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"Candida albicans Cerebral Granulomas Associated with a Nonfunctional Cerebroespinal Fluid Shunt: Case Report"

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Candida albicans Cerebral Granulomas Associated with a Nonfunctional Cerebrospinal Fluid Shunt: Case Report

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OBJECTIVE AND IMPORTANCE: We report an unusual case of basal ganglia granulomas caused by *Candida albicans* that surrounded the proximal segment of a nonfunctional cerebrospinal fluid shunt in a previously healthy patient.

CLINICAL PRESENTATION: A 22-year-old woman had undergone ventriculoatrial cerebrospinal fluid shunt placement for posttraumatic hydrocephalus 3 years previously. One year later, a shunt revision was followed by wound dehiscence with local infection at the neck level. She received oral administration of antibiotics for 3 months until the wound closed. Twelve weeks before admission, the patient experienced pulmonary emboli. She received anticoagulants, and the distal segment of the shunt was removed. Five weeks after shunt removal, she presented with headache and left-sided hemiplegia caused by right basal ganglia inflammatory masses.

INTERVENTION: A stereotactic brain biopsy was performed, and the shunt remnants were removed. Microscopically, the lesions were acutely and chronically inflamed. *C. albicans* grew in tissue and in shunt hardware cultures. The patient was treated with 1.1 g of intravenously administered amphotericin B and orally administered ketoconazole; she recovered completely.

CONCLUSION: *C. albicans* brain granulomas occur rarely in immunocompetent patients. Despite the large size of the lesions and severe brain edema, the absence of an underlying disease contributed to complete resolution after shunt removal and antifungal therapy.

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Key words: *Candida albicans*, Cerebral candidiasis, Granuloma, Stereotactic brain biopsy, Ventriculoatrial shunt

Cerebrospinal fluid (CSF) shunt infections are relatively common, with reported infection rates ranging from 2 to 39%; in recent reported series, the rate is 5 to 10% (2). More than 70% of shunt-associated infections are caused by *Staphylococcus* species (9). Gram-negative bacteria are the next most common pathogens, accounting for 19 to 22% of cases (11). Fungal infections related to CSF shunts are uncommon and have been associated with significant morbidity (3, 8, 13). Granulomas and brain abscesses attributable to *Candida* species are rare (1). In recent years, *Aspergillus* species and *Candida albicans* have been found to be the most common causes of fungal brain abscess in immunocompromised patients (5, 10). We describe an unusual case of *C. albicans* cerebral granulomas related to a nonfunctional CSF shunt in a previously healthy patient, who was successfully treated with shunt removal and antifungal therapy.

CASE REPORT

A 22-year-old woman was admitted with a 7-day history of progressive headache and left-side hemiplegia. Three years before admission, the patient had sustained multiple injuries after a fall from a second floor. She remained unconscious for 1 week at a trauma center. Hydrocephalus, probably attributable to subarachnoid hemorrhage, was identified during her hospital course, and she underwent right occipital ventriculoatrial shunt placement. She was discharged without neurological sequelae. One year later, the distal shunt was surgically revised, and she developed a wound dehiscence at the level of the neck with purulent secretion. She received orally administered antibiotics for 3 months until the wound closed. Twelve weeks before admission, the patient presented to another hospital with progressive dyspnea, fever, and cough. A pulmonary embolism and right atrial thrombus were identified, and anticoagulants were administered. The shunt was tied under local anesthesia with no evidence of symptomatic hydrocephalus, and the distal shunt catheter was removed. Blood cultures remained negative.

The patient was discharged, and 5 weeks later she presented to our hospital. At admission, she was afebrile. Keloid scars without inflammation were present on the right side of the neck. Neither tenderness nor erythema was found over the shunt catheter tract. A neurological examination revealed left hemiplegia, although the patient was

alert. Laboratory tests demonstrated hemoglobin, 12.5 g/dl; hematocrit, 40.4%; and white blood cell count, 7100/mm^3 (polymorphonuclear cells, 58%; lymphocytes, 34%). Computed tomography of the head revealed an isodense mass on the right basal ganglia producing midline shift and asymmetric hydrocephalus (*Fig. 1A*). After administration of contrast medium, two distinct round masses adjacent to the ventricular shunt catheter, as well as intense brain edema, were observed (*Fig. 1B*). Blood cultures were obtained, and antibiotic therapy with intravenously administered vancomycin was initiated. Oral anticoagulation therapy was changed to heparin. Magnetic resonance imaging, performed 3 days later, provided clear visualization of the tip of the ventricular catheter inside the brain parenchyma (*Fig. 2*). Results of an echocardiographic examination were negative for valvular vegetation, and blood cultures remained sterile.

