CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 8-2017: A 39-Year-Old Zimbabwean Man with a Severe Headache

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PRESENTATION OF CASE

Dr. A. Tariro Makadzange: A 39-year-old man was admitted to a large, urban tertiary-care hospital in Zimbabwe (where a physician affiliated with this hospital works) because of a severe headache.

The patient had been in his usual health until approximately 1 month before admission, when headaches developed. The headaches were initially intermittent and then gradually became persistent, with increasing severity. The patient took paracetamol (acetaminophen), but his condition did not improve. On the evening of admission, one episode of emesis occurred. On evaluation in the emergency department, the patient reported a severe frontal headache, neck pain, and photophobia, with no hearing loss, visual symptoms, seizures, or new rashes. He had no recent trauma, weight loss, night sweats, cough, or shortness of breath.

During the month before admission, the patient had received a diagnosis of non–insulin-dependent diabetes mellitus (NIDDM), for which metformin and glibenclamide were administered. He was otherwise well. He reported that he had not been tested for human immunodeficiency virus (HIV) in the past, and he was taking no other medications. He lived with his wife and children in a suburban area and worked as a long-distance truck driver. He had traveled to Zambia 2 weeks before admission. He had stopped drinking alcohol approximately 2 years before admission and had never smoked tobacco. His sister had NIDDM, and his children were healthy.

On examination, the temperature was 36.8°C, the blood pressure 125/78 mm Hg, the pulse 53 beats per minute, and the respiratory rate 18 breaths per minute. The patient was alert and fully oriented, with a normal level of consciousness. His neck was stiff, with nuchal rigidity, and the remainder of the examination was normal. A peripheral-blood smear and a rapid test for malaria antigen were negative for malaria. A lumbar puncture was performed without additional imaging of the brain, since the patient had no focal neurologic signs. The opening pressure was 25 cm of water (normal, <20). Results of the cerebrospinal fluid (CSF) analysis and other laboratory test results are shown in Table 1. Penicillin and chloramphenicol were administered, and diagnostic tests were performed.

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission
Blood		
Hemoglobin (g/dl)	12.0–16.0	12.8
White-cell count (per mm^3)	4000–10,000	4200
Differential count (%)		
Neutrophils	40–75	72.5
Lymphocytes	20–45	17.2
Monocytes	2–10	9.1
Eosinophils	0–6	0.9
Basophils	0–3	0.3
Platelet count (per mm^3)	150,000–400,000	322,000
Mean corpuscular volume (μm^3)	76–96	83.6
Sodium (mmol/liter)	133–146	136
Potassium (mmol/liter)	3.5–5.2	3.9
Chloride (mmol/liter)	96–109	100
Urea nitrogen (mg/dl)	5.6–18.8	8.4
Creatinine (mg/dl)	0.54–1.48	0.95
Glucose (mg/dl)	70–104	182
Cerebrospinal fluid		
Opening pressure (cm of water)	<20	25
Color	Clear	Clear
Turbidity	Colorless	Colorless
Xanthochromia	None	None
Red-cell count (per mm^3)	<5	<5
White-cell count (per mm^3)	<5	<5
Protein (g/liter)	15–45	47.5
Glucose (mg/dl)	45–80	110‡

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The reference ranges at the hospital in Zimbabwe may therefore not be appropriate for all patients.

‡ In this patient, the ratio of cerebrospinal fluid glucose to blood glucose is 0.60 (reference range, 0.55 to 0.70). A normal cerebrospinal fluid glucose level is approximately two thirds the blood glucose level.

DIFFERENTIAL DIAGNOSIS

Dr. David R. Boulware: This 39-year-old man presented with a gradual onset of headaches of worsening severity, neck pain, photophobia, and other clinical symptoms that are consistent with meningitis. Although there are many causes of meningitis, several features of this patient's presentation may allow us to efficiently narrow our differential diagnosis. First, the patient is from sub-Saharan Africa; in this region, there is a high prevalence of HIV infection, and the pathogens that most commonly cause meningitis are different from those in the United States and other high-income countries. Second, lumbar puncture revealed an elevated opening pressure, and CSF studies were notable for a white-cell count of less than 5 per cubic millimeter, an elevated protein level, and a normal glucose level. The near absence of white cells in the CSF suggests possible profound immunocompromise and underscores the importance of determining whether this patient has HIV infection.

