Intraventricular cryptococcal granuloma

Report of two cases

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Infection by Cryptococcus neoformans, a budding nonmycelial yeast, involves the central nervous system in 70% of patients at the time of diagnosis. Meningitis and meningoencephalitis are common manifestations of infection; solid granulomas occur but are unusual, and intraventricular granulomas are distinctly rare. Two cases of intraventricular cryptococcal granuloma are reported. The diagnosis and treatment of mass lesions due to cryptococcal infection are discussed, with special reference to intraventricular granulomas.

KEY WORDS • cryptococcosis • cryptococcal granuloma • intraventricular granuloma • fungal infection

THE nonmycelial yeast Cryptococcus neoformans causes opportunistic infections in man. Involvement of the central nervous system is common at the time of diagnosis, usually in the form of meningitis, meningoencephalitis, or granulomas. Intraventricular lesions due to Cryptococcus are rare. We report two cases of intraventricular lesions which illustrate the diagnostic and therapeutic difficulties associated with this form of infection. Therapeutic strategies are recommended based on our observations and those of others.

Case Reports

Case 1

This 69-year-old woman was admitted to the Yale-New Haven Hospital in December, 1985, with a 1-year history of increasing memory difficulty, confusion, and bizarre behavior. In the 2 weeks prior to admission she had experienced a right frontal headache, nausea, and vomiting. She had a history of exposure to pigeon excreta.

Examination. On admission the patient was disoriented to place and date, with poor memory function. She had a left superior-lateral homonymous quadrant-anopsia, a mild left upper-extremity weakness, left-sided sensory extinction, and a left Babinski sign. A computerized tomography (CT) scan (Fig. 1) showed hypo-density of the right temporal lobe suggestive of a trapped temporal ventricular horn. A region of noncontrast-enhancing hypodensity surrounding the atrium of the right lateral ventricle was suggestive of intrinsic tumor. Both choroid plexus glomera were prominent, and there was a moderate degree of generalized ventricular enlargement. Peripheral white blood cell (WBC) count was 4.9/cu mm. Chest x-ray films and CT scans were normal.
Operation. A right frontotemporal craniotomy was performed with aspiration of the temporal horn of the ventricle. Clear fluid was obtained and sent for culture and cytological studies. A subtotal anterior temporal lobectomy was carried out, and a firm, slightly cystic nodule in the choroid plexus which was obstructing egress of cerebrospinal fluid (CSF) from the ventricle was removed.

Pathological Examination. Microscopic examination of the surgical specimen revealed it to be choroid plexus, diffusely infiltrated by mononuclear inflammatory cells and budding yeast. The cortex was gliotic, with focal subarachnoid mononuclear infiltrates mixed with multinucleated giant cells and organisms. Postoperatively, the CSF cultures grew Cryptococcus neoformans.

Immunological work-up revealed abnormally decreased numbers of T-helper cells, T-suppressor/cytotoxic cells, total T cells, and total B cells. No human immunodeficiency virus (HIV) antibody titers were detectable. Reduced serum levels of immunoglobulin A were also found (27 mg%), but other antibody classes were present in normal quantities.

Despite intravenous administration of amphotericin B (minimum 55 mg/day, 3 gm in total), the patient deteriorated to an obtunded state, with intermittent left upper-extremity focal motor seizures. Repeat CT scans showed an enlarged ventricular system, and serial lumbar punctures were performed. Cryptococcal antigen levels in the CSF remained in the range of 1:30,000; CSF and serum cryptococcal antibodies were undetectable. Deteriorating renal function complicated amphotericin therapy. The patient developed an aspiration pneumonia and died 5 months postoperatively.

Case 2

This 60-year-old man came to medical attention at another institution in January, 1986, because of a 3-month history of progressive dementia and gait disorder associated with headaches and dizziness. Computerized tomography scans showed a dilated right temporal ventricular horn with an area of hypodensity surrounding the right atrium, generalized ventricular enlargement, and prominence of both choroid plexus glomera. A left-sided lung lesion was detected by x-ray study; a skin test for purified protein derivative of tuberculin (PPD) was negative. Analysis of CSF obtained by lumbar puncture revealed a protein level of 48 mg% with 10 WBC/cu mm, primarily neutrophils. In March, 1986, the patient underwent a right temporoparietal craniotomy and biopsy of the posterior temporal lesion, which on pathological examination was consistent with edematous infarcted tissue. The postoperative course was complicated by aspiration pneumonia. He was transferred to Yale-New Haven Hospital for further evaluation in April, 1986.