A stereotactic brain biopsy of the outer mass was performed. No abscess wall resistance was palpated during the procedure, firm yellowish tissue fragments were obtained, and no pus was aspirated. The remnant shunt hardware was removed. Microscopically, the lesion consisted of acute and chronic nonspecific inflammation. *C. albicans* was recovered in cultures of the biopsy tissue and the shunt components. During a 4-week period, the patient received a total dose of 1.1 g of intravenously administered amphotericin B. By the second week of treatment, clinical improvement was evident, and repeat computed tomographic scans exhibited reduction of lesions and no changes in ventricular size. In vitro susceptibility studies of the *Candida* isolate were performed at a reference center. It was found to be sensitive to amphotericin B, resistant to fluconazole and itraconazole, and moderately susceptible to ketoconazole. The patient received 800 mg/d of orally administered ketoconazole for 16 weeks. Follow-up magnetic resonance imaging 4 months after surgery (*Fig. 3*) revealed resolution of the lesions and mild ventricular enlargement. The patient was asymptomatic on her last outpatient visit 9 months after surgery.

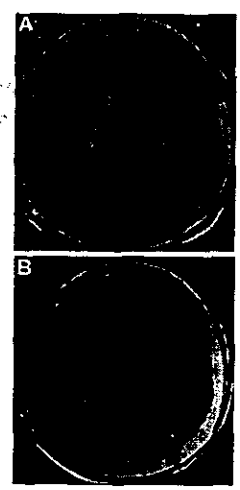

FIGURE 1. Computed tomographic scans obtained during hospitalization. *A*, plain scan showing a hypodense mass on the right basal ganglia, with midline shift and left ventricular enlargement. The shunt catheter is observed in the middle of the mass outside the ventricle. *B*, contrast-enhanced image showing two masses with irregular enhancement and hypointense central areas adjacent to the shunt catheter. Extensive parenchymal brain edema is evident.

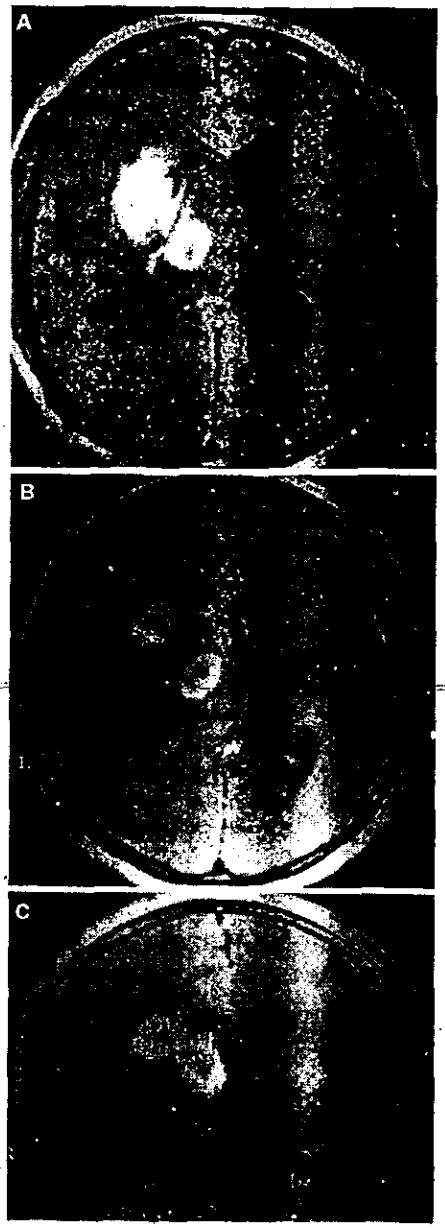

FIGURE 2. T1-weighted magnetic resonance images with gadolinium enhancement of the brain showing the lesions. *A* and *B*, axial images; *C*, coronal image.