BACTERIAL AND VIRAL MENINGITIS

In a patient with presumed meningitis, life-threatening bacterial causes need to be urgently ruled out. Although the proportion of cases of meningitis in adults that are due to bacterial infection is lower in sub-Saharan Africa than in the United States, bacterial meningitis remains an important consideration. The most common causes of bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.[1,2] *N. meningitidis* causes epidemic meningitis largely in the area known as the meningitis belt, which stretches across the semi-arid Sahel of Africa, just south of the Sahara Desert. The introduction of the meningococcal serogroup A conjugate vaccine in 2010 largely eliminated epidemic disease, but in recent years, episodic outbreaks of disease due to meningococcal serogroup C have emerged.[3] This patient is from Zimbabwe, which is located outside the meningitis belt; in this part of southern Africa, the most common cause of bacterial meningitis is *S. pneumoniae*.[1] The inclusion of the *H. influenzae* type b vaccine and the 13-valent pneumococcal conjugate vaccine in the World Health Organization (WHO) schedule of routine childhood vaccinations has led to a substantial decrease in the incidence of *H. influenzae* and pneumococcal meningitis in children and to some decrease in the incidence in adults.[2,4] Patients with bacterial meningitis usually present with the sudden onset of headache, fever, nuchal rigidity, and photophobia. CSF analysis typically reveals neutrophilic pleocytosis and an elevated protein level and often reveals hypoglycorrhachia (a low glucose level) (Table 2). This patient's gradual pre-

Table 2. Typical Laboratory Features of Bacterial, Tuberculous, Cryptococcal, and Viral Meningitis.*

Variable	Reference Range	Bacterial Meningitis	Tuberculous Meningitis	Cryptococcal Meningitis	Viral Meningitis
Cerebrospinal fluid					
Protein (mg/dl)	15–45				
Median		250	100–200	80	75
Interquartile range		90–700	80–490	40–130	40–180
White-cell count (per mm^3)	<5				
Median		500–2500	200	20	80–100
Interquartile range		350–20,000	40–700	<5–120	5–500
Neutrophils (%)	0	90	35–40	<15	<35
Frequency of clear color (% of patients)	100	2	60	>95	>95
Microscopic testing					
Traditional test		Gram's stain	Acid-fast bacilli stain	India ink stain	—
Sensitivity of the test (%)		60–90 without antibiotics	<15	80	—
Diagnostic testing					
Recommended test		Culture	Nucleic-acid amplification test, such as Xpert MTB/Rif	Cryptococcal antigen test	Polymerase-chain-reaction assay
Sensitivity of the test (%)		>95 without antibiotics	30 with 2-ml sample; 70 with 6-ml sample	>95	Varies
Cerebrospinal fluid:blood glucose ratio	0.55–0.70				
Median		0.20	0.28	0.40	0.65
Interquartile range		0.03–0.50	0.10–0.50	0.25–0.50	0.40–0.80
Serum C-reactive protein (mg/liter)	<8				
Median		140	60	40	<20
Interquartile range		50–400	20–120	20–80	0–20

* Data are from Durski et al.,[5] Bahr et al.,[6] Marais et al.,[7] and Jarvis et al.[8]

sentation over a period of weeks and the normal glucose level and absence of pleocytosis in the CSF argue strongly against a diagnosis of bacterial meningitis.

