A SOLITARY BRAIN LESION IN A PATIENT WITH AIDS

Miranda has been a challenge to care for since you first met her in 1993. At that point she was a 36 year-old woman with 4 children ages 2-12. Her third child, a 4 year-old son, was also HIV-infected. Miranda had been diagnosed with HIV in 1989 when pregnant with this child. The father of her 3 children died of AIDS in 1990. Miranda met and had her fourth child with another HIV-infected man and they both came to you for care. Miranda kept her appointments and was always in good spirits. She rarely complained and took good care of all of her children. She is a woman of very strong faith and once came in to tell you that over the previous weekend she had been saved in a religious festival and she no longer had HIV. She was thrilled about this. You asked if she would still come to see you and she said she definitely would. She reported that although saved, she would nonetheless continue her retrovir and her ongoing care with you.

Miranda was treated with the serial monotherapy and combination treatment that so many patients were offered in the early and mid-1990s: retrovir, didanosine, stavudine and eventually a saquinavir-based antiretroviral cocktail. She would agree to all of your instructions but frequently missed, ran out of or simply did not take the medications prescribed. Her counts slowly deteriorated, she developed diabetes and neuropathy. She went to another clinic for a couple of years and returned in 1999 having sequentially been placed on and taken off of most medications available to treat HIV. When you saw her in 1999 she was in the hospital with ascending paralysis. She was diagnosed with an axonal variant of Guillain-Barre syndrome and successfully treated with intravenous

immunoglobulin (IVIG). Physical therapy got her walking again and she came back to your office for ongoing care of her HIV. Her CD4 cell count was 76/mmm and her viral load was 87,000 copies/ml. Her sugar was poorly controlled, her renal function was borderline. The father of her fourth child was dead and Miranda was living with a new boyfriend, an HIV-negative man who did not want to practice safer sex.

You gave Miranda a new antiretroviral regimen, treated her neuropathy and her diabetes, kept her involved with neurology and physical therapy and most of all, assigned a dedicated nursing case manager who checked in on her frequently to ensure adherence and continuity. Her numbers improved steadily and for nearly a year her viral load was <400 copies/ml before slowly starting to rise again. With a genotype available another antiretroviral regimen was prescribed. The success of the new regimen was short-lived. Miranda, as usual, presented with few, if any complaints. She was generally cheerful and always had a positive attitude. Her pattern of adherence was little changed, however. She rarely knew the names of her medications and although she could read, it often seemed she didn't read. At least not the instructions on the medication bottles. "That was 2 times a day? Oh I only take it once." "That's supposed to be three pills at a time? I take one three times a day." "Oh I stopped taking the green pill, the bottle was empty." Her religion continued to play an important role in her life. At one point when speaking to her about it she told you that she fasted one day a week, medication included. You tried to reinforce the need for consistent adherence. She cheerfully told you she always did what you advised. Her disease progressed.

In the late spring of 2002, Miranda came to your office complaining of dizziness, unsteady gait and a headache. These symptoms had begun within the last several weeks

and were worsening. She had fallen twice at home. In your office she was afebrile, there was no stiff neck or photophobia. The baseline numbness of her feet and lower legs was unchanged. She had some loss of dexterity of her hands and her gait was uneven and wide-based. Her exam was otherwise unremarkable. Her labs showed a glucose of 180 and creatinine of 1.5. Her white blood cell count was normal as were her chemistries. Miranda's CD4 cell count was 44/mmm and her viral load was 91,000 copies/ml. She reported taking most of her medications but had stopped taking bactrim 6 months prior because "that pill was too big." She had forgotten to tell you. Her antibody titer to Toxoplasma was IgG positive. An admission chest x-ray was negative. Her recent PPD had been negative. A non-contrast computed tomogram (CT) of the head was read as normal. An MRI of the head revealed a 1.8 cm enhancing mass in the left mid-cerebellar vermis with prominent surrounding enhancement consistent with edema. There was no evidence of herniation or bleeding. She was seen by the neurosurgery service and begun on a course of sulfadiazine and pyramethamine for empiric treatment of Toxoplasmic encephalitis (TE).

On empiric therapy for TE Miranda did not initially improve but her symptoms did not worsen. After 7 days of treatment she remained afebrile. In her second week in the hospital she reported decrease in both her headaches and her dizziness. A repeat MRI done at 14 days was unchanged. With continued clinical improvement Miranda was discharged home on continued therapy. She missed 2 appointments for repeat MRI and did not have a repeat scan until 6 weeks after initial presentation. This scan showed marked improvement in the size of the lesion and surrounding edema. While in the hospital Miranda had been started on another antiretroviral regimen (recycling previous

medications). With aggressive home care support she stayed on this regimen in the weeks and months after her discharge. Her headaches and dizziness resolved completely and with documented improvement in her CD4 cell count and her viral load, the numbness in her feet and legs also improved.