DISCUSSION

This patient presented to our center with hemiplegia, remnants of a CSF shunt without inflammatory changes along the catheter tract, a remote history of a long course of antibiotics, and a recent manipulation to remove the distal catheter for pulmonary emboli. An indolent course without fever, a normal white blood cell count, and images that were not typical for a common bacterial brain abscess led us to choose a stereotactic brain biopsy of the outer mass as an appropriate method for histopathological diagnosis and identification of a causal organism.

FIGURE 3. Axial gadolinium-enhanced magnetic resonance image obtained 4 months after proximal shunt catheter removal, showing resolution of the lesions and mild ventricular enlargement.

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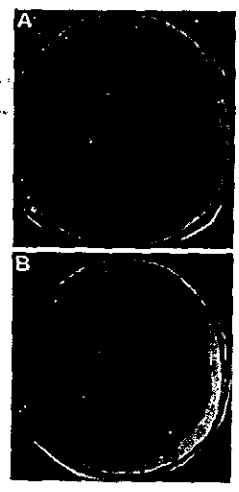

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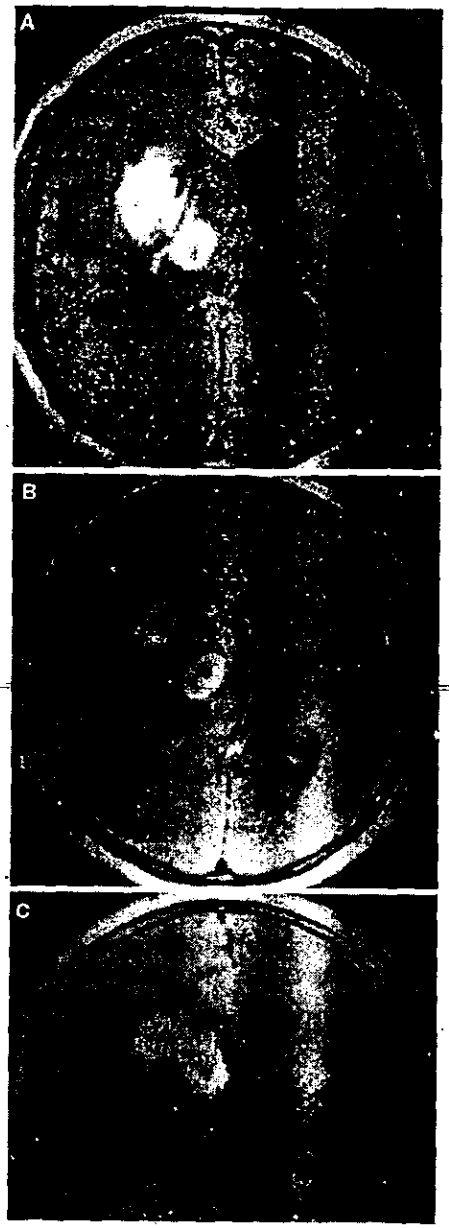

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FIGURE 3. Axial gadolinium-enhanced magnetic resonance image obtained 4 months after proximal shunt catheter removal, showing resolution of the lesions and mild ventricular enlargement.

Several errors in previous management contributed to this complication. In patients with ventriculoatrial shunt infection with evidence of ventriculitis, meningitis, wound infection, thrombophlebitis of the superior vena cava, or endocarditis, the entire shunt apparatus must be removed immediately. In this patient, at the time of neck wound dehiscence or when pulmonary emboli were identified, a complete shunt removal was clearly indicated.

With regard to the pathogenesis of this infection, the hematogenous route seems improbable considering the negative blood cultures, the normal echocardiographic results, and the absence of evidence of systemic candidiasis. We considered it more probable that the catheter was colonized with *C. albicans* and that manipulation at the time of distal segment removal allowed a retrograde ascending route of infection. The proximal catheter portion no longer communicated with the ventricular cavity, as demonstrated by imaging studies; therefore, no ventriculitis resulted. Instead, the fungal infection entered the brain parenchyma, and fungal granulomas developed during a 5-week period without systemic toxicity. This retrograde mechanism of infection is supported by positive cultures of the ventricular shunt catheter and reservoir. Young et al. (13) reported three patients in whom CSF shunts had originally been placed for treatment of hydrocephalus unrelated to fungal infection; these patients later experienced multiple shunt revisions and bacterial infections, and they received antibiotic therapy before the development of fungal shunt infections with *C. albicans*.