Examination. On admission the patient was awake, agitated, confused, and uncooperative. He was dysarthric, with bilateral sixth nerve paresis. Reflexes were hyperactive and symmetrical; Babinski signs were absent. Peripheral WBC count was 17.8/cu mm. Chest x-ray films showed a 1-cm calcified lesion in the right upper lobe, as well as right middle- and lower-lobe infiltrates. A CT scan of the brain was essentially unchanged from the earlier studies, except for volume loss of the temporal lobe and prominence of the temporal horn.

On the 2nd day of hospitalization, the patient's level of consciousness suddenly deteriorated. His neurological condition improved on removal of CSF through a ventriculostomy catheter. Examination of the CSF showed budding encapsulated yeast, 17 nucleated cells/ml (mostly lymphocytes), a protein level of 54 mg%, and a glucose content of 26 mg% (serum glucose 299 mg%). India-ink examination of the CSF demonstrated Cryptococcus organisms, which grew from all cultures. A course of intravenous amphotericin was begun.

Operation. Rapid neurological deterioration on the 5th day of hospitalization associated with increased intracranial pressure led to reopening of the right craniotomy and a subtotal removal of a grossly necrotic temporal lobe. A frontal Ommaya reservoir was placed. Postoperatively the patient remained obtunded. Persistent problems with CSF absorption were managed by serial spinal and Ommaya reservoir taps. Intravenous amphotericin was continued at a dose of 40 mg/day, and because of persistent elevation of cryptococcal antigen in the CSF, 5-fluorouracil was given.

Pathological Examination. Pathological examination of the surgical specimen revealed many mononuclear inflammatory infiltrates in the subarachnoid space mixed with round or ovoid budding yeast cells. Cryptococcal organisms grew from cultures of temporal lobe tissue.

Immunological investigations revealed a low gamma globulin level (0.5 mg%, normal 0.8 to 1.5 mg%) and low serum albumin (2.4 mg%). Skin tests for mumps, Candida, and PPD antigens were negative. Cryptococcal antigen levels in the CSF were initially 1:65,536, but 1 month postoperatively they rose to 1:1,048,576. A CSF antibody to Cryptococcus was undetectable. The patient suffered a gastrointestinal hemorrhage and died approximately 3 months after the first operation.

Postmortem Examination. Autopsy revealed fibrous pericarditis and left-sided multifocal pneumonia. The leptomeninges were distended with turbid gelatinous material, particularly at the base of the brain. Gelatinous material was seen covering the ventricular wall as well. The choroid plexus of the lateral ventricles was enlarged. On microscopic examination, yeast forms were seen in the subarachnoid space and choroid plexus, along with mononuclear inflammatory cells and occasional multinucleated giant cells (Fig. 2). Well-defined intraparenchymal foci of organisms were seen in the cortex, white matter, basal ganglia, dentate nucleus of the cerebellum, and pons.

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FIG. 2. Photomicrograph of the choroid plexus of the lateral ventricles from Case 2. The choroid plexus is almost completely replaced by cryptococcal granuloma. Some preserved choroid plexus fronds are indicated (arrowhead). H & E, x 54. Inset: Cryptococci of varying sizes. Budding yeast cells are indicated by the arrowheads. Grocott silver stain, x 500.

Discussion

Cryptococcus neoformans, a budding mycelial yeast with a polysaccharide capsule, is a common soil organism which causes opportunistic infections in man. A common source of infection is bird feces, particularly that of pigeons. 13,16 The respiratory tract is the primary site of infection in man, and hematogenous dissemination occurs in 30% to 50% of patients, usually associated with depression of cell-mediated immunity such as with chronic corticosteroid use, reticuloendothelial malignancies, diabetes mellitus, and malnutrition. 13,16,19 The central nervous system is involved in 70% of patients at the time of diagnosis 14 in the form of basilar meningitis, meningoencephalitis, and mass lesions such as granulomas or cysts.

