Cerebellar cryptococcoma in an immunocompetent child

Case report

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✓This is the first report of a cerebellar cryptococcoma in a previously healthy, HIV-negative child. Cryptococcus neoformans is an opportunistic fungus that typically affects patients who are HIV-positive and other patients with compromised immune systems. Isolated cryptococcomas of the central nervous system (CNS) have been previously described in immunocompetent adults; however, this is the first report of a cryptococcoma in a child. The patient presented with progressive headaches and nausea and was found to have a large cerebellar hemispheric mass. The patient underwent excision of the mass, and analysis of frozen sections suggested the presence of an astrocytic tumor with pilocytic features; therefore gross-total resection was performed. Once the definitive diagnosis of a cryptococcal abscess was obtained, medical treatment with antifungal medications led to the resolution of all symptoms and the normalization of serum titers. Cryptococcoma is a rare cause of ring enhancing lesions in the cerebellum, even in apparently immunocompetent patients. The authors’ experience with this case and the patient’s postoperative care lead them to advocate resection of large isolated cryptococcomas of the CNS, especially those situated in the posterior fossa.

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KEY WORDS • brain tumor • cryptococcoma • fungal abscess • juvenile pilocytic astrocytoma • pediatric neurosurgery

Cryptococcus neoformans is a cosmopolite opportunistic fungus that primarily affects HIV-infected or other immunocompromised patients. Central nervous system involvement of cryptococcosis typically manifests with signs and symptoms of meningitis or meningoencephalitis, but is highly variable, relating in part to underlying medical conditions (for example diabetes, sarcoidosis, or glucocorticoid use) and the immune status of the host. The classic appearances of neurocryptococcosis on CT and MR images have been described previously for both immunocompetent adults and immunocompromised patients. However, cryptococcoma is rarely considered in the differential diagnosis for posterior fossa masses in the pediatric population. Prior case reports of isolated cryptococcoma have been described in immunocompetent hosts, but in the majority of these cases, the patients were eventually found to have underlying diabetes mellitus or another cause for having previously unrecognized compromised immune status. We present a case of cerebellar cryptococcoma in an immunocompetent and previously healthy 11-year-old boy. The child was taken to the operating room for resection of a posterior fossa mass, which was found on pathological analysis to be an isolated cryptococcoma without other systemic disease or other CNS manifestations of cryptococcosis. A brief review of the related literature is also presented.

Case Report

History and Examination. This 11-year-old boy with no significant medical history presented with a 2-week history of progressively worsening headaches and emesis. The headaches were diffuse, were not related to position or time of day, and did not improve with acetaminophen. He had several episodes of nonbloody, nonbilious emesis daily, until the day of admission when it occurred more frequently. Three days prior to admission he was febrile with a temperature of 100.9°F. A comprehensive review of his body systems was not significant for any pertinent findings. The patient was an alert, interactive, cooperative, and obese African-American boy. Physical examination was notable for a positive Rhomberg test, clumsy tandem walking, mild dysmetria in all four
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limbs, but no dysdiakinesis. On fundoscopy there was no evidence of papilledema. Results of complete blood cell count, electrolyte, and liver function tests were within normal limits. The patient’s white blood cell count was 6.3 at admission, with an essentially normal differential.

Imaging Examination. Abdominal and chest radiographs were nondiagnostic. An unenhanced CT scan of the head demonstrated a 2.5 × 2.3 × 2.4–cm mass in the right cerebellar hemisphere (Fig. 1A) with adjacent edema and mass effect on the fourth ventricle but no hydrocephalus. Subsequent MR images obtained with and without contrast demonstrated a 1.8 × 2.1 × 1.9–cm rim-enhancing lesion (Fig. 1B–G). The lesion had moderate signal intensity on diffusion-weighted images and a low signal on apparent diffusion coefficient maps. A signal void that enhanced after administration of contrast agent was seen throughout the lesion. On MR spectroscopy, high lactate levels and the absence of a choline peak were demonstrated (Fig. 1H and I). The MR images were interpreted by a neuroradiologist as suggestive of the presence of a bleeding vascular malformation, and both infectious and neoplastic processes were thought to be less likely. With this information, the patient was transferred to our institution for definitive management of a presumed vascular lesion in the posterior fossa.