In our patient, we chose the term *granulomas* because no pus was aspirated and no organized abscess wall was found microscopically. Fungal brain abscess attributable to *C. albicans* is associated with a high mortality in patients undergoing bone marrow transplantation and in solid organ transplant recipients (5, 10). Guppy et al. (4) recently reviewed central nervous system fungal infections in immunocompromised patients.

Twenty-four well-documented cases of *Candida* shunt infections were reviewed by Sanchez-Portocarrero et al. (8). Twenty-three patients had ventriculoperitoneal shunts, and one had external ventricular drainage. The relevant predisposing factors were recent bacterial meningitis, neurosurgery other than the shunt placement, and abdominal complications in five patients. In 36% of patients, the main clinical manifestation was hydrocephalus. An indolent clinical presentation with fever was observed in only 31% of patients. Six (28.5%) of 21 patients died. Two patients (9%) died from the infection; one of them was the only patient whose catheter was not removed. Four patients died from unrelated causes. An interesting observation was that in four patients in that series, shunt removal was followed by an apparent cure without specific antifungal treatment. Imaging studies are not reported in the review article. The recommended treatment by the authors was shunt removal plus intravenously administered amphotericin B.

Chiou et al. (3) reported eight children with fungal infections of ventriculoperitoneal shunts. The patients were premature infants, five of whom had artificial ventilation and parenteral nutrition as predisposing factors. *C. albicans* was isolated in five of the patients. In seven patients, management consisted of shunt removal, extraventricular drainage, systemic amphotericin B therapy, and insertion of a new shunt. Satisfactory results without acute mortality were achieved.

Some case reports of large *Candida* granulomas without systemic candidiasis have been published with information regarding the clinical course and imaging studies. Ikeda et al. (6) reported a 24-year-old woman who had developed bacterial arthritis at age 9 years and received a large amount of antibiotics. She developed candidal cerebral granulomas and required a ventriculoperitoneal shunt. Fifteen years later, she presented with multiple enhanced mass lesions in the right cerebral hemisphere and ventriculitis. She recovered after a 4-month hospital stay, including three operations, antifungal therapy with amphotericin B, and later intravenously and intraventricularly administered miconazole. Thron and Wiethölter (12) reported a young woman with hereditary immunodeficiency who developed several granulomatous masses in the frontal lobe and left basal ganglia. Marked improvement without scarring was observed on imaging studies 1 year after therapy with amphotericin B and 5-fluorocytosine. Ilgren et al. (7) published the case of a previously healthy 14-year-old boy with a cerebellar mass and obstructive hydrocephalus. After ventriculoatrial shunt placement, an avascular tumor of greenish hue was removed. Microscopically, the mass consisted of granulomatous tissue with fungal hyphae, confirmed as *Candida* species by immunofluorescent staining and serum mannan precipitins. The patient received amphotericin B and was well and active at the 6-month follow-up examination.

CONCLUSION

We describe one immunocompetent patient with large cerebral granulomas caused by *C. albicans* associated with CSF shunt remnants. Although *Candida* shunt infections are rare, the large numbers of patients with hydrocephalus who require shunt revisions and receive antibiotics are at risk. This case report illustrates that errors in management may contribute to the production of unusual infections, and stereotactic brain biopsy is important for early diagnosis of atypical deep inflammatory lesions. Shunt removal and antifungal therapy, guided, if possible, by fungal susceptibility tests, seem to provide safer therapy. We think that the absence of both ventriculitis and underlying disease were crucial for the cure of our patient. Close monitoring of these patients during treatment and long-term clinical and neuroimaging follow-up are warranted.

ACKNOWLEDGMENTS

We thank José Sifuentes Osornio, M.D., Chief of the Microbiology Department of the Instituto Nacional de la Nutricion Salvador Zubiran, for in vitro susceptibility studies of the *C. albicans* isolate.

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COMMENTS

The authors report a patient with proven *Candida albicans* ventriculoatrial shunt infection involving the ventricular catheter portion of the shunt. It is not entirely clear when the fungal infection began, because, 2 years before the infection, a long course of antibiotics had been administered for a purulent wound dehiscence involving the cervical portion of the atrial catheter. The distal catheter was again exposed, manipulated, and partially removed just 12 weeks before the fungal infection. It is certainly possible that the shunt was chronically infected with *C. albicans*, and the more recent procedure allowed retrograde infection into the brain catheter, but it seems rather unlikely that the patient would have been asymptomatic for 2 years. The fungus may have been blood-borne, or it may simply have been introduced when the distal catheter was removed.

