-nausea medications and outpatient follow-up would not be appropriate for this patient, given his progressive neurological abnormalities and CT findings. Although brain lesions can increase the risk of seizures, the patient did not present with signs or symptoms of seizure activity. Thus, electroencephalogram is not indicated. The symptoms along with the CT findings of marked ventriculomegaly and innumerable cysts raise a concern for elevated intracranial pressure (ICP). Performing an LP in this setting puts the patient at high risk for cerebral herniation. Given the CT images that were highly suggestive of neurocysticercosis (NCC), MRI is indicated for the diagnosis and further

See end of article for correct answers to questions.

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characterization of brain lesions. Moreover, MRI of the spine is recommended for patients with basal subarachnoid involvement given the strong association with spinal subarachnoid cysticerci.[1] In rare cases, if advanced imaging and extended laboratory tests are unrevealing, brain biopsy may be necessary for diagnostic purposes.

Brain and spine MRI with fast imaging employing steady-state acquisition and 3-dimensional constructive interference in steady-state sequences revealed widely disseminated, racemose NCC in varying stages, with subarachnoid, intraventricular, and paraspinal involvement. There were also meningeal inflammation and obstructive hydrocephalus, partly secondary to cyst location in the cerebral aqueduct and fourth ventricle. Echinococcus and cysticercosis serum IgG antibodies were positive.

2. **Which *one* of the following is the *most likely* pathogen responsible for the imaging and serological findings in this patient?**
   a. *Naegleria fowleri*
   b. *Schistosoma* spp.
   c. *Giardia* spp.
   d. *Taenia solium*
   e. *Echinococcus granulosus*

Naegleria fowleri is the causative organism for primary amebic meningoencephalitis. Diagnosis is made by LP and cerebral spinal fluid analysis. Neuroimaging findings are nonspecific and may include hydrocephalus, lesions, and meningeal enhancements. *Schistosoma* spp. may cause neuroschistosomiasis with symptoms of seizures and neurological deficits. Serology, urine antigen detection, and microscopy of the stool or urine are used for diagnosis. *Giardia* spp. is a protozoan that causes diarrhea and diagnosed by serology, nucleic acid assays, and stool microscopy; giardiasis infection does not present with central nervous system lesions. Infection with *T solium*, or pork tapeworm, can present as taeniasis (digestive system infection by a tapeworm) or cysticercosis (cyst formation by larvae). Cysticercosis is diagnosed with a combination of clinical symptoms, neuroimaging findings, and epidemiological exposures. Cystic echinococcosis (CE) is caused by *E granulosus* and most commonly involves the liver and lungs. Less commonly, CE may involve the brain, muscle, kidneys, and spleen. Although the sensitivity of serological testing for *E granulosus* is high, the specificity (as observed in this patient's laboratory testing) is low.[2] The larger cyst size, presence of daughter cysts, and radiological appearance can help to differentiate CE from NCC. In addition, although there is an elevated risk of secondary CE with a spillage of viable *Echinococcus* parasite during cyst resection, postoperative inflammation in response to NCC spillage has not been described.[3]

Given the diagnosis of widespread racemose NCC with viable cysts, immediate antiparasitic therapy was contraindicated because of the risk of severe inflammation until the patient's hydrocephalus and elevated ICP were adequately managed. The patient was initiated on high-dose corticosteroids and subsequently underwent a ventriculoperitoneal shunt placement and endoscopic septostomy for NCC. Unfortunately, third ventriculostomy and cystectomy were deemed too high risk because of the patient's anatomy and risk of cyst spillage.

3. **Which *one* of the following antiparasitic therapies would you *most likely* recommend for this patient?**
   a. Albendazole and praziquantel
   b. Niclosamide
   c. Metronidazole
   d. Chloroquine
   e. Ivermectin

Neurocysticercosis presenting with more than 2 cysts should be treated with albendazole and praziquantel.[4] Niclosamide is an anthelmintic medication that has been used for taeniasis, but is not effective for

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cysticercosis. Metronidazole is a treatment of giardiasis, trichomoniasis, and amebiasis, not for infection with *T solium*. Chloroquine, an antimalarial agent, is not an effective therapy for this patient. Ivermectin is antiparasitic therapy for onchocerciasis and strongyloidiasis.