CHANGING PICTURE OF AIDS

You felt glad that Miranda had improved and her brain lesion had responded so well to therapy for TE. This opportunistic infection, like so many others, has decreased in incidence in recent years among your AIDS patients. The decline in incidence of opportunistic infections such as Pneumocystis carinii pneumonia (PCP), systemic Cytomegalovirus (CMV) and disseminated Mycobacterium avium complex (MAC) has been well-documented since the use of highly active antiretroviral therapy (HAART) has become widespread [1,2,3]. Other AIDS-related conditions that were previously without cure such as Kaposi's sarcoma, Cryptosporidiosis or progressive multifocal leukoencephalopathy (PML) can resolve completely on effective antiretroviral therapy [4,5,6]. The post-HAART era has seen a significant decrease in the incidence of neurologic diseases such as HIV dementia, cryptococcal meningitis and lymphoma [7]. Incidence rates of toxoplasmosis have also declined in this period. A MACS cohort study noted the incidence of CNS toxoplasmosis among gay men in the 1990-1992 period was 5.4 cases per 1000 person-years. In the 1996-1998 period that incidence was 2.2 cases/1000 person-years [7]. Despite this decreased incidence in the post-HAART era, Miranda's case demonstrates what can happen to patients in the absence of effective antiretroviral therapy.

Resistance against Toxoplasmosis gondii requires an intact immune system producing a complicated network of molecules. Gamma interferon is crucial to this network and is produced by T cells in response to a number of factors. T cell destruction results in a loss of gamma interferon production and reduction in natural resistance. This and a lack of adequate prophylaxis renders one vulnerable to reactivation of what is one of the most common latent infections in humans [8]. Toxoplasmic encephalitis remains a very real threat to patients with advanced AIDS.

EPIDEMIOLOGY

Focal brain lesions in patients with AIDS can be caused by a variety of infectious and noninfectious etiologies. Toxoplasmic encephalitis (TE) and primary CNS lymphoma (PCNSL) are at the top of a list that also includes tuberculomas, cryptococcomas, bacterial abcesses, PML, other neoplasms, viruses such as HSV or CMV and vascular disorders. In the United States, 10%-40% of adults with AIDS are IgG seropositive for toxoplasmosis, indicating latent infection. In the late 1980s, before bactrim was recognized to prophylax against TE as well as PCP, toxoplasmosis developed in up to one third of AIDS patients with latent Toxoplasma [9]. Outside the U.S., 25%-50% of AIDS patients who are seropositive for Toxoplasma will develope TE [10,11]

Toxoplasmosis gondii is an intracellular parasite with worldwide distribution. Rates of antibody seropositivity are dependent upon geographic location and socioeconomic status. Over 90% of adults in France and Central America are seropositive for antibodies to Toxoplasmosis [12]. New infections can be acquired in three ways: by ingestion of Toxoplasma oocysts in cat feces that contaminates the soil, from ingestion of

undercooked meat containing Toxoplasma cysts or transplacentally. Transplacental infection occurs when the mother is infected during pregnancy; seropositivity of a latent infection poses no risk. Rates of Toxoplasma infection during pregnancy in the United States (among immunocompetent women) are .1%-.8% [13].

CNS toxoplasmosis in AIDS patients in the United States is nearly always a reactivation disease. Primary infection in this country is unusual but less so in other parts of the world. In 1991 a study done in France demonstrated a 5.5% seroconversion rate during a median observation period of 28 months [14]. Worldwide, Toxoplasmosis gondii in AIDS patients most commonly presents as encephalitis but it has been documented in multiple organ systems including the eye, heart, lungs and GI tract [15].

