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Not Your “Typical Patient”: Cryptococcal Meningitis in an Immunocompetent Patient

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Abstract

Meningitis, when caused by the fungal mycoses *Cryptococcus neoformans*, is normally seen in immunocompromised hosts. However, immunocompetent patients are also susceptible to cryptococcal meningitis (CM). In patients with an intact immune system, CM usually presents with the typical signs and symptoms of meningitis: fever, stiff neck, and headache. Major implications for the primary and advanced practice nursing plans of care for CM patients include a thorough history and physical exam, early diagnosis and treatment, and an individualized plan of care focused on minimizing sequelae and side effects of treatment and maximizing functional recovery.

Cryptococcal meningitis (CM) is caused by an infection from the encapsulated yeast, *Cryptococcus neoformans* (*C. neoformans*). In patients with HIV/AIDS, it often is the first opportunistic infection to be diagnosed, with incidences ranging from 10% in the United States to as high as 30% in Africa (Jones & Nathwani, 1995). Persons with intact immune systems also can be infected, however. Infection occurs when the fungus is inhaled and the spores are spread systemically via the lungs. Meningitis is the most common presenting infection in patients, but pneumonia, skin infections, and osteomyelitis also have also been linked to *C. neoformans* (Jones & Nathwani; Portegies et al., 2004). If intact, the immune system forms a mucous capsule around the fungus to isolate it, thus offering some protection to the host. When the yeast spreads to the brain in immunocompetent hosts, the encapsulated fungus spurs a local granulomatous response, and the fungus becomes “walled off,” which may appear on computed tomography (CT) as a ring-enhancing lesion. Patients who present with CM often have relapses following initial treatment, with similar presentations for each relapse. This article discusses the case of one such patient, J, and presents reasons why he did not fit the “typical” patient profile for an initial diagnosis of CM. This patient's presentation and clinical findings are discussed in context with the assessment findings and diagnostic test results characteristic of this disease. The major implications for both primary and advanced practice nursing care are discussed within the framework of the case study and the research to date.

Case Presentation

J, a 46-year-old man, presented to the emergency department (ED) with a 7-week history of headache, nausea, and fatigue and new onset (2 days) altered mental status. Six weeks prior to admission, J had visited his primary care physician for these symptoms, at which time migraine headache was diagnosed and treatment initiated. Upon admission to the ED, a CT scan of his head revealed three ring-enhancing lesions in the right frontal and parietal lobes. J was admitted to the neurosurgical unit for further evaluation and a biopsy. Differential diagnoses included central nervous system infection and brain tumor.

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Upon admission to the unit, nurses gathered data from his significant other. J had no significant past medical or surgical history and had been in good health until 7 weeks ago. Family history was significant for coronary artery disease, and he had no known drug allergies. A social history revealed that J had smoked 10 cigarettes a day for more than 20 years, he did not drink, and he never tried street drugs. J was homosexual, had fewer than 10 partners throughout his lifetime, and had been in a monogamous relationship for 20 years. Both partners were tested for HIV in 1996 and had negative results. J worked full-time in the garden industry before his admission. His hobbies included gardening and caring for the birds in his large avium.

Later on the admission day, J had a needle aspiration biopsy that, when cultured, grew *C. neoformans*. A 6-week course of amphotericin B and flucytosine was initiated, and HIV retesting remained negative. Additional testing was completed to rule out other immunocompromising conditions. Postbiopsy, J's mental status fluctuated, and his gait was markedly ataxic. Serial lumbar punctures were performed in an effort to relieve the increased pressure, but 4 weeks into therapy, J developed signs and symptoms of hydrocephalus, including lethargy, worsening ataxia, and altered mental status. As a result, physicians placed a ventriculo-peritoneal shunt. J's condition improved postshunt placement, and he was discharged to the hospital's rehabilitation unit on flucytosine. At the time of discharge from rehabilitation, he had undetectable antigen levels and his CT revealed no ventricular enlargement.

Discussion

A patient with CM usually is immunocompromised. Until the advent of HIV/AIDS, more than 85% of patients diagnosed with CM had some associated deficiency of cell-mediated immunity, and this number is likely higher today (Jones & Nathwani, 1995). Other immunocompromised conditions associated with a typical presentation include a history of alcoholism, cancer, or transplantation; sarcoidosis; Hodgkin's lymphoma; collagen vascular disease; splenectomy; chronic organ failure; or systemic corticosteroid treatment. J's history did not include any of these risk factors; instead, homosexuality was his major CM risk factor. However, J and his partner had been in a monogamous relationship for 20 years and both had previously tested negative for HIV. While it was appropriate to repeat J's HIV test, the search for the cause needed to focus elsewhere.

