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Case Report

Fatal immune reconstitution inflammatory syndrome with human immunodeficiency virus infection and *Candida* meningitis: Case report and review of the literature

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Immune reconstitution inflammatory syndrome (IRIS) is an increasingly recognized phenomenon of paradoxical worsening of patients with acquired immunodeficiency syndrome (AIDS) upon initiation of highly active antiretroviral therapy (HAART). To date, there have been limited reports of IRIS in the central nervous system (CNS). Here, the authors describe a 43-year-old man with AIDS who presented with subacute meningitis. No pathogenic organism was identified by routine diagnostic tests, and he was treated empirically with an antituberculous regimen and initiated on HAART therapy. Soon after, he had a precipitous neurologic decline leading to his death. Postmortem evaluation showed a basilar *Candida* meningitis as well as vasculitis characterized by CD8+ T-cell infiltration, consistent with IRIS. The authors discuss the challenges in diagnosing fungal meningitides and the risks of initiating HAART therapy in those with possible undiagnosed underlying opportunistic infections. Additionally, the authors review the literature regarding CNS IRIS. *Journal of NeuroVirology* (2008) **14,** 267–276.

Keywords: AIDS; fungal meningitis; HAART; IRIS

Introduction

Candida meningitis is rare in both immunocompetent and human immunodeficiency virus (HIV)-infected patients. To date, most reported cases have occurred in neonates, postoperative neurosurgical patients, or those immunocompromised due to malignancy or transplant (Chen *et al*, 2004; Cohen-Wolkowiez *et al*, 2007). In fact, HIV infection has not been shown to be an independent risk factor for *Candida* meningitis, despite the high prevalence of oral candidiasis in this population. The few available studies do not suggest that HIV infection alters the clinical course of *Candida* meningitis.

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In the reported cases of *Candida* meningitis in the setting of HIV infection, patients were moderately to severely immunocompromised, with an average CD4 count of 135 cells/ml (range 25 to 312), and mortality was 31%, despite antifungal treatment (Casado *et al*, 1998). However, the effect of treatment with highly active antiretroviral therapy (HAART) on the clinical course of *Candida* meningitis has not yet been explored. Most recently, immune reconstitution following HAART in HIV patients has opened new challenges in clinical management of acquired immunodeficiency syndrome (AIDS) as the syndrome known as immune reconstitution inflammatory syndrome (IRIS) has become more widely recognized. IRIS most commonly occurs when a patient with an underlying opportunistic infection (mycobacterial infections, cryptococcus, or cytomegaloinclusion virus) begins treatment with HAART and has a paradoxical worsening. To our knowledge, there has not been a reported case of IRIS in a patient with *Candida* meningitis. Here, we describe such a case that

underscores the importance of early accurate diagnosis of *Candida* meningitis as well as the risks of initiating HAART therapy in HIV patients with undiagnosed opportunistic infections. Finally, we discuss the cellular immune mechanisms involved in IRIS triggered by *Candida* meningitis.

Case report

A 43-year-old man with HIV infection of at least 8 years presented to our hospital emergency department with a 2-week history of bifrontal headache. He had a history of oral candidiasis, hepatitis C infection, and a recent genital herpes infection for which he was taking valacyclocir. He had no history of diabetes. He was an active intravenous heroin and cocaine user, with his last use 1 month prior to presentation. His headaches increased in intensity without relief from over-the-counter analgesics. He then developed a stiff neck, photophobia, low back pain, and malaise. He had subjective fevers, chills, and night sweats and a 5-pound weight loss due to decreased oral intake. His CD4 count 1 year prior to presentation had been 20 cells/mm^3 and HIV-1 viral load of 81,000 copies/ml. He had been on HAART several years prior but was not currently taking any antiretroviral therapy.

The patient was afebrile with normal vital signs. He was photophobic. There was no evidence of oral thrush. He had palpable submandibular lymph nodes bilaterally. His neck was stiff with restricted flexion. He had no skin rash and no active genital herpetic lesions. His neurological examination was normal. His peripheral white blood cell count was 2860 cells/mm^3, with 38% neutrophils and 54% lymphocytes. Cerebrospinal fluid (CSF) results at presentation, and throughout his admission, are shown in Table 1.

Empiric treatment was initiated with ceftriaxone, ampicillin, vancomycin, and acyclovir; however, all except for acyclovir were discontinued after CSF cultures were negative for 48 h. No causative organism was identified. Table 2 lists the laboratory studies performed and the results. His CD4 count during this admission was 20 cells/mm^3 and plasma HIV-1 viral load was 173,000 copies/ml. Magnetic resonance (MR) images of the brain are shown in Figure 1A and show only periventricular white matter changes thought to be consistent with HIV encephalopathy.

