Torulomas (cryptococcal granulomata) of the central nervous system

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Three new cases of cryptococcal granuloma of the central nervous system are reported and compared with 37 previously described cases. The lesion may appear with or without evidence of meningitis. Resection of the granuloma followed by prophylactic or therapeutic chemotherapy is recommended as the treatment of choice. Serial lumbar punctures and blood and CSF antigen levels are of value in determining response to treatment.

KEY WORDS: toruloma, cryptococcus neoformans, meningitis, 5-fluorocytosine, amphotericin B

The occurrence of isolated cryptococcal granuloma in the central nervous system (CNS) was reported for the first time by LeCount and Myers in 1907. We are adding three new cases to the 37 similar cases reported.

Case Reports

Case 1

This 46-year-old Indian man was admitted on October 28, 1969, because of neck stiffness, headache, and nausea lasting 4 months.

Examination. He had recognized diabetes. The neurological examination was normal. Lumbar puncture disclosed opening pressure of 230 mm of water; protein 500 mg%, sugar 28 mg%, 400 WBC (19% lymphocytes), xanthochromia, negative smear for Cryptococci and tuberculous bacilli; three repeat punctures gave similar results. Serum Wassermann reaction was positive. Sputum and gastric lavage were negative for tuberculosi. An electroencephalogram (EEG) was normal. Because of the serologic findings he received penicillin for 2 weeks. His temperature ranged between 98.6° and 99.6°F. Two weeks later he became confused and disoriented. Because of a strong family history of tuberculosis he was treated as a case of tuberculous meningitis. He steadily deteriorated and developed left hemiplegia. A right carotid angiogram showed an avascular space-occupying lesion in the right temporal lobe (Fig. 1). When transferred to the neurosurgical service on October 28, 1969, he was barely responsive, had a dilated non-reactive right pupil and left hemiplegia.

Operation. A right temporal craniotomy exposed a cystic lesion in communication with the temporal horn of the lateral ventricle. The cyst contained 12 cc of fluid with a protein content of 104 mg%. Numerous encapsulated organisms were seen in this fluid. The wall of the cyst was only partially removed because of its attachment to the middle cerebral artery. The patient was immediately started on Amphotericin B and 5-fluorocytosine (0.25 mg/kg/day and 200 mg/kg/day, respectively). A postoperative spinal puncture revealed Cryptococcus neofo
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mans. A portable chest film showed a small nodular lesion in the right lower lung field. On November 1 he lapsed into coma and died the next day. Permission for postmortem examination was not obtained.

Case 2

This 30-year-old Chinese man was admitted on May 1, 1967, with signs of meningitis of 4 months' duration. He had been admitted to another hospital on January 25, 1967, where the neurological examination was normal. The CSF then was clear and colorless and contained 133 cells (83% lymphocytes), sugar 35 mg%, and protein 140 mg%. The chest film showed an ill-defined shadow in the right upper lobe. Antituberculous therapy was started. A Babinski sign appeared on the right. Left carotid angiography was normal. Repeat lumbar puncture revealed an opening pressure of 230 mm of water, sugar 3 mg%, protein 80 mg% and lymphocytic pleocytosis. Smears for tubercle bacilli, gram stain, and India ink preparations were negative. Thereafter he had experienced remissions and exacerbations of the symptoms of meningitis. Several CSF samples obtained in the ensuing months gave similar results.

Examination. When examined 4 months after the onset of symptoms, he was stuporous with bilateral sixth nerve palsies, ataxic gait, left hemiparesis, and papilledema. A right carotid angiogram was normal. The lesion of the right upper lobe had almost disappeared. Amphotericin B, 45 mg/day, was given empirically, for a period of 2 weeks with dramatic clinical improvement. When fever and vomiting followed this therapy it was suspended. Thirty days later he was ambulatory. A pneumoencephalogram revealed communicating hydrocephalus, and a ventriculoperitoneal shunt was inserted. The CSF cultures were still negative. Another course of Amphotericin B was given, 20 mg/day for 2 weeks, and the patient was discharged.

In December, 1968, 2 years after the beginning of symptoms, he was readmitted in status epilepticus. The neurological examination revealed a dilated left pupil, marked nerve deafness, spastic left hemiparesis, bilateral ankle clonus, and papilledema. The ventriculoperitoneal shunt was patent. A right carotid angiogram demonstrated an avascular mass in the right temporal lobe.

Operation. A right subtemporal craniectomy was carried out and a cannula passed into the temporal lobe. Some resistance was encountered. The biopsy material revealed a cryptococcal granuloma. A few days later a firm encapsulated intratemporal granuloma measuring about 4 cm in diameter was removed through a temporal craniotomy (Fig. 2).