Operation. The patient was taken to the operating room for resection of the cerebellar mass. The operation was performed via a suboccipital craniotomy with the patient in the prone position. Intraoperatively, the pial interface appeared somewhat thickened and opaque; subcortical dissection was performed until an avascular, firm mass was identified. A portion of the mass was sent for pathological analysis, and the neuropathologist determined that the frozen specimen was a glial neoplasm with pilocytic features. Shortly after beginning a sharp dissection of the mass, a purulent exudate was encountered. At this point, although the diagnosis of astrocytoma was in doubt, clear margins were visible and gross-total excision of the rind and cyst contents was performed (Fig. 2). The patient tolerated the surgery well, his trachea was extubated, and he was returned to the pediatric intensive care unit in stable neurological condition.

Postoperative Course. On postsurgical Day 1, a KOH prep procedure was reported with budding yeast. The acid-fast bacillus smear was negative and no bacterial organisms were identified. An infectious disease service consultation was requested. When questioned, the family could recall no relevant history of travel, and they confirmed that the patient did not live near any construction sites and had not had any contact with animals or birds.

Amphotericin B was added to his postoperative regimen of ceftazidime, metronidazole, and vancomycin. A CSF sample was obtained via lumbar tap, a purified protein derivative was placed, and HIV testing was initiated. Oral/maxillofacial and cardiology consultations revealed no evidence of a dental abscess and no cardiac shunting that could explain the brain abscess. The yeast was identified as Cryptococcus within 72 hours, at which point the antibacterial medications were discontinued, and oral flucytosine was started. A cryptococcal serum antigen test was sent, and the titer returned positive at 1:32. The patient had severe nausea, suffered multiple episodes of emesis postoperatively, and was found to have significant edema surrounding the resection cavity (Fig 2A), but hydrocephalus did not develop. Dexamethasone and hypertonic saline therapy were initiated to help reduce the posterior fossa edema, which resolved over several days.

The results of the patient’s purified protein derivative test were negative and he also tested negative for HIV, but he had a positive cryptococcal serum agglutination. Cultures of CSF were negative for fungal elements. The patient’s CD4 count was 308, but returned over several weeks to the lower range of normal values. After 2 weeks of treatment with amphotericin and flucytosine, a repeated lumbar puncture was performed from which a fungal culture was again negative. Results of repeated cryptococcal antigen tests obtained after 2 weeks of treatment showed a decrease to 1:4.

Follow-Up Examination. The patient was discharged home to complete 10 weeks of oral fluconazole therapy. Immune evaluation results—including B and T cell enumeration (total and subset), total complement, C3, C4, immunoglobulin G subclasses, quantitative immunoglobulin G, A, M, and E—were within normal limits. His response to Hemophilus influenzae and Streptococcal pneumoniae vaccines was normal. Serological tests for HIV 1 and 2, and human T lymphotropic virus were negative. Lymphocyte function, as measured by standard mitogen assays was normal. After 10 weeks of fluconazole therapy, a serum antigen test was negative, and therapy was discontinued. The child continues to have some problems with short-term memory and balance, but has otherwise returned to his baseline condition.

Discussion

Cryptococcus neoformans is an opportunistic fungus that
There are two recognized varieties of J. Neurosurg: Pediatrics / Volume 107 / October, 2007. The clinical manifestations of CNS involvement of cryptococcosis are highly variable, depending not only on the patient’s risk factors, but also on the yeast variety involved. There are two recognized varieties of C. neoformans: C. neoformans var. neoformans (serotypes A and D) with worldwide distribution, isolated from soil contaminated with mammal and avian (especially pigeon) feces; and C. neoformans var. gattii. The former predominantly infects HIV-infected and other immunocompromised patients. Serotype A has been proposed to be separated from C. neoformans var. neoformans into a new distinct variety called C. neoformans var. grubii, based on capsular differences. Cryptococcus neoformans var. gattii (serotypes B and C) arises mainly in temperate and tropical climates, is found in the soil of eucalyptus trees, and infects immunocompetent patients.