The patient's hospital course was notable for intermittent fevers, persistent meningismus, and photophobia. He was empirically treated for herpes simplex virus meningitis with a 2-week course of acyclovir and for *Listeria* meningitis for 3 weeks with ampicillin. Due to a lack of clinical response to the above treatments, on hospital day 10, he was empirically treated for tuberculous (TB) meningitis with a four-drug anti-TB regimen. Soon after this treatment was initiated, the patient defervesced and his photophobia and meningismus resolved. Furthermore, his CSF profile improved with a decrease in the white blood cell count (WBC) and a rise in the glucose, despite an increase in the protein. On hospital day 21, HAART was restarted. The patient was discharged home on hospital day 31 on a four-drug anti-TB regimen, HAART, as well as pneumocystis carinii pneumonia (PCP) and mycobacterium avium intracellular (MAI) prophylactic medications.

After only a few days at home, he developed weakness, lethargy, and confusion, which progressed over 2 weeks. He was readmitted on day 46 from his initial presentation. His CD4 count had decreased to 12 cells/mm^3 though his plasma HIV-1 viral load was now less than 400 copies/ml. His CSF profile had improved showing 22 WBCs/mm^3, now with a mononuclear predominance (18 mononuclear cells and 4 polymorphonuclear cells), a CSF glucose of 52 mg/dl, and protein of 407 mg/dl. Again all cultures and viral polymerase chain reaction (PCR) studies were negative. Nonetheless, despite this improvement in his laboratory studies, the patient was clinically much worse. At times, he was difficult to arouse with confusion and generalized weakness. A repeat magnetic resonance imaging (MRI) of the patient's brain is shown in Figure 1B and demonstrated multiple hyperintensities through the brainstem and thalamus on the FLAIR sequences. Studies for cardioembolic disease, including a transthoracic echocardiogram, were negative. The patient then became progressively obtunded, required intubation for tachypnea and airway protection. Ten days after this second presentation (day 55), the patient died.

Pathological evaluation

A partial autopsy was performed and restricted to the brain. Neuropathological studies of brain tissues obtained at autopsy showed significant meningeal inflammation surrounding the brainstem characteristic of basilar meningitis (Figure 2). There was relatively little inflammation of the cortical meninges. There was a dramatic infiltration of inflammatory cells into the blood vessels of the vertebrobasilar system of the brainstem. Specifically, the basilar artery walls were virtually destroyed by inflammation. Although the majority of the cells were lymphocytes with very rare polymorphonuclear cells, there were several multinucleated giant cells and plasma cells, suggesting chronic inflammation. An examination of the brainstem parenchyma revealed multiple microinfarctions of varying ages, characterized by axonal ballooning, microglial activation, and vacuolization of the parenchyma.

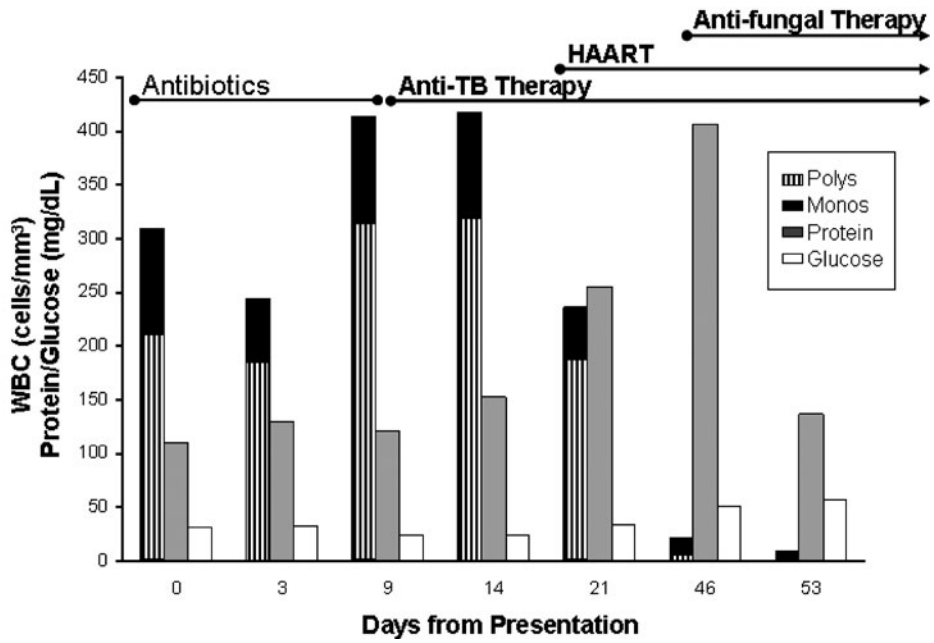
Special stains were performed to identify a causative organism for this brainstem meningitis and vasculitis. Periodic acid–Schiff (PAS) stain for fungus demonstrated hyphae and yeast forms in the meninges surrounding the midbrain, pons, medulla, and cerebellum morphologically consistent with *Candida* (Figure 3). Some yeast were present

Table 1 (**A**) CSF results from the seven lumbar punctures performed during the patient's two hospitalizaions. (**B**) Graphical representation of the data from **A** correlating the CSF results to initiation of various pharmacologic treatments.

A

Day	0	3	9	14	21	46	53
WBC	309	244	413	418	237	22	10
Polys	201	181	306	318	187	4	1
Monos	108	63	107	100	50	18	9
Protein	109	130	122	153	255	407	137
Glucose	31	32	25	25	34	52	57

B



within giant cells and macrophages at the base of the pons. *Candida* structures were restricted to the meninges with very few intraparechymal organisms seen. Gram-Weigert, acid-fast bacilli (AFB), and Warthin-Starry stains were all negative for other microorganisms.

