Brief Report

Two Central Nervous System Infectious Diseases in a Patient with AIDS

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As medical interventions prolong the lives of patients with acquired immunodeficiency syndrome (AIDS), we have begun to observe multiple infections occurring simultaneously in a single patient. This report describes two central nervous system (CNS) infections, cryptococcal meningitis and cerebral toxoplasmosis, coexisting in a patient with AIDS. Although the treatment strategies for these CNS infections are generally established, often the physician must make management decisions based on clinical and statistical data and patient response to empiric trials of therapy rather than on the results of invasive diagnostic tests.

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This report describes two infectious diseases of the central nervous system (CNS), cryptococcal meningitis and cerebral toxoplasmosis, coexisting in a patient with acquired immunodeficiency syndrome (AIDS). No other case could be found in the literature in which a patient had two AIDS-related CNS infections from separate foci.

Case Presentation

A 33-year-old man was examined in the emergency department for complaint of a headache and stiff neck that had become progressively worse over the previous week. His pain was intermittently accompanied by nausea and vomiting, night sweats, and a low-grade fever. In addition to the presenting symptoms, the patient reported having had sores in his mouth for approximately 1 year.

Risk factors for human immunodeficiency virus (HIV) infection in his history included past occasional intravenous drug use (8 to 10 years before the onset of symptoms) and an incident of being sodomized while in prison more than 5 years before.

A physical examination revealed a thin man in mild distress. Findings from a neurologic examination were normal. His oral mucosa had multiple superficial ulcerations and white plaques. He had a monilial rash involving the groin area and several scattered red-brown, slightly raised lesions over both tibial areas and one lesion superior to the umbilicus. Multiple small lymph nodes could be palpated in the anterior cervical chains and inguinal areas bilaterally.

Initial noncontrast computed tomography (CT) of the head was normal and a lumbar puncture was performed. Magnetic resonance imaging (MRI) of the head with gadolinium enhancement revealed no abnormalities. Results of the lumbar puncture suggested meningitis, with 144 white blood cells, 85% lymphocytes, 3% polycytes, 5% monocytes, 7% reactive lymphocytes, cerebrospinal fluid (CSF) glucose level 48 mg/dL, serum glucose level 109 mg/dL, and CSF protein 150 mg/dL. An India ink test demonstrated the presence of fungi, and cultures grew *Cryptococcus neoformans*. The patient's initial CSF cryptococcal antigen (CrAG) test was positive.

Additional investigative studies included a complete blood count with 7.2 white blood cells and normal differential. The hemoglobin level was 15.7 g/dL, hematocrit 45.5%, platelets 236,000 μL, and protein 8.7 mg/dL. He had normal electrolyte values and renal and liver panels. Arterial blood gases and oxygen saturation on room air were normal. Blood and urine cultures were sterile. A wet mount of his oral lesions showed yeast and

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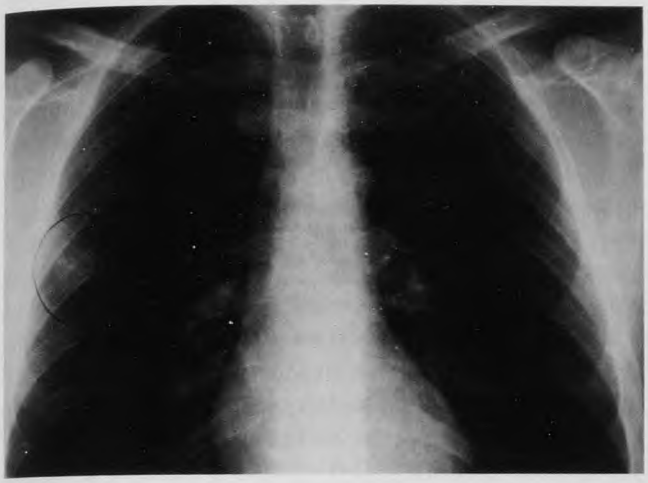

Figure 1. This routine chest radiograph of a 33-year-old man with AIDS and culture-proven cryptococcal meningitis reveals a density in the mid-right lung field (circled). Sputum culture and bronchoscopy were nondiagnostic. The lesion was presumed to be fungal after resolution with amphotericin B.

budding hyphae. Serum tests for syphilis were negative. Both purified protein derivative and anergy panel were negative.