Does this patient have meningitis due to a viral infection? Persons with acute HIV infection can present with headache, neck pain, and photophobia. Findings in the CSF are typically characterized by an elevated white-cell count (with the cells composed predominantly of lymphocytes) and an increased protein level. The clinical presentation may also include rash, fever, sore throat, myalgia, and in rare cases, mental-status changes that are consistent with encephalitis.[9,10] This patient did not have the CSF pleocytosis, rash, or pharyngeal symptoms that would be suggestive of acute HIV infection. Other common causes of viral meningitis, such as enterovirus, herpes simplex virus, and lymphocytic choriomeningitis virus, are also unlikely in this patient, given the near absence of white cells in the CSF and the gradual onset of worsening headaches over a period of 1 month.

CHRONIC HIV INFECTION

The differential diagnosis for meningitis is highly influenced by the immune status of the patient. In many parts of southern Africa, where the prevalence of HIV exceeds 10% among adults and 70% among hospitalized patients,[11]

HIV has had a massive effect on the causes of meningitis. Of the hospitalized adults with meningitis in sub-Saharan Africa, 85% or more have chronic HIV infection,[5,11,12] which suggests that this patient is likely to be infected with HIV. The differential diagnosis for subacute meningitis in a person with HIV infection is broad; however, the most frequent causes in Africa are *Cryptococcus neoformans* and *Mycobacterium tuberculosis*. In central, east, and southern Africa, cryptococcal meningitis is more common than all other types of meningitis combined.[5] Thus, the most important consideration in formulating a differential diagnosis in this patient is his HIV status. If he has HIV, the most likely diagnosis is cryptococcal meningitis or tuberculous meningitis. Although these two diagnoses are often difficult to distinguish from each other without laboratory testing, several features of this patient's presentation may help us to arrive at the correct diagnosis.

CRYPTOCOCCAL MENINGITIS

Cryptococcus is a ubiquitous yeast that is most likely acquired during childhood through inhalation.[13] In patients with intact cellular immunity, the infection is typically asymptomatic or manifested by mild lower-respiratory-tract symptoms. The organism is usually eradicated by the cellular immune system, but latency is often established. The subsequent development of an immunocompromised state, which may be due to HIV infection, liver cirrhosis, or long-term use of glucocorticoids, can result in disease reactivation, with hematologic spread to the central nervous system. In this patient, the recent diagnosis of NIDDM would not necessarily increase his risk of cryptococcal meningitis, but the presence of both HIV infection and diabetes would confer a greater likelihood of this diagnosis.

HIV-infected patients with cryptococcal meningitis are usually severely immunocompromised, with a CD4+ T-cell count of less than 100 per cubic millimeter. Such patients often present with subacute-to-chronic headaches that have lasted for several days or weeks (similar to the headaches seen in this case). Nausea and vomiting are common, but fever is present in only approximately half of patients. Thus, the absence of fever in this patient does not rule out cryptococcosis. Seizures and focal neurologic signs can be present, particularly in patients who present with advanced disease.

In patients with cryptococcal meningitis, findings in the CSF are highly variable, and up to 40% of such patients have a normal CSF profile. The CSF white-cell count is generally relatively low, with the cells composed predominantly of lymphocytes; the median count is approximately 20 per cubic millimeter, and only 25% of patients have a count of more than 100 per cubic millimeter. CSF white-cell counts can often be higher in patients receiving antiretroviral therapy. The CSF glucose level may be low or normal, and the CSF protein level is sometimes elevated (Table 2). In this patient, the normal white-cell count, elevated protein level, and normal glucose level in the CSF are consistent with the diagnosis of cryptococcal meningitis.

TUBERCULOUS MENINGITIS

Tuberculous meningitis has features similar to those of cryptococcal meningitis. If this patient were to have HIV, tuberculous meningitis would be an important consideration, because the presence of HIV infection markedly increases the likelihood of *M. tuberculosis* reactivation. In countries in which the rates of tuberculosis and HIV infection are high, such as Zimbabwe, *M. tuberculosis* is the second leading cause of meningitis. Patients with tuberculous meningitis often present with nonspecific symptoms, including generalized malaise, fever, and the gradual onset of headaches over a period of 1 or 2 weeks (similar to the headaches seen in this patient). Findings in the CSF are similar to those seen in cryptococcal meningitis, although pleocytosis and a low glucose level are often present (Table 2). As compared with cryptococcal meningitis, tuberculous meningitis generally causes a more pronounced increase in the CSF white-cell count. In this patient, the CSF white-cell count was less than 5 per cubic millimeter and the CSF glucose level was normal; these findings favor the diagnosis of cryptococcal meningitis.