Immunohistochemical studies were also done to evaluate the nature of the inflammatory cells (Figure 4). Immunostaining for CD4 showed very few CD4+ cells, consistent with the patient's low CD4 count. The inflammatory cells in the meninges and the walls of the brainstem blood vessels were predominantly CD8+. Interestingly, despite the absence of organisms in the parenchyma, there were also many CD8+ cells distributed diffusely throughout the brainstem parenchyma. Areas of the brainstem that exhibited features of microinfarctions showed marked infiltration by microglia and CD68+ cells.

Discussion

We present here a patient with AIDS who developed a meningoencephalitis process in the setting of HAART treatment. The presence of PAS+ yeast forms and diffuse inflammation in the basilar

Table 2 Extensive infectious disease work-up did not reveal a causative organism for the patient's meningitis.

Test	No. of repeats	Result
CSF		
Bacterial culture	5	No growth
Fungal culture	5	No growth
Mycobacterial culture	4	No growth
Viral culture	1	No virus isolated
Cryptococcal antigen	5	Not detected
VDRL	2	Non-reactive
JC virus PCR	4	Not detected
Epstein-Barr virus PCR	4	Not detected
Cytomegalovirus PCR	4	Not detected
Herpes simplex virus PCR	4	Not detected
Varicella-Zoster virus PCR	4	Not detected
Enterovirus PCR	3	Not detected
Toxoplasma IgG Ab	1	Negative
Arbovirus PCRs	1	Not detected
West Nile virus IgM Ab	1	Negative
Eastern equine encephalitis virus IgM Ab	1	Negative
Coccidiodes Ab	1	<1:2 titer
Mycobacterium tuberculosis PCR	1	Not detected
Histoplasma antigen	1	0.51 units
Flow cytometry	2	No abnormal cell population
Cytopathology	1	Increased cellularity, no organisms or neoplasm identified
Oligoclonal bands	1	1 band detected
Serum		
Bacterial culture	11	No growth
Fungal culture	1	No growth
Mycobacterial culture	2	No growth
RPR	2	Nonreactive
Sporothrix Ab	1	1:8 titer
Ehrlichia PCRs	1	Not detected
Lyme Ab	1	Negative

meninges, including multinucleated giant cells and macrophages, some containing fungi, are consistent with pathological features of a chronic fungal meningitis produced by *Candida*. The vasculitic process that affected the arteries at the base of the brain resulted in multiple infarcts of the brainstem and basal ganglia, which were the most likely cause of the patient's neurological deterioration.

This patient exhibited some of the common pathological features described for candidiasis of the central nervous system (CNS) as well as some atypical features. Up to 23% of patients with CNS candidiasis have some evidence of vascular invasion (Sanchez-Portocarrero *et al*, 2000) and there is one reported case of basilar thrombosis in a patient with *Candida* meningitis (Grimes *et al*, 1998). The cases of CNS candidiasis described in the pre-AIDS era or in non–HIV-infected patients occur in late stages of systemic disease, mostly associated with immunosuppression due to chemotherapy or radiation therapy. In such cases, neuropathological studies show that early stages of the *Candida* lesions were characterized by hemorrhagic infarcts that evolved to abcesses and/or granulomas. The inflammatory reaction has been described as minimal and characterized by variable infiltration by lymphocytes, plasma cells, polymorphonuclear cells, and giant cell formation (Otero *et al*, 1978; Parker *et al*, 1981)

In the case presented here, there was no evidence of direct vessel wall invasion by the *Candida* organisms, rather there was an overwhelming presence of inflammatory cells characteristic of a severe vasculitic process. One explanation for this observation is that yeast organisms had previously invaded the vessel but had been destroyed by the immune system. Alternatively, the yeast had stimulated a vasculitic immune response without being invasive upon the initiation of HAART. We favor the latter explanation because, despite the presence of a few multinucleated giant and plasma cells, the majority of the immune cells were CD8+ lymphocytes and not phagocytic cells, which is consistent with IRIS. Furthermore, CD8+ cells were seen diffusely throughout the brainstem parenchyma in areas without fungal invasion. Thus, our diagnosis in this case was IRIS resulting from initiation of HAART therapy in a patient with chronic *Candida* meningitis.