To date, three serotype varieties of *C. neoformans* have been identified: *C. neoformans neoformans* (n), *C. neoformans grubii* (gr), and *C. neoformans gattii* (g). Serotyping is important because of the fungal contact mechanism and virulence of individual strains. The *neoformans* (n) variety is found predominantly in contaminated soil and in bird droppings, and is responsible for the majority of CM cases in immunosuppressed patients (Mitchell et al., 1995; Speed & Dunt, 1995). Because J owned an avium, he could have inhaled bird feces. When the (n) variety was present in immunocompetent patients, a positive outcome (complete recovery or mild sequelae) was achieved 89% of the time (Mitchell, et al.). In the Mitchell study (1995), the (g) variety was found in 74% of immunocompetent CM patients. It was associated with longer hospital stays, significant sequelae, and prolonged therapy, and necessitated additional antifungal treatment (2.4 gm vs. 1.4 gm), compared with those infected with the (n) variety (Mitchell et al., 1995; Speed and Dunt, 1995). The (gr) variety recently was distinguished as a separate strain from the (n) variety based on biochemical properties, and it usually infects patients with AIDS or other immunocompromised states (Steenbergen & Casadevall, 2000). The (g) variety spreads primarily through exposure to several varieties of tropical plants and the bark and leaves of gum trees. Because J worked in the garden industry, he also could have been exposed to the (g) variety. Cryptococcal antigen serotyping was warranted in his case to help determine treatment.

CM patients with intact immune systems usually present with the typical signs and symptoms of meningitis: fever, stiff neck, and headache (Vandemark, Lovasik, Neatherlin, & Omert, 2004). In patients with AIDS, CM symptoms may be subtle and include fever and lethargy. Signs of a lesion rarely are seen even when cryptococcal elements are present in cerebral spinal fluid (CSF; Turner & Scaravilli 2002; Vandemark et al, 2004). J's was an atypical case, however. His immune system was intact, and his first symptom, headache, was subtle and nonspecific. But 7 weeks later, his symptoms progressed to include nausea, fatigue, lethargy, and altered mentation. These signs and symptoms are nonspecific for meningitis. At initial presentation, J's symptoms seemed more related to the three space-occupying lesions than to meningitis. Speed and Dunt (1995) found that patients with *C. neoformans* (g) infection had more nonspecific symptoms at onset and a longer duration of symptoms before presentation. They also found that it usually took extra time to assign a diagnosis to these patients, and the patients tended to relapse after therapy. Unfortunately, this pattern held true in J's case.

J's Course of Care

J adhered to his medication regimen and completed a 10-week course of therapy and routine follow-up. He returned emergently to the neurology clinic, 3 months postdischarge with a 2-day history of nausea, vomiting, decreased appetite, headache, and confusion. He had quit smoking, was working part-time, and was using outpatient occupational and physical therapy services. His review of symptoms was significant for fatigue, a weight loss of more than 50 pounds during the last 3 months, headache, inability to use his left arm, blurred vision, photophobia, nausea and vomiting, and anorexia. On physical examination, J was thin (height 5'10", weight 131 pounds), alert, and oriented to name only. His temperature was 99.1°F, his pulse was 88/min, R 16/min, BP 104/68 mm/Hg. His CN II was impaired as evidenced by a visual field deficit (quadrantanopsia). Strength was 4/5 in the right upper and lower extremities, 0/5 in the left upper extremity, and 3/5 left lower extremity. His neck was moderately rigid, with decreased range of motion. Palpable postauricular and posterior cervical nodes were noted. J was urine incontinent, with 1+ positive non-pitting edema of the left hand; all peripheral pulses were intact at 2+. All other systems were grossly normal. Complete blood count on admission revealed a white blood cell (WBC) count of 11.2% with increased granulocytes, a hemoglobin of 14.8%, a hematocrit of 44%, and a platelet count of 436 K/ μ . A head CT revealed enlarged ventricles without shift and cerebral edema. A lumbar puncture (LP) was performed carefully to determine if there was a CM relapse. Opening pressure was 40 cm H₂O, and CSF analysis revealed an elevated white blood cell count of (>100/K/ μ), and a positive cryptococcal antigen titer (>1:32). J was closely monitored during and after the LP for any signs of neurologic deterioration.