A preferable course of treatment might have been complete removal of the shunt system, either when the neck wound was infected or during removal of the distal catheter. Once a process appeared around the brain catheter, simply removing and culturing the catheter might have sufficed rather than performing a separate stereotactic biopsy.

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Soto-Hernández et al. describe a patient who developed a *C. albicans* granuloma around a nonfunctioning shunt catheter that had been placed approximately 3 years earlier. The patient required a shunt revision and then experienced a wound dehiscence, which was treated with prolonged antibiotic therapy. The distal end of the ventriculoatrial shunt was removed owing to pulmonary emboli, and the patient presented with a central nervous system infection 5 weeks later. After removal of the proximal end of the shunt, the patient had not developed symptoms of hydrocephalus, which raises questions regarding the indications for which the shunt was initially placed. If the shunt had never been placed, this infection would not have occurred. This emphasizes the importance of appropriate indications for shunt placement and highlights the severity of complications that can occur after a shunt is placed. The patient is very fortunate that she made a good neurological recovery, given the location and size of the *C. albicans* granuloma.

The prolonged intravenous or oral administration of antibiotics is not without risk. Antibiotics reduce normal skin flora and allow for fungal overgrowth even in immunocompetent patients. The authors were correct in assuming that the fungus gained access to the brain through the ventricular catheter extending from the skin.

Treatment for the *C. albicans* granuloma included a month of intravenously administered amphotericin B and 16 weeks of orally administered ketoconazole. The use of the ketoconazole was based on the sensitivity of the fungus in culture. Amphotericin B is the mainstay of treatment for this infection, and many clinicians would have treated the patient with this drug for a longer duration (1). Long-term follow-up for at least 1 year is necessary the exclude recurrence, particularly because the use of azoles for this infection is still under investigation (1). The removal of all shunt hardware cannot be overemphasized. As is true for many bacterial shunt infections, it is very difficult to eradicate infection if infected material is present in the central nervous system. Unlike other more virulent fungi such as *Aspergillus fumigatus*, *C. albicans* infections of the brain can be cured with antifungal therapy. In individuals with normal immune systems who have had shunt infections attributable to this agent, some reports have demonstrated resolution of the infection by removal of the shunt hardware alone.

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1. Anker L, Hall WA: Fungal infections of the central nervous system, in Hall WA, McCutcheon IA (eds): *Infections in Neurosurgery.* Park Ridge, AANS, 1999, pp 219–235.

The authors report an unusual case of *C. albicans* brain abscess formation that occurred as a complication of a ventriculoatrial shunt in a 22-year-old woman. Two years previously, the patient had developed cervical wound dehiscence and infection after a shunt revision. The wound was closed, and the patient was treated with orally administered antibiotics for several months. Three months before admission, the patient presented with a pulmonary embolism and right atrial thrombus. The atrial catheter was removed, but the ventricular catheter was

left in place. One week before admission, the patient reported headache and left-sided weakness. A magnetic resonance imaging scan of the brain demonstrated multiple abscesses in the right basal ganglia.

After admission to the authors' hospital, the ventricular catheter was removed and a stereotactic brain biopsy was performed. Cultures of the tissue and shunt hardware were positive for *C. albicans*. Treatment consisted of intravenous administration of amphotericin B for 1 month and oral administration of ketoconazole for 4 months. The patient made a good clinical recovery, and magnetic resonance imaging at 7 months demonstrated complete resolution of the basal ganglia abscesses. Longer follow-up will be required to rule out delayed recurrence of infection.

This most unusual complication can be attributed directly to errors in management of the original shunt infection. In patients with ventriculoatrial shunts who exhibit evidence of ventriculitis, meningitis, wound infection, thrombophlebitis of the jugular vein or superior vena cava, or endocarditis, the entire shunt must be removed without delay. Antibiotics should be administered intravenously, and in some patients it may be necessary to institute external ventricular drainage to control intracranial pressure or drain infected cerebrospinal fluid. A new shunt should always be implanted to a site other than the bloodstream. These principles have not changed over the years, although ventriculoatrial shunts are rarely placed today.

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