CLINICAL PRESENTATION

Toxoplasmic encephalitis can present with a whole spectrum of symptoms of CNS dysfunction. Symptoms can be focal, nonfocal, insidious or sudden in onset, accompanied or not by fever and or malaise. The signs and symptoms of TE reflect both the multifocal nature of the disease and the results of the accompanying edema, hemorrhage and inflammation. Miranda presented with headache, dizziness and ataxia and had a single lesion in the cerebellar vermis on MRI surronded by edema. Other patients present with specific focal abnormalities such as hemiparesis, hemiplegia, focal seizures, aphasia or cranial nerve deficits. Nonfocal signs may include generalized weakness, psychosis, confusion, grand mal seizures or coma. TE may be difficult to distinguish from HIV dementia in a patient with AIDS who presents with global cognitive impairment [16]. A retrospective analysis of 115 patients with CNS

toxoplasmosis published in 1992 reported that more than 50% of patients presented with headache or confusion and nearly 70% presented with some focal neurological sign. Forty-seven percent of patients presented with fever. In this study more that 40% of patients presented with an abnormal level of consciousness [17].

DIAGNOSIS

In an adult with AIDS, toxoplasmosis is the most common cause of an intracerebral lesion [18, 19]. Treatment for TE is often started based on a presumed diagnosis. MRI has improved the diagnosis of TE as 80% of cases will present with multiple lesions on MRI scanning [20]. In contrast, patients with PCNSL more often will have a single lesion on MRI. PCNSL lesions are frequently seen in the white matter proximal to the lateral ventricles. A patient with TE virtually always has a positive antibody titer. A 1992 study reported that as many as 16% of cases of CNS toxoplasmosis were seronegative for IgG on immunofluorescence assay but subsequent assays use the more sensitive ELISA technique and as a result it is felt that a seronegative patient is highly unlikely to have or develop TE [17].

CSF studies should be performed on patients with headache, fevers, mental status changes and/or meningeal signs. In patients with TE the CSF may be entirely normal. Positive DNA for toxoplasmosis found by polymerase chain reaction (PCR) in the CSF may be a remnant from a latent infection and does not determine a diagnosis of active disease.

Thallium-201 single photon emission computed tomography (SPECT) testing has been used to help support or discard a diagnosis of CNS toxoplasmosis in the case where a patient has a single brain lesion on MRI and is seropositive for toxoplasma antibodies.

In this case a negative SPECT supports a diagnosis of TE. PCNSL in most cases will yield a positive SPECT study. This test, combined with a positive CSF Epstein-Barr virus PCR, is enough to warrant treatment for PCNSL with radiation therapy [21].

Stereotactic brain biopsy has been used to establish a diagnosis in patients with focal brain lesions and AIDS. The indications for brain biopsy in AIDS patients were reviewed and published in 1997 by the American Academy of Neurology [22]. Large lesions with mass effect threatening herniation, brain lesions in an HIV-infected child or single lesions with negative toxoplasmosis serologies were all situations warranting biopsy. Therapy for TE was recommended for all cases of focal brain lesion with positive toxoplasma serologies. Worsening clinical picture or progression radiographically indicate a need for biopsy. Special attention is paid to patients treated with corticosteroids alone as clinical improvement in the absence of radiographic improvement of the lesion itself may occur [21]. A review of 246 brain biopsies in AIDS patients published in 2000 revealed that 98% of biopsies yielded abnormal tissue and in one third of cases the tissue diagnosis was different from the pre-operative diagnosis [23]. Brain biopsy in patients with AIDS does not have a higher complication rate than brain biopsy performed on immunocompetent patients.

TREATMENT

TE can be effectively treated. First line treatment consists of a loading dose of pyrimethamine at 100-200 mg followed by a maintenance dose of 50-100 mg/day in combination with sulfadiazine at a dose of 4-8mg/day. Patients require maintenance therapy but, as with other opportunistic infections such as MAC and CMV, patients with sustained response to HAART and stable immune reconstitution, may be able to

successfully discontinue their maintenance therapy. An alternative to sulfadiazine is clindamycin, whether PO or IV. Other choices can include azithromycin, clarithromycin and atovaquone. Pyramethamine should be given with folinic acid to avoid the bone marrow suppressive effects.

Most patients will respond to treatment in 5-14 days. Radiographic improvement is usually seen by 3 weeks. Clinical deterioration is seen as an indication of treatment failure and need for biopsy. There may actually be radiographic worsening in the presence of clinical improvement. Superficial lesions tend to clear more rapidly on scanning. Deeper lesions may take up to 6 months to clear entirely [24, 25].

Miranda responded well to therapy and her lesion improved markedly on MRI. Given her vast experience with antiretroviral therapy it is uncertain that her immune function will ever improve enough to be safely taken off anti-toxoplasmosis medication. Unfortunately, in a patient whose adherence is already problematic, the addition of more medication is burdensome. You will keep your nursing case managers on the case and continue to encourage the patient to take her medications.

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