J had a CM recurrence, and amphotericin B and flucytosine were reinitiated. His opening CSF pressure was of concern, as his valve should have opened at a lower pressure (30 cm H₂O). He was experiencing shunt failure, overwhelming hydrocephalus, or cerebral edema secondary to the recurrent CM. The neurosurgery service assessed his shunt function, and determined it was working properly. Dexamethasone (Decadron) and acetazolamide (Diamox) were initiated to decrease edema and CSF production. The LP was to be repeated later to evaluate therapy effectiveness.

Therapeutic and Nursing Implications

Diagnostic evaluation for CM requires an LP with measurement of opening pressure; CSF analysis including cell counts, protein and glucose levels; India ink staining; fungal culture; and cryptococcal antigen (Portegies et al., 2004; Vandemark et al., 2004). Serum cryptococcal latex agglutination titers also should be drawn; these are 87% sensitive in HIV-negative patients (Ross & Katz, 2002). A definitive diagnosis of CM can be made by either visualizing the fungus

in CSF using India ink preparation (75%–85% sensitive), CSF latex agglutination assay (95% sensitive), or a positive CSF culture for *C. neoformans* (Portegies et al., 2004). The CSF of patients with CM may be clear with increased lymphocytes and protein and decreased CSF glucose, or it may be turbid with increased cells, including polymorphonuclear leukocytes (Turner & Scaravilli, 2002). Serum cryptococcal latex agglutination titers will be positive, and WBC counts will be elevated in patients with intact immune systems.

If suspicion is high and CSF and serum results are negative, the LP should be repeated. In some cases, the CSF may be antigen-negative, but cultures of suspected lesions obtained through brain biopsy will grow *C. neoformans* (Jones & Nathwani, 1995). Most patients with non-AIDS CM have evidence of raised intracranial pressure (ICP), but in one study, there were no clinical symptoms in 10% of patients, and CT scanning for all suspected cases was recommended (Jones & Nathwani, 1995). In J's case, the CT scan led to the brain biopsy and culture and his CM diagnosis (due to the ring-enhancing lesions), confirming that his was not a typical case that proceeded in a "normal" fashion.

Once a diagnosis is confirmed, patients should remain in the hospital for initial treatment to adequately monitor their response to therapy and its potential side effects. Pharmacologic therapy depends upon HIV status (Table 1). Serotyping based upon patient history may be indicated to guide dosing and length of therapy. The concomitant administration of interferon-gamma or interleukin-12 also has been suggested as adjuvant therapy in HIV-positive patients with CM to enhance natural killer cell function when given with flucytosine (Turner & Scaravilli, 2002; Pappas, 2004). Patients with a CM diagnosis may benefit by consulting with the infectious disease service to manage antifungal therapy, particularly if relapses occur (as in J's case). Intrathecal administration of amphotericin B may be initiated in some refractory cases.

The neuroscience nursing team works together to develop a plan of care for CM patients. When using amphotericin B, nurses must ensure adequate hydration and premedication (acetaminophen and/or diphenhydramine for fever, chills, and headache to prevent therapy-related side effects). Because flucytosine is associated with nausea and vomiting, it is important to ensure the patient has medications for prophylaxis or treatment.

CM patients clearly are at risk for decreased intracranial adaptive capacity. In J's case, his decreased adaptive capacity may have been related to many factors: shunt failure, overwhelming hydrocephalus, or cerebral edema. The neurosurgery service ruled out shunt failure, so cerebral edema or overwhelming hydrocephalus may have caused J's decreased adaptive capacity. It is essential to assess carefully CM patients' vital signs, particularly blood pressure. CM patients are at risk of septic shock (hypotensive episodes to maintain adequate cerebral perfusion pressure; Vandemark et al., 2004). Other interventions include elevating the head of the bed to allow CSF outflow, and continued neurological checks every 2 hours. Maintaining normal body temperature also is critical for CM patients to prevent secondary consequences of hyperthermia on ICP and neurologic outcome (Vandemark et al.). Recommended cerebral edema treatment includes dexamethasone and acetazolamide. Additional considerations for J included the use of sedatives and mannitol (Osmitrol) and continued monitoring for signs and symptoms of shunt failure (Vandemark et al.).

It is important to monitor patients for medication side effects. Finger sticks should be ordered to assess blood glucose, because dexamethasone may cause a significant rise in glucose. Other interventions include repeating the crypto antigen test to determine ratio and response to therapy.