Challenges in diagnosis of Candida *meningitis*

This case highlights the difficulties in diagnosing *Candida* meningitis. This patient had at least five evaluations of his CSF sent for Gram stain and fungal cultures without identification of an organism. This is especially surprising given the multitude of fungi seen in the postmortem evaluation. The rate of detecting *Candida* by staining of CSF is approximately 30% to 40% (Casado *et al*, 1998; Sanchez-Portocarrero *et al*, 2000). The rate of CSF culture positivity has been reported as high as 80%, but this often requires multiple high volume (10 to 15 ml) lumbar punctures and special techniques (Sanchez-Portocarrero *et al*, 2000). Although several PCR-based techniques for detecting *Candida* in the serum have been developed, none are widely used, nor have they been validated in the CSF (Ahmad *et al*, 2004). Though the CSF profile in this case was consistent with previous reports of *Candida* meningitis, the findings were nonspecific and therefore of little diagnostic utility. There was a persistent pleocytosis with an approximately 3:1 polymorphonuclear to lymphocyte predominance. In *Candida* meningitis, there may be either a polymorphonuclear or lymphocytic predominance (Bayer *et al*, 1976). Our patient's low CSF glucose was also consistent with previous reports that show 60% to 78% of patients with *Candida* meningitis have CSF glucose less than 40 mg/dl (Casado *et al*, 1998; Sanchez-Portocarrero *et al*, 2000). Cases with a persistent neutrophilic pleocytosis with hypoglycorrachia were the most difficult to diagnose correctly (Sanchez-Portocarrero *et al*, 2000). In addition to fungal meningitis, the

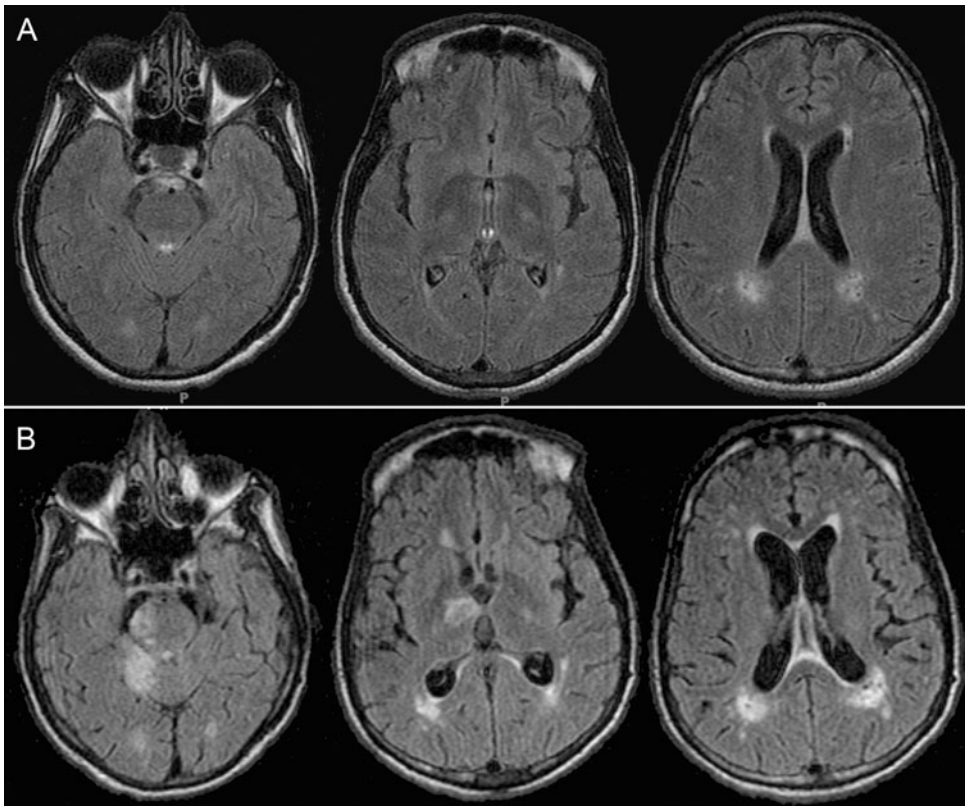


Figure 1 (**A**) Brain MRI at time of initial presentation. FLAIR sequence shows mild periventricular white matter changes particularly prominent at the posterior lateral aspects of the lateral ventricles. There was no gadolinium enhancement (not shown). (**B**) MRI at time of second presentation. There are now multiple hyperintense lesions throughout the brain, including in the brainstem, cerebellum, thalamus, and periventricular white matter. (MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery pulse sequence.)

differential diagnosis for a patient presenting with a subacute meningitis with this CSF profile includes TB meningitis, cytomegalovirus encephalitis, histoplasmosis, and meningeal lymphomatosis or carcinomatosis. As a result of this diagnostic challenge, one study showed that up to 50% of HIV-infected patients ultimately diagnosed with *Candida* meningitis were initially treated with medications for TB meningtitis, as occurred in our patient (Sanchez-Portocarrero *et al*, 2000).

Empiric treatment of undiagnosed meningitis

Due to the inherent difficulties in making the diagnosis of *Candida* meningitis and the potential similarities in presentation and CSF profile to TB meningitis, empiric treatment with both antifungal and anti-TB regimens is warranted in HIV patients with undiagnosed meningitis. Yet, the challenge in initiating empiric therapy in such a case is that treatment may limit the yield of further diagnostic studies. A stepwise approach to initiating empiric therapies would be ideal: starting therapy for one organism, evaluating it for efficacy, then beginning a second empiric regimen directed against the other organism if the first does not appear efficacious. However, in the case of TB meningitis, treatment (even when appropriate and effective) can initially worsen a patient's clinical picture as well as all CSF parameters. Furthermore, it is unknown how quickly appropriate treatment for a fungal meningitis would be expected to improve the patient's clinical presentation and CSF profile. Therefore, because there is no way to evaluate the efficacy of a given treatment in a short period of time, treatment for both organisms should be started simultaneously. Unfortunately, beginning anti-TB and antifungal therapies simultaneously would commit a patient to a long-term course of both treatments unless cultures eventually become positive and a causative organism is identified.