In general and for unknown reasons, C. neoformans var. gattii rarely infects immunocompromised persons. Rather, patients infected with C. neoformans var. gattii are usually immunocompetent, respond slowly to treatment, and are at risk for developing intracerebral mass lesions (such as cryptococcomas). Hallett and Beilke identified only nine cases of intracranial cryptococcomas in HIV-negative patients reported between 1973 and 1996; the majority of these patients suffered from underlying diabetes mellitus, recent steroid use, or some other cause for relative immunosuppression; another cohort were predominantly infected by C. neoformans var. gattii. These authors also reported a cerebellar cryptococcoma in a 62-year-old HIV-negative man with diabetes. More recent reports of isolated cryptococcal infection in adults include cryptococcomas in the pituitary, pons, midbrain, basal ganglia, and parietal cortex. The present case is, to our knowledge, the first report of such a lesion in the pediatric population.

The CNS is the second most common site of infection for cryptococcosis after the lungs, but is the most common site of disease manifestation because of the strong neurotropic tendency of cryptococci. It has been hypothesized that this tropism stems from the nutritional requirements of the fungus: the CSF provides the exact and optimal nutritional milieu. Also, soluble anticycrococcal factors present in serum are absent in the CSF. This form of infection is invariably fatal without appropriate therapy, and death may occur anytime from 2 weeks to several years after the onset of symptoms. Cryptococcal CNS infections usually present in one of two forms: meningeal or parenchymal. Meningitis is the predominant manifestation, and is usually most pronounced at the skull base. Parenchymal involvement may be in the form of cryptococcomas or torulomas, dilated Virchow–Robin spaces, multiple enhancing cortical nodules, or a mixed variety of entities.

The clinical course of CNS cryptococcosis is highly variable, relating in part to underlying medical conditions (such as diabetes, sarcoidosis, or glucocorticoid use) and the immune status of the host. Immunocompromised patients may present with headache, nausea, vomiting, altered mental status, personality changes, confusion, lethargy, obtundation, or coma. However, patients may also present with minimal or nonspecific symptoms. Fever and nuchal rigidity are characteristically absent, as was the case in our patient. Hydrocephalus may develop as a result of meningeal scarring, with dementia as a possible late complication. Other possible symptoms include hearing defects, seizures, ataxia, aphasia, choreoathetoid movements, blurred vision, photophobia, and diplopia, which may occur secondary to arachnoiditis, papilledema, optic nerve neuritis, and chorioretinitis. Immunocompetent hosts may present with either meningitis or focal cryptococcomas.

In general, the preferred protocol for presumed diagnosis involves serial microbiological investigations of the CSF and blood. Cerebrospinal fluid examination is essential to the diagnosis of CNS disease; however, patients should also undergo CT or MR imaging to rule out a mass lesion. If a mass is identified, lumbar puncture should be avoided and a CSF sample obtained in a different fashion. Elevated opening pressure is associated with a poor prognosis. The CSF profile will show low glucose, elevated protein, and elevated leukocyte counts, with relative lymphocytosis. The CSF in immunocompromised patients may be normal or just marginally abnormal, owing to their inability to mount an adequate inflammatory response, whereas CSF samples obtained from previously healthy patients will invariably show changes. The CSF should also be examined for the presence of microorganisms using India ink staining and sent for culturing. Cryptococcal antigen latex agglutination titers in the CSF and blood are important adjuncts in the diagnosis; in patients with meningitis, CSF cryptococcal antigen is positive in more than 90% of cases and the serum...
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TABLE I
Magnetic resonance imaging findings suggestive of neurocryptococcosis