DIAGNOSTIC TESTING IN A RESOURCE-LIMITED SETTING

Diagnostic tests for cryptococcal meningitis include cryptococcal antigen testing, India ink staining, and culture. The most sensitive test is a cryptococcal antigen lateral flow assay.[14] India ink staining is commonly used in resource-limited settings, but the sensitivity is only approximately 80%. If the patient has a low organism burden,

the sensitivity is lower; when there are less than 1000 yeast cells per milliliter of CSF, the sensitivity is only approximately 40%.[15] In addition, 5 to 10% of persons with cryptococcal meningitis present with early disseminated cryptococcal infection, with detectable cryptococcal antigen in the peripheral blood and a possibly abnormal CSF profile but with a negative CSF test for cryptococcal antigen.[16] In the absence of treatment, many of these persons will eventually have a positive culture for cryptococcal meningitis.[15]

The diagnosis of tuberculous meningitis remains a challenge. The WHO recommends the use of a nucleic-acid amplification test such as the Xpert MTB/Rif assay (Cepheid) as the initial diagnostic assay for tuberculous meningitis.[17] However, the sensitivity of this test is highly dependent on whether an adequate volume of CSF is tested,[6] and a negative test does not rule out tuberculous meningitis. A clinical diagnosis that is based on physician judgment remains the cornerstone of the diagnosis.

I think this patient most likely has cryptococcal meningitis, but it can be difficult to distinguish tuberculous meningitis from cryptococcal meningitis solely on the basis of the CSF profile, without specific diagnostic testing. I suspect the diagnosis in this case was based on a positive CSF test for cryptococcal antigen or on direct visualization of yeast consistent with cryptococcus on India ink staining.

DR. DAVID R. BOULWARE'S DIAGNOSIS

Cryptococcal meningitis in a patient with chronic human immunodeficiency virus type 1 infection.

DISCUSSION OF MANAGEMENT

Dr. Makadzange: On the second hospital day, a CSF test for cryptococcal antigen was positive. Penicillin and chloramphenicol were discontinued. On the third hospital day, HIV testing was positive for HIV type 1 (HIV-1), and the CD4+ T-cell count was 31 per cubic millimeter. Prophylactic therapy with sulfamethoxazole–trimethoprim for *Pneumocystis jirovecii* pneumonia was started.

Once the result of the cryptococcal antigen test was known, combination antifungal therapy, which is the recommended treatment for cryptococcal meningitis, was begun.[18] Because of the cost of some antifungal medications, treatment strategies differ between the United States and resource-limited settings. In the United States, standard treatment includes induction therapy with amphotericin B (typically liposomal amphotericin B) plus flucytosine for 14 days, consolidation therapy with high-dose fluconazole, and maintenance therapy and secondary prophylaxis with a lower dose of fluconazole.[19] The addition of flucytosine to amphotericin B results in a clinically significant increase in 6-month survival[18]; however, flucytosine costs more than $2,000 per day in the United States and is unavailable in resource-limited countries. In resource-limited countries, recommended therapy consists of amphotericin B deoxycholate plus high-dose fluconazole,[20] which is the treatment this patient received.