Chest radiographs revealed an irregular density in the periphery of the right mid-lung field (Figure 1). Computed tomography images confirmed the presence of the lesion; however, because of its patchy configuration, it was not amenable to biopsy. Sputum samples were negative for fungi, acid-fast bacilli, *Pneumocystis carinii*, and atypical cells. Bronchoscopy was nondiagnostic.

The patient was subsequently confirmed to be seropositive for HIV infection. His initial CD4 count was $70/mL^3$. He therefore was started on zidovudine and *pneumocystis carinii* pneumonia prophylaxis with inhaled pentamidine. Daily infusions of amphotericin B also were begun.

A repeat CSF culture taken on the 11th day, after 353 mg of amphotericin B had been administered, remained positive for *Cryptococcus*, and his CSF CrAG was 34. The patient, however, remained free of headache and other symptoms from the 3rd day after initiation of amphotericin treatment.

He was discharged on the 23rd day of hospitalization with improvement of his CNS symptoms and oral candidiasis, after receiving a total of 555 mg of amphotericin B. The pulmonary nodule was smaller on subsequent chest radiographs. He was followed closely and continued to have outpatient amphotericin therapy twice weekly.

Approximately 10 days after discharge, the patient suddenly developed aphasia and right-sided hemiplegia

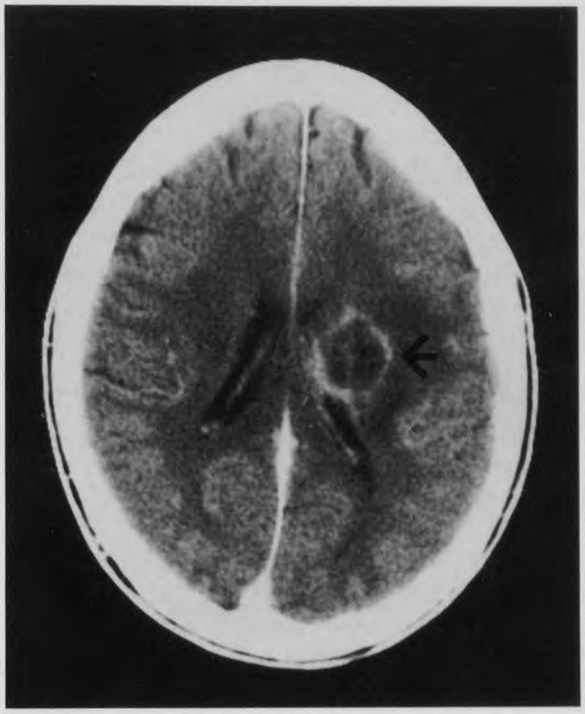

Figure 2. A head CT scan of a 33-year-old man with AIDS shows a single left-sided round lesion in the basal ganglia. An MRI of his head taken 10 days earlier, before treatment for cryptococcal meningitis, had been normal. He presented on the day the CT was performed with right-sided hemiplegia. He was empirically treated for toxoplasmosis with excellent results.

that involved his upper extremity more than his lower. Repeat CT scans of the patient's head revealed a single left-sided, round lesion in the area of the basal ganglia (Figure 2). A presumptive diagnosis of CNS toxoplasmosis was made. Empiric therapy using pyrimethamine, sulfadiazine, and supplemental leucovorin was initiated.

The patient responded rapidly. Within 1 week he improved from being wheelchair-dependent to walking with a cane. He remained only mildly aphasic and regained some motor use of his upper extremity. CT scans taken at 2-week intervals revealed decreases in edema and in the size of the mass lesion (Figure 3).

After 8 months of treatment, the patient began experiencing generalized side effects of amphotericin B. His serum creatinine level reached 3.8 mg/dL, and amphotericin B was changed to oral fluconazole. Administration of pyrimethamine and sulfadiazine to treat toxoplasmosis and fluconazole to treat cryptococcal meningitis were continued at standard maintenance doses.