Albendazole and praziquantel were initiated for the patient after surgery and resolution of elevated ICP. Levetiracetam was initiated for seizure prophylaxis. Because of prolonged treatment with corticosteroids, the patient was screened for latent tuberculosis (TB) infection (LTBI) and strongyloidiasis. Strongyloidiasis serum IgG antibody was negative. The QuantiFERON-Tb Gold Plus test result was positive. Chest radiography did not reveal any signs of active TB.

4. **Given this patient's NCC medication regimen, concurrent treatment with which *one* of the following anti-TB medications should be *best* avoided?**
   a. Isoniazid
   b. Ethambutol
   c. Moxifloxacin
   d. Kanamycin
   e. Cycloserine

Because of the association of hepatotoxicity with albendazole, isoniazid should be avoided because of the high risk of liver injury with combined antiparasitic and anti-TB therapy. Peripheral neuropathy and agranulocytosis have also been reported with isoniazid. Ethambutol is more commonly associated with visual disturbances and retrobulbar neuritis. Rifampicin and pyrazinamide are also associated with hepatitis. Fluroquinolones, such as moxifloxacin, can cause gastrointestinal disturbances, tendinitis, and QT interval prolongation. Adverse effects associated with kanamycin include ototoxicity and nephrotoxicity. Cycloserine can cause neurological symptoms such as confusion, dizziness, and psychosis.

Unfortunately, despite deferring LTBI therapy, the patient had transaminitis. Trimethoprim-sulfamethoxazole was transitioned to pentamidine and the dose of albendazole was reduced.

5. **Which *one* of the following is *true* regarding the transmission and prevention of NCC?**
   a. Humans can get cysticercosis by consuming *T solium* cysts undercooked pork.
   b. Humans can get cysticercosis after ingesting *T solium* eggs.
   c. Pickling and salting meat are methods of eliminating viable cysticerci.
   d. Hand hygiene before food preparation does not adequately prevent cysticercosis.
   e. Vaccination for humans living in endemic areas can prevent cysticercosis.

Eating cysterici in undercooked pork causes a tapeworm infection, also known as taeniasis, but will not directly cause cysticercosis. Instead, cysticercosis occurs after an individual ingests *T solium* eggs found in contaminated foods or more commonly autoinoculation of eggs excreted stool from self or a household tapeworm carrier.[5] Pickling and salting pork do not adequately eliminate viable cysticerci in meat. Instead, freezing or cooking the meat can destroy viable cysticerci. Good hygiene after toileting and before food preparation with soap and water can prevent transmission of *T solium* eggs from tapeworm carriers to other people. No vaccine for cysticercosis has been approved in humans. In some endemic countries, vaccination of pigs has been used to prevent porcine cysticercosis and subsequent transmission to humans.[6]

Ultimately, his transaminitis resolved and was felt to be from trimethoprim-sulfamethoxazole. Albendazole was reinitiated at a lower dose, but adequate dose for NCC. The patient was discharged from the hospital with the plan to initiate LTBI treatment in the outpatient setting and screen household contacts for taeniasis.

DISCUSSION

Cysticercosis is endemic to regions Latin America, sub-Saharan Africa, and South and Southeast Asia.[1] Humans become the dead-end host after ingesting the embryonated eggs of *T solium*, which is found in the stool of tapeworm carriers such as pigs

and human household members. The embryos hatch in the gastrointestinal tract, invade through the bowel wall, and disseminate hematogenously to present as cysticercosis. In contrast, humans are the definite host after ingesting the larval cysts of *T solium* found in undercooked pork. After consuming the cysts, humans have taeniasis with adult tapeworm infection of the intestinal tract. Tapeworm infestation, although not a direct cause of cysticercosis, does increase the risk of fecal-oral autoinfection of *T solium* eggs, leading to the future development of cysticercosis.