To mitigate the toxic effects of amphotericin B deoxycholate, the patient received intravenous fluid support and electrolyte replacement.[20] Amphotericin-induced nephrotoxicity is a well-known cumulative toxic effect; among patients who receive amphotericin, severe acute kidney injury is relatively rare (occurring in <5% of patients)[15] but severe potassium deficiency is common and can be life-threatening.[21] After 5 days of treatment with amphotericin B deoxycholate, massive losses of potassium and magnesium in the urine are common. In resource-limited settings, standardized electrolyte supplementation and replacement and laboratory monitoring of electrolyte levels increase 30-day survival by up to 25%.[21]

Because this patient presented with elevated intracranial pressure (>20 cm of water), he underwent repeat therapeutic lumbar punctures. Elevated intracranial pressure is common and occurs in up to 65% of persons with cryptococcal meningitis. The increased pressure is caused by mechanical obstruction of CSF outflow through the arachnoid villi by large encapsulated yeast. The large polysaccharide capsules surrounding the yeast correlate with high intracranial pressure.[22] When the intracranial pressure is controlled, the risk of death decreases.[13] In patients with cryptococcal meningitis, the median amount of CSF that needs to be drained at the time of diagnosis to normalize the intracranial pressure is typically 20 ml (interquartile range, 15 to 25). If a second therapeutic lumbar puncture is performed, the relative risk of death during the first 10 days is decreased by 70%.[23] This patient received both

combination antifungal therapy and management of increased intracranial pressure with therapeutic lumbar puncture. Fortunately, he had clinical improvement and ultimately had an uneventful recovery.

The final consideration in this patient's care was the timing of the initiation of antiretroviral therapy. In most patients presenting with an opportunistic infection and a CD4+ T-cell count of less than 50 per cubic millimeter, early initiation of HIV therapy results in a higher rate of survival but also probably results in a higher risk of developing the paradoxical immune reconstitution inflammatory syndrome (IRIS).[24,25] However, there is a clear exception in patients with cryptococcal meningitis, in whom early initiation of HIV therapy results in an approximately 15% increase in the rate of death occurring during the first 30 days, which is most likely due to IRIS.[15,26] In such patients, both immediate initiation of HIV therapy and initiation during the second week of hospitalization are associated with higher mortality.[15,26] Patients with a very low CSF white-cell count (i.e., <5 per cubic millimeter) have a higher risk of death if HIV therapy is started within 10 days after the initiation of antifungal therapy. Guidelines in the United States recommend deferring the initiation of HIV therapy until 4 to 6 weeks after the initiation of antifungal therapy.[27]

On the basis of these considerations, it was decided that this patient should start to receive antiretroviral therapy approximately 4 weeks after the initiation of antifungal therapy. Before hospital discharge, the patient received counseling about HIV, was registered in the outpatient HIV clinic, and was scheduled for outpatient follow-up. He returned to the HIV clinic 2 weeks later (4 weeks after the original diagnosis), and antiretroviral therapy with stavudine, lamivudine, and nevirapine was initiated. Nine months after the initiation of antiretroviral therapy, the patient's CD4+ T-cell count had increased to 218 per cubic millimeter. Two and a half years after the initiation of antiretroviral therapy, his CD4+ T-cell count had risen to 244 per cubic millimeter, and the secondary prophylaxis with fluconazole was discontinued. Four years after the initiation of antiretroviral therapy, he continues to receive clinical care, including treatment with once-daily doses of tenofovir, lamivudine, and efavirenz, and his HIV-1 viral load is less than 20 copies per milliliter.

FINAL DIAGNOSIS

Cryptococcal meningitis in a patient with chronic human immunodeficiency virus infection.

This case was presented at the Ninth Annual Workshop on Advanced Clinical Care–AIDS in Durban, South Africa (organized by Drs. Henry Sunpath and Mahomed-Yunus S. Moosa [Infectious Diseases Unit, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal] and Dr. Rajesh T. Gandhi [Massachusetts General Hospital and the Ragon Institute] and sponsored by the Harvard University Center for AIDS Research [NIH P30 AI060354], McCord Hospital, the University of KwaZulu-Natal, the South African HIV Clinicians Society, and the KwaZulu-Natal Department of Health).

Dr. Makadzange reports receiving honoraria from GlaxoSmithKline and Janssen Pharmaceuticals and being an employee of Gilead Sciences. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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