We propose the following algorithm for treating HIV patients with difficult to diagnose meningitides. Upon initial presentation, a lumbar puncture should be performed and CSF should be sent for bacterial, fungal, and mycobacterial cultures, as well as for PCR studies for viral pathogens. Antibiotics and antiviral therapies directed against common bacterial and viral pathogens should be started. If there is no clinical improvement and Gram stain and bacterial cultures remain negative after 48 h, the antibiotics should be discontinued. The discontinuation of the antibiotics can be a difficult decision, particularly in cases of an acute presentation of meningitis where there is a high suspicion for bacterial meningitis. Nonetheless, we recommend relying on the laboratory data and

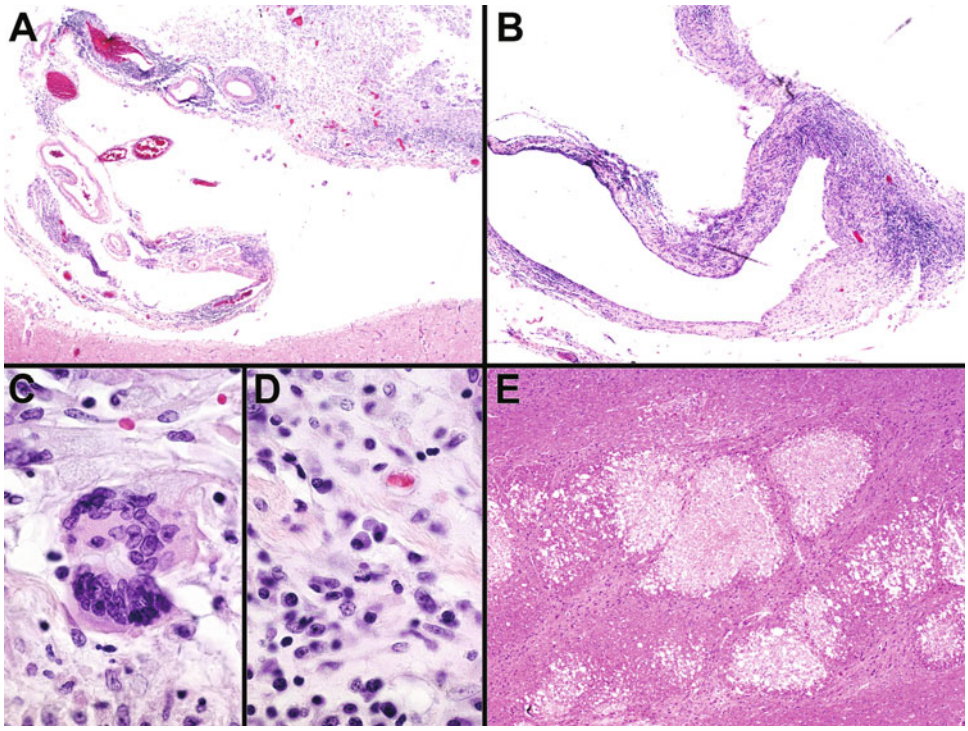


Figure 2 Neuropathological findings. (**A**) Basilar meninges visualized with H&E stain shows diffuse inflammation of the leptomeninges, subarachnoid compartment, and the vasculature. The adjacent parenchyma is part of the medulla oblongata (10×). (**B**) Inflammatory cells are present throughout every layer of the wall of the basilar artery virtually destroying it (10×). (**C**) At high magnificaltion, a multinucleated giant cell can be seen in the meninges (160×). (**D**) Plasma cells can also be seen throughout the meninges (160×). (**E**) Cross section through the medulla shows microinfarcts of various ages. The older infarcts are those that are more vacuolated (10×). (H&E, hematoxylin and eosin.)

discontinuing the routine antibiotics. One exception may be the continuation of ampicillin treatment for *Listeria*, as this bacteria is difficult to culture in the laboratory and may require weeks for cultures to become positive. In patients with a subacute presentation and in whom there is no improvement, antibiotics can be stopped with more confidence as bacterial meningitis is a less likely etiology.

At this time, a repeat lumbar puncture should be performed, and the CSF should be sent for fungal and mycobacterial cultures, AFB staining, and TB PCR if not sent with the original cultures (these studies are commonly omitted in lumbar punctures performed in the Emergency Department). Special techniques to improve the yield of diagnosing fungus should be employed, such as culture in hypertonic medium or filtration of CSF with microscopic examination and culture of the filter (Igra-Siegman *et al*, 1981; Voice *et al*, 1994). In addition, CNS lymphoma should be considered and fluid sent for cytopathology and flow cytometry. Empiric therapy with anti-TB and antifungal agents should be started at this time and continued until an organism is identified. If no organism is identified after 3 to 4 weeks, meningeal biopsy can be considered. Alternatively, long-term treatment with anti-TB and antifungal medications should be continued for 6 to 12 months, followed by prophylaxis unless the patient's CD4 count rises above 200 cells/mm^3.