| Focal (<3 mm), hypointense on T1- & hyperintense on T2-weighted images w/o enhancement w/ Gd, round or oval, punctate lesions seen often bilaterally in the basal ganglia, internal capsule, thalamus, brainstem, & white matter of the cerebellar peduncles. These represent the spread of cryptococcal organisms spread from the basal eisterns through the Virchow–Robin spaces, dilated by the voluminous mucinous material produced by the organisms. A single, focal (>3 mm) parenchymal mass, hypointense on T1- & hyperintense on T2-weighted images, isoointense to CSF, in the basal ganglia, temporoparietal region, brainstem, or cerebellum. This lesion represents the cryptococcoma, a collection of organisms, inflammatory cells, & gelatinous mucoid material in the brain parenchyma that can develop when organisms have extend- ed directly from perivascular spaces, meningeal, or ependymal surfaces into the adjacent tissues. Depending on the host’s immunological status, may be a subtle rim of enhancement w/ Gd, & possible edema. Unilat or bilat enlargement & dense enhancement of the choroid plexus in the lat & 4th ventricles, or enhancing intraventricular mass, often in association w/ clinical findings of leptomeningitis. This represents choroid plexitis. An associated unilateral cystic dilation of the temporal horn of the lateral ventricle has been de- scribed, presumably secondary to entrapment of the temporal horn by the inflamed choroid plexus & extensive edema around the ipsilateral ventricle. Multiple, miliary, hypointense T1- & hyperintense T2-weighted images, enhancing parenchymal & leptomeningeal–cisternal nodules, representing small granulomas. A mixed pattern that involves nonenhancing dilated Virchow–Robin spaces as well as enhancing cryptococcomas. |


titer is positive in approximately 75% of cases. Positive ser- um results should be confirmed with blood cultures.

Imaging of the CNS is essential in any patient who pre- sent with new onset neurological dysfunction. Results of CT scanning in patients with confirmed neurocryptococcosis may be normal, but may show nonspecific findings such as diffuse atrophy, hydrocephalus, or diffuse cerebral edema.1,3 When present, cryptococcomas usually appear as round, hypo- or isoattenuating lesions with possible ring enhance- ment located mainly in the cerebral white matter and basal ganglia region, that correspond to granulomas or abscesses, or less commonly, gelatinous pseudocysts, often depending on the immunological state of the host. Findings on MR imaging may similarly be suggestive, but not pathognomonic, of neurocryptococcosis (Table 1).

Untreated, neurocryptococcosis is invariably fatal; early diagnosis and initiation of treatment is thus essential. For patients who have coinfection with HIV, the therapeutic goal is to control the initial infection, followed by requisite life-long suppression of C. neoformans. For patients with cryptococcal disease not complicated by HIV infection, the therapeutic goal is to achieve a permanent cure of the fun- gal infection. For both subsets of patients, initial therapy is with intravenous amphotericin B at 0.7 to 1 mg/kg/day, pre- ferably in combination with oral fluconazole at 100 mg/kg/ day for 2 weeks, followed by oral fluconazole at 400 mg/ day for a minimum of 10 weeks. Cerebrospinal fluid should be sampled after 2 weeks of initial therapy to assess for the clearance of fungus. In patients with concomitant HIV in- fection, lifelong maintenance therapy is achieved after in- duction therapy by administering fluconazole at 200 to 400 mg/day.

Conclusions

The role of neurosurgical intervention in neurocryptococ- cosis is usually for treatment of communicating hydroceph- alus due to arachnoid scarring. Rarely neurosurgeons may be called to intervene in unique circumstances such as a mass cryptococcoma causing obstructive hydrocephalus or neurological decline secondary to perilesional edema. The excellent long-term neurological and immunological status of the otherwise healthy child in this unique case of cerebel- lar cryptococcoma leads us to advocate surgical excision of large mass lesions when possible. The radiologic findings of cryptococcoma will probably remain unrecognized in healthy patients, but for the immunocompromised population, in whom cryptococcomas are not as infrequent, infectious dis- ease specialists and neurosurgical teams should collaborate in assessing the risks and benefits of early resection com- pared with careful observation during initiation of medical therapy.

References


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