Amphotericin B was administered for 7

Fig. 1. Case 1. Phase contrast photomicrographs. H & E, x250. Left: Cysts containing cryptococci in wall of temporal horn. Right: Ependymitis and organisms adjacent to granuloma.

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days prior to the craniotomy, 45 mg/day, then 5-fluorocytosine was substituted, 1.5 gm/6 hr for 2 months. He was discharged on anticonvulsant medication. When last seen 2 years after craniotomy there was residual left spastic hemiparesis and marked nerve deafness, the latter probably secondary to streptomycin; CSF examination showed 3 cells, protein 143 mg%, sugar 53 mg%. Cultures and India ink preparations were still negative.

Case 3

This 35-year-old Mexican man was admitted on September 1, 1970, complaining of weakness of the right hand and foot for 5 months, and severe headaches and blurred vision for 2 weeks.

Examination. The general physical examination was normal. The patient was afebrile, alert, and oriented. There was bilateral papilledema with retinal hemorrhages, right hemiparesis, and decreased position sense of the right leg and foot. Left carotid angiography showed evidence of an avascular space-occupying lesion in the superior central region on the left side. Brain scan (sodium pertechnetate Tc99m) showed a well-delineated area of increased uptake in the upper central region of the left side.

Operation. On September 3, craniotomy was performed. A well-encapsulated, hard, gray mass was removed in one place. It was located immediately beneath the cortex, and measured $2.5 \times 2 \times 2$ cm. The surgical specimen was a cryptococcal granuloma with abundant fungi. Cultures were positive. There was little inflammatory reaction to the organisms (Fig. 3).
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The postoperative period was uneventful. Amphotericin B was begun 2 days later and continued for 7 days, beginning with 0.5 mg/kg/day and increasing with daily increments up to 1 mg/kg/day. Nausea, vomiting and anorexia occurred, and Amphotericin B was discontinued. The patient was then started on 5-fluorocytosine (Ancoban) (100 mg/kg divided in four doses per day) and continued for 60 days; no side effects were observed. A careful search for other lesions was negative. The cerebrospinal fluid (CSF) was normal. India ink preparations and cultures were negative for Cryptococcus neoformans. The blood antigen level was slightly elevated (Latex agglutination) showing a titer of 4 on September 16; on September 28 it had dropped to 2. No antibodies were found. Examination 15 months after the operation showed mild spasticity of the right side. The serological tests for cryptococcal antigens and antibodies (serum and CSF) were negative as were cultures from the blood, CSF, urine, and sputum.

Discussion

Cases 1 and 2 illustrate the close clinical similarity of tuberculous and cryptococcal meningitis\textsuperscript{14,15} both of which produce a picture of subacute or chronic meningoencephalitis. The spinal fluid findings may be identical. The absence of an organism in routine smears of the CSF is not infrequent in either disease. A pulmonary lesion may be present in either instance. Moreover, the possible concomitance of these two infections has to be kept in mind.\textsuperscript{16} The development of communicating hydrocephalus was recognized and treated in Case 2. This complication is well recognized in tuberculous meningitis, but it has been verified in cryptococcosis as well.\textsuperscript{5,16,15,32} Non-communicating hydrocephalus has been observed by others.\textsuperscript{12}

Among the 40 reported patients presenting a localized cryptococcal granuloma in the CNS, 23 (approximately 57\%) were found to have no clinical manifestations of meningitis upon admission. All underwent surgery. Our Case 3 belongs in this group. With one exception\textsuperscript{19} all of the lesions were partially or totally removed at surgery. In the 25 patients whose CSF was submitted for smears (India ink technique) and/or cultures for Cryptococcus neoformans, 13 were positive, eight negative and four became positive following surgery. Among the