Prognosis of Candida meningitis

The mortality of untreated *Candida* meningitis is high, though exact numbers are unclear given the low number of patients. With treatment, however, mortality drops to 10% to 30% (Casado *et al*, 1997; Sanchez-Portocarrero *et al*, 1993, 1994; Voice *et al*, 1994). Predictors of poor outcome and mortality include symptoms greater than 2 weeks' duration prior to diagnosis, CSF glucose less than 35 mg/dl, intracranial hypertension, and focal neurological deficits (Bayer *et al*, 1976). At initial presentation, our patient already met two of these criteria, making his prognosis poor regardless of whether appropriate treatment was initiated promptly. However, his case illustrates an additional reason that early accurate diagnosis is crucial, especially in patients with AIDS; undiagnosed opportunistic infections predispose AIDS patients to IRIS upon initiation of HAART. Although our patient's prognosis from the *Candida* meningitis alone was poor, initiation of HAART prior to diagnosis and treatment of his infection led to IRIS, which accelerated his neurological decline and death.

Clinical diagnosis of IRIS

Although an immune response directed against *Candida* organisms is quite plausible, it is impossible to conclude that the IRIS occurred exclusively due to the reconstituted immune system's reaction to the *Candida* alone. In fact, there are several documented

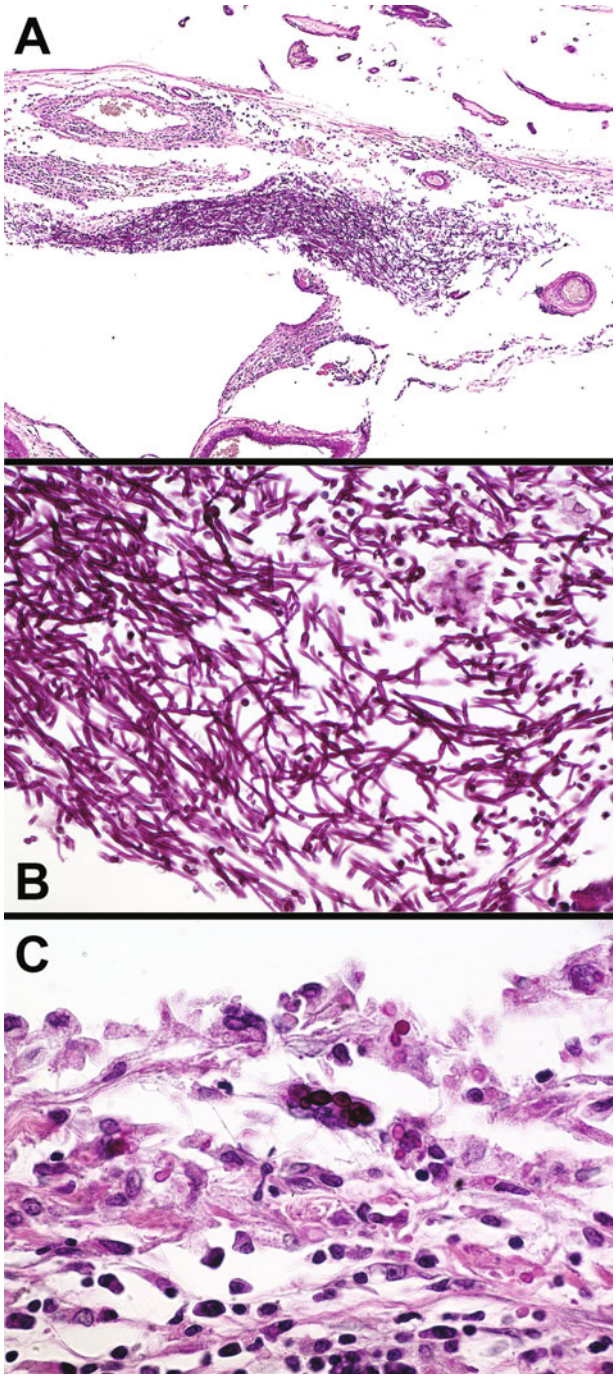


Figure 3 Visualization of fungal structures with PAS stain. (**A**) Low-power view of the basilar meninges show a large cluster of PAS-positive organisms (20×). (**B**) Higher power shows PAS-positive hyphae with branching and yeast consistent with the morphology of *Candida* species (100×). (**C**) Yeast can be seen intracellularly in macrophages in the basilar meninges (160×). (PAS, periodic acid–Schiff.)

cases of IRIS occurring in response to HIV viral reservoirs in the brain. In these cases, other infectious etiologies were excluded prior to concluding that the IRIS was directed against the HIV (Riedel *et al*, 2006). Therefore, both HIV and *Candida* may have been the precipitants of the IRIS.