Headache associated with meningeal irritation can be difficult for nurses to manage. J described a headache that had lasted for more than 7 weeks at his initial presentation, and he continued

to complain of headache pain at his subsequent admission. J's plan of care included assessment of pain, including location and quality; providing a dark, quiet room; administering analgesics as necessary and assessing response to therapy; and instituting nonpharmacological measures for pain control (e.g., relaxation techniques). Advanced practice nursing interventions include managing the pain medication regimen and changing or augmenting medications as needed (independently or in consultation with the attending physician).

J also was at high risk for injury due to his seizure and fall potential, and fall and seizure precautions were added to his treatment. The bed should be placed in the low position, and food and toileting should be offered at least every 2 hours, if appropriate. Safety checks should be instituted per institutional policy (Vandemark et al., 2004).

J's altered mental status upon his first admission and his CM diagnosis put him at risk for inadequate nutrition. By his second admission, he had lost more than 50 pounds and was malnourished. Because fluconazole therapy often is associated with nausea and vomiting, nurses should communicate these potential adverse events to patients before starting therapy. Small, frequent meals during the prescribed therapy interval often helps patients meet their nutritional needs. An as-needed antiemetic such as ondansetron should be offered.

J's total protein was low, and his albumin level was 2.8 g/dL. His primary care planning included bowel sound and nutritional status assessments, laboratory value assessment, intake and output monitoring, administration of nausea-inducing medications 1–2 hours after meals, and daily weigh-in. Other interventions included a high-protein, high-calorie diet, dietician consultations, supplemental nutritional support, nausea medications such as meclizine 25 mg by mouth every day, and continued evaluation of laboratory values and response to therapy.

J's neurologic assessment revealed a flaccid left upper extremity, which, combined with his altered mental status, yielded a self-care deficit. Care planning now included maximal self-participation in activities of daily living (ADL), left hand elevation to reduce dependent edema, and a request for an occupational therapy consultation for ADL assistance.

Patients and their families must address the psychosocial implications of CM, including risk for anxiety and fear related to the diagnosis and prognosis.

Patients and their families must address the psychosocial implications of CM, including risk for anxiety and fear related to the diagnosis and prognosis. Much of this anxiety and fear may be related to a knowledge deficit regarding the disease, testing procedures, and interventions. Neuroscience nurses play a unique role in relieving some of these fears through education.

J experienced several CM recurrences that caused further neurologic deficits and a decline in his quality of life. Eighteen months after his initial diagnosis, J died from secondary complications of CM (an unusual outcome). Secondary complications may include seizure disorders, deep vein thrombosis/pulmonary embolism, or, in J's case, secondary infection. While immunocompetent CM patients are more likely to have a symptom relapse, they are less likely to die than their immunosuppressed host counterparts (Speed & Dunt, 1995). Using multiple regression analysis, two studies examined multiple predictors of poor CM outcomes in patients who were HIV negative. Only one predictor was consistent in both studies: altered mental status at initial presentation (Lu, Chang, Chang, & Chuang, 1999; Pappas et al., 2001). The possibility of altered mental status at initial presentation, which occurred with J, reinforces the need for early diagnosis and treatment initiation.

Summary

CM is a debilitating and potentially deadly disease that affects patients with both intact and impaired immune systems. J's case illustrates how subtle the initial signs and symptoms of this infection may be, and how early diagnosis and treatment is essential for optimal outcomes. Patients with CM have multisystem disturbances and require a well-organized and executed plan of care, and neuroscience nurses play an integral role in influencing the outcomes for these complex patients.

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Table 1
Pharmacologic Therapy for the Treatment of Cryptococcal Meningitis

Patient Type	Drug	Dose	Length of Therapy
HIV-negative, healthy host	amphotericin B	0.7–1 mg/kg/day	6–10 weeks
	plus 5-flucytosine	100 mg/kg/day	6–10 weeks
	Alternative Therapy		
	amphotericin B	0.7–1 mg/kg/day	2 weeks
HIV-negative, immunocompromised host	plus 5-flucytosine	100 mg/kg/day	2 weeks
	followed by fluconazole*	400 mg/day	10 weeks (minimum)
	Same regimens as above		
	amphotericin B	0.7–1 mg/kg/day	2 weeks
HIV-positive host	plus 5-flucytosine	100 mg/kg/day	2 weeks
	followed by fluconazole	400 mg/day*	10 weeks (minimum)

* Itraconazole (200–400 mg/day) is an acceptable alternative for patients who cannot tolerate fluconazole. Source: Saag et al., 2000.