In the 18 months after the patient's initial presentation, he required only one blood transfusion, necessitated by a drop in his hemoglobin level to 8.2 g/dL accompanied by fatigue. After experiencing intolerable nausea and

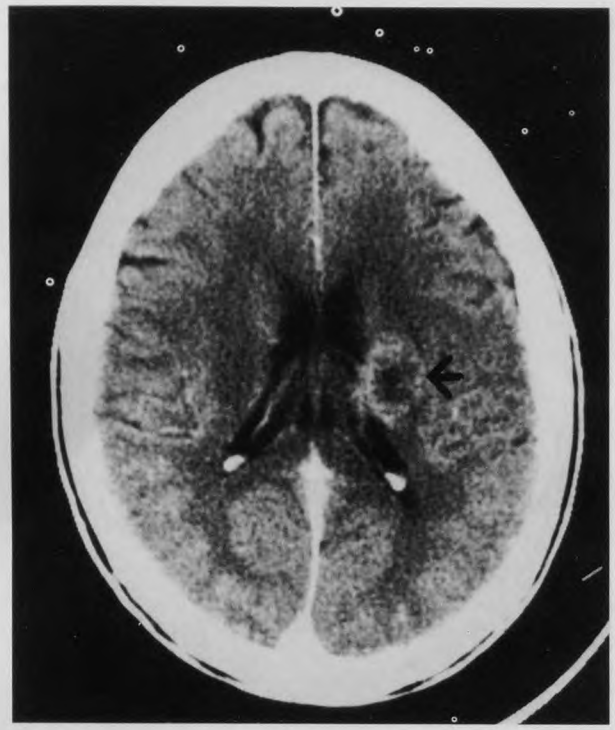

Figure 3. Follow-up head CT scan of the same 33-year-old man with AIDS after 2 weeks of treatment with pyrimethamine and sulfadiazine for presumed cerebral toxoplasmosis. The CT scan shows decrease in edema and size of the mass lesion. The patient had marked clinical improvement.

gastrointestinal side effects, which he attributed to the zidovudine, his medication was changed to dideoxyinosine (ddI), which he tolerated well.

The patient has had no further deterioration of his neurologic status. He does, however, have depression and decreased short- and long-term memory, both of which are presumed to be AIDS-related dementia.

Discussion

Neurologic symptoms, both central and peripheral, develop in 40% of patients with AIDS. It is estimated that more than 90% of all such patients have autopsy-proven evidence of neurologic disease, of either infectious or noninfectious origin. *Toxoplasma gondii* accounts for 50% to 70% of all focal brain lesions. Primary CNS lymphoma accounts for an additional 10% to 25% of lesions. Fungal and tubercular abscesses, metastatic Kaposi's sarcoma, and viral encephalitis are less common.[1] The presence of more than one infectious agent in a single CNS lesion has been reported in several cases.[2]

The incidence of CNS *T gondii* in patients with AIDS ranges from 25% to 80%.[3] It is a life-threatening infection; a mortality rate greater than 60% has been found in some studies. Relapses after treatment have been reported in 30% to 100% of patients, unless long-term maintenance therapy is administered.[4]

Toxoplasma gondii is a protozoan species found worldwide. Its transmission occurs from ingestion of uncooked, infected meat or oocytes shed by cats. In adults, *T gondii* was previously a rare cause of symptomatic infection. With the recent increase in the numbers of immunocompromised hosts, however, this organism has emerged as a major cause of CNS disease.[3]

Natural exposure to *T gondii* varies considerably. In the United States, studies have shown that 20% to 70% of inhabitants show serologic evidence of past exposure,[1] depending on the locale. In Europe, in a study of Parisians, 80% were identified as having positive serology. Therefore, it is believed that serologic studies (of IgG Ab levels) are of limited value in diagnosing cerebral toxoplasmosis or differentiating it from other diagnoses.[5] However, a negative serology in a patient with a CNS mass lesion is strong presumptive evidence against the diagnosis of toxoplasmosis.

There is still controversy over the need to do brain biopsies of mass lesions in patients with AIDS. Stereotactic brain biopsy is diagnostic in only 85% of patients and has a mortality rate of 5% to 22%. It is the only way, however, of establishing a definitive diagnosis.[2] Most authors prefer a 5- to 10-day therapeutic trial when clinical and CT findings are consistent with a diagnosis of cerebral toxoplasmosis. The diagnosis can be accepted as accurate if there is clinical improvement in response to antitoxoplasmosis therapy.