IRIS involving the CNS, while rare, is emerging as a potentially devastating complication of HAART. However, given the variable presentations of IRIS, simply defining it has become a challenge. One current definition states that a patient must (1) be HIV positive, (2) be receiving HAART, (3) have a decrease in HIV-1 RNA level, (4) have clinical symptoms consistent with an inflammatory process, and (5) have a clinical course not consistent with drug toxicity or the course of a new or previously diagnosed opportunistic infection (Riedel *et al*, 2006; Shelburne *et al*, 2002). Although these criteria seem straight forward, our patient's case illustrates some of the difficulties in making a clinical diagnosis of IRIS. Our patient certainly meets the first four criteria. His HIV-1 viral load decreased from 173,000 to <400 copies/mm^3. Interestingly, as is often seen in IRIS, he did not have a corresponding rise in CD4 count. A decrease in viral load is a more sensitive marker of immune reconstitution than changes in CD4 count, which often lag behind (French *et al*, 2004; Shelburne *et al*, 2005b). The challenge in making a clinical diagnosis of IRIS, however, comes from the fifth criterion: distinguishing whether the patient's clinical worsening is due to the expected course of an underlying opportunistic infection or due to the inflammatory response of a newly reconstituted immune system. One clue that our patient's course was due to IRIS and not his underlying meningitis was the precipitous decline within 2 weeks of the initiation of HAART. Prior to that, he had a chronic meningitis but was clinically stable with no neurologic deficits. Nonetheless, without the pathology, it would remain impossible to state conclusively that his deterioration was not due to the natural course of his *Candida* meningitis.

Cellular immune response in IRIS

In the reported cases of CNS IRIS, the most consistent pathologic finding in biopsy and postmortem studies is a CD8+ T-cell lymphocytosis. The CD8+ cells are primarily perivascular, in some cases causing an apparent CNS vasculitis (Gray *et al*, 2005; van der Ven *et al*, 2002). However, parenchymal infiltration of CD8+ cells is also seen. In a review of eight cases of CNS IRIS, the most severe fatal cases were characterized by a predominance of CD8+ lymphocytes, whereas CD4+ cells were virtually absent (Gray *et al*, 2005). Interestingly, in most of these cases, the patients had increases of their peripheral CD4 counts, yet few of these cells crossed the blood-brain barrier and penetrated the CNS. These findings led the authors to hypothesize that a dysregulation of the ratio of CD8+ to CD4+ lymphocytes is a pathogenic mechanism of IRIS.

These typical pathologic findings of IRIS were all present in our patient. There was a pronounced vascular infiltration of CD8+ T cells. In fact, the apparent brainstem vasculitis was the likely immediate cause of death as the patient suffered multiple brainstem

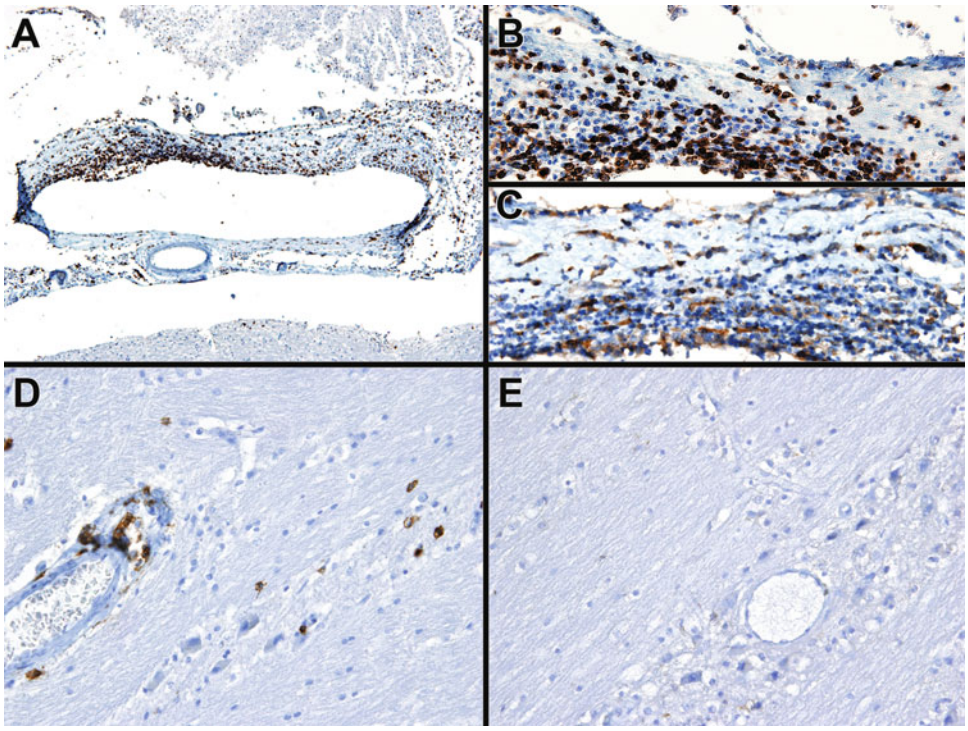


Figure 4 Characterization of inflammatory changes by immunohistochemistry. (**A**) CD8 immunostaining of the basilar meninges shows diffuse infiltration of the blood vessel walls and the meninges with CD8+ T cells (10×). (**B**) Higher-power imaging of the upper wall of the vessel shown in A shows CD8+ T cells in all layers of the vessel wall (40×). (**C**) CD4 immunostaining of an adjacent section shows very few CD4+ T cells (40×). (**D**) CD8 immunostaining of the medulla shows CD8+ T cells both in the blood vessel walls as well as scattered in the parenchyma (40×). (**E**) CD4 immunostaining of the medulla shows no positively stained cells (40×).