Cysticercosis may be divided into NCC and extraneural cysticercosis. Neurocysticercosis may be further characterized as parenchymal and/or extraparenchymal. After ingestion of *T solium*, the phases of infection consists of an initial viable phase, early inflammatory phase, degenerating phase, and nonviable phase. The most common presenting symptom of intraparenchymal NCC is seizures.[5] Altered vision, focal neurological symptoms, meningitis, and encephalitis have also been reported.[5] Although symptom onset is usually within 3 to 5 years, patients may present more than 30 years after initial ingestion.[7] Extraparenchymal NCC can involve the ventricles, subarachnoid space, spine, and eye. Patients with extraparenchymal involvement often report symptoms of elevated ICP, including headache, nausea, vomiting, altered mental status, and decreased visual acuity. They may also present with seizures and focal neurological deficits. Spinal cysticerci can affect the spinal cord and peripheral nerve roots, causing radicular pain, paresthesia, and sphincter dysfunction. Racemose NCC is a severe form of extraparenchymal NCC characterized by multiple confluent cysts seen in the subarachnoid space.[3]

Routine laboratory evaluation is of lower diagnostic yield. Patients with cysticercosis often have normal liver function test results and eosinophil counts. Ova and parasite stool testing is often insensitive, because most patients do not have live intestinal tapeworms on presentation but may be useful in endemic regions. Instead, the diagnosis of cysticercosis is made on the basis of symptoms, neuroimaging, and epidemiological exposures.[1] Computed tomography of the head and MRI of the brain should be performed on patients suspected of having NCC. Patients with basal subarachnoid involvement should undergo MRI of the spine.[1] Imaging may reveal cystic, enhancing, and/or "cigar-shaped" calcified lesions. Leptomeningeal enhancement and hydrocephalus may also be seen. Serological testing may aid in diagnosis, but negative serological test results do not exclude NCC, especially in patients with characteristic clinical symptoms and imaging findings, nor do positive test results indicate an active infection, as patients from endemic areas may have developed antibodies because of a previous infection.[8] The sensitivity for NCC determined by enzyme-linked immunotransfer blot serology has been reported to be 86%.[1] However, serological test results may be negative in disease with low cyst burden. Finally, the real-time polymerase chain reaction assay for *T solium* DNA is highly sensitive and specific for active subarachnoid and ventricular NCC and is even more sensitive when performed on cerebrospinal fluid.[9] Quantitative polymerase chain reaction results are furthermore correlated with response to therapy.

The treatment of NCC is individualized and dependent on symptoms. Patients with clinical manifestations of elevated ICP, such as headache, nausea, vomiting, papilledema, and somnolence, should first be treated with corticosteroids to lower inflammation and cerebral edema. This patient's case was complicated by a diagnosis of LTBI. Previous research suggests that patients treated with corticosteroids have a 5-fold increased risk of developing a new diagnosis of TB.[10] Less is known about the risk of reactivation of TB in patients with LTBI. Because of the progression of symptoms and concern for worsening ICP, our care team decided that the risk of TB reactivation was outweighed by the benefit of corticosteroid treatment. However, it remains clear

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that treating such complex cases should be individualized.

Coinfection with *T solium* and *M tuberculosis* is not unexpected given their overlapping widespread distributions and has been previously reported.[11] The diagnostic differential for brain lesions includes NCC and cystic tuberculomas. Latent TB infection treatment is individualized and consists of a rifamycin-based regimen or isoniazid monotherapy regimen.

Obstructive hydrocephalus secondary to NCC is managed with surgical removal of the offending cysticercus or placement of an external ventricular shunt.[1] Communicating hydrocephalus is treated with ventriculoperitoneal shunt placement or third ventriculostomy.[1] Once the elevated ICP has resolved, antiparasitic therapy may be initiated for patients with viable and/or degenerating cysts. The treatment for patients with low cystic burden (1 to 2 cysts) consists of albendazole. Patients with more than 2 cysts should be treated with a combination of albendazole and praziquantel, given evidence of the higher radiographic resolution as compared with albendazole alone.[4] The duration of treatment is typically between 10 and 14 days but may be extended depending on the cyst burden. Because antiparasitic medications can cause life-threatening inflammation as viable cysts degenerate, adjunctive corticosteroids are recommended to decrease the seizure risk.[1] A typical corticosteroid regimen begins 1 day before the initiation of antiparasitic medications, is continued for 1 to 2 weeks, and ends with a taper.[12] Repeat neuroimaging should be performed every 6 months to monitor cyst resolution.[1]

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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