The diagnosis of cryptococcal meningitis is well described 13,12,13,16. The organism can be seen on India-ink examination of the CSF and may be cultured from spinal CSF obtained by tap or from the ventricles. The most reliable diagnostic study is detection of capsular antigen in the CSF by complement-fixation tests. Antigen may also be identified in serum and urine.

Approximately 55 cases of cryptococcal mass lesions have been reported, usually occurring in the subependymal regions of the thalamus, basal ganglia, or caudate nucleus. 8 Multiple lesions are found in 35% of these patients; 80% of patients are male, with a median age in the fifth decade. 8,18 Both cystic and granulomatous lesions have been identified. Approximately 60% of patients with mass lesions have had meningitis on admission. 7,18 No underlying reticuloendothelial system abnormalities have been documented, although more recent cases are seen in the context of the acquired immunodeficiency syndrome (AIDS). 18

The most common CT abnormality in cases of meningitis alone is hydrocephalus. 4,5,11 The appearance of mass lesions on CT scans has been variously reported as low-density regions which homogeneously enhance with contrast material, 5,7,20 hypodense nonenhancing lesions, 8 and isodense lesions with an enhancing rim. 20

Intraventricular mass lesions are distinctly rare. Three autopsy-proven cases (patients aged 15, 42, and 61 years) have been reported. 10,14,24 All presented with lymphocytic meningitis and rapid neurological deterioration, and underwent surgical resection of mass lesions obstructing the right temporal horn of the ventricle. Postoperative survival times ranged from 10 days to 7 months. At autopsy, all had choroid plexus that was bilaterally enlarged with granulomatous lesions, as did the patient in our Case 2. In both of our cases, CT scans demonstrated prominent hypodense choroid glomera. Death following resection is common, as in the case of a 46-year-old woman reported by Benvenuti, et al. 3 She had a subependymal cryptococcal mass at the left trigone and underwent biopsy of the lesion and opening of the lateral ventricle; she subsequently deteriorated rapidly and died on the 4th postoperative day.

The choroid plexus of the lateral ventricle and trigone seems to be a preferred site for these mass lesions. Cornell and Jacoby 4 reported a patient with an enhancing trigonal Cryptococcus granuloma and a left temporal horn dilatation on CT scanning; apparently this lesion was not resected. Although obstruction at the foramen of Monro secondary to bilateral ventriculitis has been observed, 1 temporal horn obstruction due to cryptococcal lesions represents a particularly difficult surgical problem which may become more frequent with an increase in the incidence of AIDS.

The mainstay of therapy for cryptococcal meningitis alone is amphotericin B. 6,12 Approximately 75% to 80% of patients respond to one or more courses. 5,19 Accurate and objective assessment of response to therapy can be accomplished by measurement of capsular antigen titers in the CSF. 5 Patients not responsive to antifungal agents more often have leukemia or lymphoma, a high CSF opening pressure, low CSF glucose levels, less than 20 leukocytes/cu mm, cryptococci visible on CSF smears, and high titers of antigen in CSF and serum. 6

The treatment of mass lesions is controversial. Primary resection has been advocated, followed by optional chemotherapy for cases of multiple lesions, acciden-
tal spillage of granuloma contents intraoperatively, and ongoing active disease. However, successful treatment of mass lesions can be accomplished in some instances with chemotherapy alone using intravenous amphotericin with or without 5-fluorouracil. Large lesions (greater than 3 cm) are more likely to fail antibiotic therapy and require resection. Intraventricular mass lesions become a particularly difficult problem when presenting with symptomatic ventricular obstruction, considering the disastrous results obtained when these lesions are resected. The risk of subarachnoid contamination with organisms during a surgical procedure has been pointed out. External drainage has been suggested rather than shunt placement in cases of fungal meningitis, as hydrocephalus may resolve with chemotherapy alone. In the situation of focal ventricular obstruction, every attempt should be made to treat the patient with antifungal agents, perhaps with external drainage, rather than with immediate primary excision of the intraventricular component.

References

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