infarctions. In addition to the vascular and perivascular inflammation, there was also a less prominent, but diffuse, parenchymal infiltration of CD8+ cells. Virtually no CD4+ T cells were seen, consistent with the findings in the most lethal cases of IRIS. We also compared this immune response to that of an earlier case of CNS candidiasis in an AIDS patient who had not received HAART (not shown). In this other case, the immune reaction consisted primarily of CD68+ cells: macrophages and microglia. Although there were some CD8+ T cells scattered diffusely throughout the parenchyma, there were none in the vessel walls or perivascular spaces, suggesting that the reaction seen in our patient was not typical of CNS candidiasis alone. Thus, the pathological findings of our patient's postmortem examination confirmed the clinical suspicion of IRIS.

Treatment of CNS IRIS

One of the most difficult aspects of managing CNS IRIS is the variability of presentations and outcomes. Though the frequency of IRIS diagnoses is increasing, there is no consensus as to the optimal treatment, or even whether treatment is indicated. A recent description of three nonfatal cases of CNS IRIS highlights this dilemma. Outcomes in these cases ranged from spontaneous improvement with no new additional therapy and continuation of HAART, improvement with corticosteroids along with treatment of the underlying opportunistic infection and continuation of HAART, and finally, improvement with a prolonged course of corticosteroids and an adjustment of the HAART regimen (Venkataramana *et al*, 2006). In other cases that present with a rapidly progressive course, which is often ultimately fatal, no clear role of treatment has been established, and in all cases the role of corticosteroids remains controversial.

Another area of controversy is whether to delay, and for how long, the initiation of HAART in severely immunosuppressed patients with opportunistic infections. Several studies have shown that 15% to 25% of patients who are started on HAART develop IRIS. Those percentages increase to up to 45% in those with underlying opportunistic infections (Shelburne *et al*, 2006). However, studies that have examined whether the risk of IRIS increases depending on the proximity of initiation of treatment of the opportunistic infection and initiation of HAART have not yielded consistent findings (Shelburne *et al*, 2006). Thus, although it is clear that the opportunistic infection must be treated immediately upon diagnosis, it is unclear whether patients might benefit from a delay before initiating HAART. Such a delay has the drawback of putting the most severely immunosuppressed patients at risk for other opportunistic infections. An additional dilemma arose in our patient's case in that

he had an undiagnosed, and therefore untreated, opportunistic infection. This put him at extremely high risk for developing IRIS, as risk factors for developing the syndrome include an active opportunistic infection and a very low CD4 count (<50 cells/mm^3) (French *et al*, 2004; Shelburne *et al*, 2005a). Our patient was also an active intravenous drug abuser, which combined with the low CD4 count put him at a high risk for an underlying opportunistic infection.

One hypothesis as to why an active infection might predispose an individual to IRIS is that there is a large amount of foreign antigen against which the immune system mounts an enhanced immune response. Thus, with our current understanding of CNS IRIS, a prudent approach might be to delay initiation of HAART until appropriate treatment for the meningitis is initiated and there are signs of clinical improvement. In cases such as our patient's where diagnosis of the underlying infection is difficult or delayed and the treatment for the meningitis is purely empiric, HAART initiation should be delayed at least until there are clinical and laboratory (CSF profile) evidence of response to therapy. It is not, however, necessary to await a complete course of treatment for the infection before beginning HAART. Signs of clinical exacerbation following the initiation of HAART should prompt the consideration of corticosteroids therapy, but HAART should not be discontinued. Discontinuation of HAART increases the risk of development of drug resistant strains of HIV and there may still be a continued risk for development of IRIS when HAART is reinitiated.

Conclusion

In conclusion, we have presented the first reported case of IRIS in a patient with *Candida* meningitis. This case highlights several important features of *Candida* meningitis and IRIS, as well as areas in which more research needs to be done to treat both successfully. First, although all of the standard techniques used to detect fungus in the CNS were performed (namely multiple high volume lumbar punctures), the diagnosis of *Candida* meningitis was not made until the postmortem evaluation. Improved assays, such as PCR-based tests, to detect fungal infections are imperative. Until such tests with higher sensitivity are available, there is a need for a high index of suspicion for fungal infections in those with difficult to diagnose meningitides, especially those that mimic TB meningitis. Early consideration of empiric antifungal treatment is especially important given that there are no reliable early indicators to determine if anti-TB therapy is working. Secondly, this case demonstrates the risk of initiating HAART in severely immunosuppressed patients, particularly as they may harbor an undiagnosed opportunistic infection. There is a clear need for prospective studies to evaluate if there is an optimal time to initiate HAART following treatment of an opportunistic infection. Finally, in those cases in which a diagnosis of IRIS has been established, there is no consensus as to the best management approach; however, in patients with rapid clinical deterioration, the use of corticosteroids can be considered.

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