Brain biopsy currently is recommended for patients with progressive deterioration, unusual presentations, or failure to respond to empiric therapy.[3]

Identification of *T gondii* is difficult. The actual organisms are inconspicuous on routine stains, necessitating the use of immunoperioxidase histochemistry stains. In one study, *T gondii* was not detected in more than one half of the 48 confirmed cases of cerebral toxoplasmosis.[3] Magnetic resonance imaging seems to be more sensitive than CT in detecting CNS lesions, but again its usefulness in distinguishing between various diseases is unproven.[2,6]

Headache is the predominant symptom in patients with cerebral toxoplasmosis, and is largely the result of increased intracranial pressure. Neurologic findings range from slight focal deficits to dense hemiparesis. Seizures are not common, but can occur late in the course of the disease or with relapse, and are most often generalized.[3]

Almost one third of patients with cerebral toxoplasmosis will show clinical improvement and changes on CT scans within 3 days of initiating therapy with py-

rimethamine and sulfadiazine. The remaining patients usually respond to treatment within 2 weeks.[2]

Combined pyrimethamine and sulfadiazine therapy is the standard treatment for cerebral toxoplasmosis.[4,7] Leucovorin, initially at 10 to 15 mg/d, should also be given.[8]

Induction therapy with pyrimethamine and sulfadiazine and leucovorin should be continued for 4 to 6 weeks after resolution of all signs and symptoms of active infection. Treatment eradicates free trophozoites, but cysts are resistant to therapy and may result in relapse at a later date.[9] Because of the high frequency of relapse, up to 80% within 7 weeks of discontinuation of therapy, lifelong suppressive therapy is recommended.[7]

For those who cannot tolerate sulfonamides, clindamycin may be used in place of sulfadiazine.[7] Recently the use of clarithromycin has also been shown to be effective.[10,11]

Cryptococcus neoformans is the most common life-threatening fungal CNS pathogen and is the initial manifestation of AIDS in 40% to 45% of such patients.[12,13] *Cryptococcus* species are found worldwide, most commonly isolated from soil and pigeon droppings.

Although *Cryptococcus* is most widely known for CNS infection, it may also infect skin, bone, lymph nodes, and retina, as well as genitourinary, respiratory, and cardiovascular systems.[8,14] It is introduced into the body primarily through inhalation and may appear on chest radiographs as a single, poorly defined mass, usually in the lung periphery and often pleural based. The radiographic pattern is usually indistinguishable from other chronic granulomas,[15] and a negative sputum culture does not rule out *Cryptococcus*. Whenever *Cryptococcus* is identified at any site, disseminated infection should be suspected.[14]

In a recent study by the Centers for Disease Control (CDC), the prevalence of cryptococcal meningitis in AIDS patients was at least 5.4%, with the highest incidence existing among intravenous drug abusers and Haitians.[13] The organism can often be recovered from multiple extraneural sites as well.

Headache, which can be very mild, is the presenting symptom in approximately 70% of patients with cryptococcal meningitis.[13] The diagnosis, therefore, should be entertained if patients are at risk for HIV infection and complain of headache. Other symptoms include stiff neck, photophobia, vomiting, fever, and altered mental or neurologic status. These clinical symptoms are indistinguishable from those of acute toxoplasmosis.

The most sensitive method for the diagnosis of *Cryptococcus* is demonstration of the organism in the CSF by culture. Direct examination of CSF using India ink can usually reveal the presence of the fungus. However, only 75% of culture-proven *Cryptococcus* results in a positive India ink preparation test. The CSF often exhibits few or no white cells, a minimal lymphocytosis, and a glucose level that is normal or near normal.[13,16] Another reliable marker is CrAG. In one study CrAG was positive in 99% of those patients diagnosed with cryptococcal meningitis.[17]

The usual treatment of cryptococcal meningitis in AIDS patients is daily intravenous amphotericin B until the symptoms resolve.[8,12–14,18] Then the dose is decreased and given only 2 or 3 times per week, or the patient's treatment is changed to oral fluconazole taken daily. If symptoms reappear, reinstitution of daily amphotericin therapy may be necessary. The total dose of amphotericin B does not appear predictive of relapse. Relapse rates are reportedly as high as 60% within 13 weeks of cessation of therapy.[13]

Fluconazole has been widely used as maintenance therapy in patients with cryptococcal meningitis.[12–14,18,19] Recent studies comparing the use of amphotericin B and fluconazole in patients with AIDS-associated cryptococcal meningitis indicate that fluconazole is as effective as amphotericin B in the primary treatment of this disease. Fluconazole is an attractive alternative because it can be administered orally and has a limited side-effects profile.[20]