\begin{table}
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Author, Year & CSF Culture and/or Smear Complete & Follow-up Results & Surgical Excision & Toruloma Type and Location \\
& Preop & Postop & & \\
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Dickman, et al. (1942) & + & 1 mo & yes & left cerebellar \\
Krainer, et al. (1946) & - & 1 yr: asymptomatic & yes & left frontal lobe; solid \\
Ley, et al. (1950) & - & 21 yrs: asymptomatic & yes & intradural-extradural cervical; solid \\
Carton & Mount (1951) & - & 2 yrs: asymptomatic & no & intradural-cauda equina cyst \\
Balakrishna & Lilawala (1952) & - & 15 mos: asymptomatic & yes & right parietal lobe; solid \\
Liu (1953) & - & 5 yrs: asymptomatic & yes & right frontal lobe; cyst \\
Alajouanine, et al. (1953) & - & 8 wks & no & intradural-cauda equina cyst \\
Ramamurthi & Angulli (1954) & - & 18 yrs: asymptomatic & yes & intramedullary-T-3; solid \\
Alvisi & Giordano (1958) & - & 1 mo & no & left temporal lobe cyst \\
Rish & Meacham (1968) & - & 4 yrs & yes & left temporal lobe cyst \\
Rao, P. V. R., et al. (1968) & - & 2 yrs: asymptomatic & yes & right frontal lobe cyst \\
Selby & - & 2 yr: residual left & yes & right temporal lobe; solid \\
 & & hemiparesis & & \\
Selby & - & 1 yr: asymptomatic & yes & right frontal lobe; solid \\
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\caption{Clinical summary of surviving patients operated on for CNS toruloma}
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patients who presented no clinical evidence of meningitis, the CSF was examined and/or cultured for *Cryptococcus neoformans* in 17 patients; six were positive, eight negative, and three became positive after surgery.

Only 14 patients (approximately 36%) are still alive at this time with postoperative follow-up ranging from 1 month to 21 years (Table 1). Seven of these who had complete excision of their lesions were asymptomatic with normal spinal fluid examinations and no evidence of the disease elsewhere. Two others whose toruloma had been completely removed were also asymptomatic, but postoperative spinal fluid smears and/or cultures were not available. In two patients who had total excision the CSF was found to be positive postoperatively, one having clinical evidence of meningitis. The remaining 3 had partial surgical excision. Two patients with cauda equina lesions have survived 2 years and 8 weeks respectively. A third died immediately postoperatively.

Amphotericin B was administered to Rish's patient who had a positive CSF (*Cryptococcus neoformans*) and who is alive four years following surgery; this patient experienced recurrence of chronic meningitis on three occasions, responding temporarily to Amphotericin B each time. Our Cases 2 and 3 received a combination of Amphotericin B and 5-fluorocytosine and were asymptomatic of meningitis 2 years and 15 months after the surgery respectively. A third died immediately postoperatively.

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The duration of the neurological symptoms in the 40 patients with localized involvement ranged from 1 week to 6 years (average, 10 months). Stevenson, et al., had three patients who never presented neurological symptoms and who died of other diseases (myocardial infarction, abdominal malignancy, heart failure); at autopsy a well-encapsulated cryptococcal granuloma was found in the supratentorial compartment in each.

The coexistence of cryptococcosis and malignant diseases of the reticuloendothelial system has been observed by many, and a comprehensive analysis of the subject is found in Zimmerman and Rappaport's article. None of the 40 patients with toruloma had concomitant disease of the reticuloendothelial system.

Contrary to Rao, we believe for the following reasons that even in the absence of meningeal involvement a course of chemotherapy should follow surgery: 1) the possibility of multiple lesions; 2) accidental spillage during the operation; 3) misleading CSF results obtained from smear and cultures which frequently are negative in the presence of active disease; 4) availability of effective chemotherapy and good tolerance to 5-fluorocytosine; and 5) the seriousness of cryptococcal meningitis and its sequelae.

If Amphotericin B is undesirable because of its side effects, 5-fluorocytosine (Ancoban) can be used. We have used this drug to treat five patients with CNS cryptococcosis and no complication was observed. A fall in hemoglobin and a rise in the serum glutamic oxalacetic transaminase was observed by Utz, et al., Elevated transaminase in two patients, mild leukopenia in one and a mild skin rash in one patient were reported by Grunberg, et al., Three patients without complication; one received 2500 gm of 5-fluorocytosine over a 10-month period. Grunberg, et al., reported objective and subjective signs of response to 5-fluorocytosine (Ancoban). In 1968 Tassel and Madoff had favorable results with 5-fluorocytosine in another patient having the same disease. Since then this agent has been used by others. Combined treatment with both drugs appears to be justified in some instances since apparent resistance is sometimes observed in vitro and in vivo.

Recently a variety of serological studies have become available for clinical use. The presence of demonstrable antigen, antibody or both in the serum and/or CSF of 92% of the patients with cryptococcosis shows the value of these relatively new diagnostic aids; their role in the assessment of the infection and its course has been stressed. Cross-reactivity with other mycotic infections has been found namely, with blastomycosis, histoplasmosis and candidiasis. Nevertheless, a
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combination of several serological tests such as complement fixation, latex agglutination, indirect fluorescence and the tube agglutination seems to be highly specific.

Previous treatment with Amphotericin B may cause a fall in the antigen titers. The existence of rheumatoid factor, elevated cold agglutinins titers and previous exposure to skin test for cryptococcosis, are listed causes for false positive results in some of the serologic tests.

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