Cryptococcal meningitis is usually a terminal event, but the combination of acute and maintenance therapy is increasing the postinfection life span of patients from 100 to about 240 days.[12,13]

Summary

This patient illustrates a particularly interesting and worrisome aspect of AIDS. He developed a cerebral lesion, presumed to be toxoplasmosis, within a few weeks of beginning therapy for cryptococcal meningitis. He had sudden focal neurologic changes that responded to antitoxoplasmosis therapy, as evidenced clinically and radiographically. His CT scan is unusual in that it showed only one lesion. *Toxoplasma gondii* infection usually is characterized by multiple rounded lesions. The location of this patient's lesion, however, is quite typical of toxoplasmosis.

At the time of this writing, the patient is beginning to have memory loss. It is possible that he may have three different CNS processes: cryptococcal meningitis, toxoplasmosis, and AIDS-related dementia.

Patients with AIDS are surviving longer, in part because of keener diagnostic skills and the use of antiretroviral and prophylactic and therapeutic antimicrobial medications. As a result, we are able to identify patients

who develop multiple infections. These infections may occur singly or may coexist, as in the patient described in this report.

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References

1. Harrison PB, Carke SD, Silver SF. Focal brain lesions on computed tomography in patients with acquired immune deficiency syndrome. J Can Assoc Radiol 1990; 4:83–6.
2. Montgomery H. Cerebral mass lesions in patients with AIDS. BMJ 1990; 301:226–8.
3. Rossitch E Jr, Carrazana EJ, Samuels MA. Cerebral toxoplasmosis in patients with AIDS. Am Fam Physician 1990:867–73.
4. Pedrol E, Gonzalez-Gerente JM, Gafcic JM, et al. Central nervous system toxoplasmosis in AIDS patients: efficacy of an intermittent maintenance therapy. AIDS 1990; 6:511–7.
5. Hassl A, Aspöck H. Antigens of Toxoplasma gondii recognized by sera of AIDS patients before, during and after clinically important infections. Int J Med Microbiol 1990; 272:514–25.
6. Whelan M. Acquired immunodeficiency syndrome: cerebral computed tomographic manifestations. Radiology 1983; 149:477–84.
7. McCabe R, Oster S. Current recommendations and future prospects in the treatment of toxoplasmosis. Drugs 1989; 38:973–87.
8. Holliman R. Folate supplements and the treatment of cerebral toxoplasmosis. Scand J Infect Dis 1989; 21:475–6.
9. Snyder H. CNS toxoplasmosis as the initial presentation of the acquired immunodeficiency syndrome. Am J Emerg Med 1989; 7:588–92.
10. Sighinolfi L, Catalini MG, Antonucci G, et al. Evaluation of different treatment regimens for neurotoxoplasmosis. Proceedings from International Conference on AIDS. World Health Organization 1991; 7(2):253.
11. Fernardez-Martin J, Lepert C, Morlat P, Meyohas MC, Cirauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute toxoplasma encephalitis in patients with AIDS. Antimicrob Agents Chemother 1991:2049–52.
12. Brooke GL, Safran G, Perlmutter BL, Perez J, Zatlin G. HIV disease: a review for the family physician, part II, secondary infections, malignancy and experimental therapy. Am Fam Physician, 1990; 42:1299–1308.
13. Panther LA, Sande MA. Cryptococcal meningitis in the acquired immunodeficiency syndrome. Semin Respir Infect 1990; 5:138–45.
14. Diamond RD. Cryptococcus neoformans. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990:1981–8.
15. Feigin D. Pulmonary cryptococcus: radiologic-pathologic correlates of its three forms. Am J Radiol 1983; 141:1263–72.
16. Levy RM, Bredesen DE, Rosenblaum ML. Neurologic complications of HIV infection. Am Fam Physician 1990; 41:517–36.
17. Chuck SL, Sande MA. Infection with cryptococcus neoformans. N Engl J Med 1989; 321:794–9.
18. Scheld WM. Treating systemic fungal infections in AIDS patients. Postgrad Med 1990; 88:97–104.
19. Bozzette SA, Larsen RA, Chiu J, Leal MA, Jacobsen J, Rothman P, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324: 580–4.
20. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. N Engl J Med 1992; 326:83–9.