CASE REPORTS AND TECHNICAL NOTES

CEREBRAL GRANULOMA CAUSED BY CRYPTOCOCCUS NEOFORMANS

REPORT OF A CASE

JAMES W. MARKHAM, M.D., DONALD L. ALCOTT, M.D., AND R. MORTON MANSON, M.D.
Division of Neurological Surgery, Department of Pathology, and Thoracic Service,
Santa Clara County Hospital, San Jose, California

(Received for publication June 7, 1957)

In recent years the reported incidence of cryptococcosis has risen sharply. Slightly more than 300 cases of this disease are now on record. Littman and Zimmerman stated that there were 151 fatal cases reported by the National Office of Vital Statistics in a recent 4-year period. Although cryptococcosis has been reported from many countries around the world, the largest number of cases have occurred in Australia and the United States, particularly the latter.

Since the central nervous system is involved sooner or later in the majority of the cases, neurologists and neurosurgeons are apt to be confronted with the diagnostic and therapeutic problems of this disease. Not infrequently the history and neurological findings closely resemble the clinical picture of brain tumor because of the association of headaches, papilledema and progressive cerebral involvement. Yet in a thorough review of the literature, we were able to find but 18 examples of intracranial tumor caused by Cryptococcus neoformans (Table 1). Only those cases verified surgically or at autopsy were considered. Instances of minute, miliary lesions of the brain, of which there were numerous cases, were excluded for the purpose of this report.

Because of the rare occurrence of cryptococcosis in the form of cerebral granuloma of surgical importance, the following case is reported.

TABLE 1
Cases of intracerebral granuloma caused by cryptococcosis

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1907</td>
<td>LeCount &amp; Myers</td>
</tr>
<tr>
<td>2</td>
<td>1929</td>
<td>Gáspár</td>
</tr>
<tr>
<td>3</td>
<td>1930</td>
<td>Freeman</td>
</tr>
<tr>
<td>4</td>
<td>1936</td>
<td>Mook &amp; Moore</td>
</tr>
<tr>
<td>5</td>
<td>1939</td>
<td>Longmire &amp; Goodwin</td>
</tr>
<tr>
<td>6</td>
<td>1942</td>
<td>Dickmann et al.</td>
</tr>
<tr>
<td>7-8</td>
<td>1944</td>
<td>Swanson &amp; Smith (Cases 1 and 2)</td>
</tr>
<tr>
<td>9</td>
<td>1946</td>
<td>Krainer et al.</td>
</tr>
<tr>
<td>10-13</td>
<td>1946</td>
<td>Cox &amp; Tollehurst (Cases 4, 6, 10 and 12)</td>
</tr>
<tr>
<td>14</td>
<td>1947</td>
<td>Hassin</td>
</tr>
<tr>
<td>15</td>
<td>1949</td>
<td>Daniel et al.</td>
</tr>
<tr>
<td>16</td>
<td>1952</td>
<td>Balakrishna Rao &amp; Lilauwala</td>
</tr>
<tr>
<td>17</td>
<td>1953</td>
<td>Liu</td>
</tr>
<tr>
<td>18</td>
<td>1955</td>
<td>Manganiello &amp; Nichols</td>
</tr>
</tbody>
</table>

562
CEREBRAL GRANULOMA CAUSED BY CRYPTOCOCCUS NEOFORMANS 563

CASE REPORT


History. The patient, a 25-year-old divorced, American waitress, was admitted to the Santa Clara County Hospital on Nov. 5, 1952. A productive cough had been present for 5 years. Night sweats had been noted for 2 months, together with fatigue, loss of weight, and occasional episodes of chills and fever. A roentgenogram of the chest taken 9 months prior to admission was reported as negative. Another roentgenogram shortly before admission revealed extensive bilateral inflammatory disease with multiple cavities in the right upper lobe. There was a minimal pleural effusion on the left. Close contact with two individuals with active tuberculosis in the previous 5 years was admitted. Two years before admission, a spontaneous abortion occurred at 4 months.

Examination. She was tall, thin and sallow in appearance, with frequent cough. Her blood pressure was 94/58, pulse rate 100, and temperature 99°F. There was slight dullness over both apices on percussion. Breath sounds were distant but no rales were heard. The axillary lymph nodes were slightly enlarged. Neurological findings were normal with the exception of the left ankle jerk, which was slightly increased.

Laboratory Data. The blood count, urinalysis and serology were normal. The tuberculin skin test was positive in a dilution of 1:10,000 (OT). The coccidioidin skin test was negative in a dilution of 1:1,000. The sputum was positive for acid-fast bacilli on direct smear and by culture in November 1952.

Hospital Course. Therapy was started with streptomycin, paraaminosalicylic acid and pneumoperitoneum. In June 1953 chest films showed improvement in the right apical disease but also revealed a new lesion in the right lower lobe. A painful swelling developed in the right sternoclavicular region. Bloody fluid aspirated from this mass on July 8 was negative for tubercle bacilli. Headache, nausea and vomiting occurred during the next 2 days. Roentgenograms of the skull were normal. Spinal fluid pressure on July 10 was 290 mm. of water. The spinal fluid contained 57 white blood cells per c.mm. (lymphocytes 92 per cent, polymorphonuclear cells 8 per cent); total protein was 27 mg. per cent, and total sugar 54 mg. per cent. Acid-fast stains were negative for tubercle bacilli. Analysis of the spinal fluid on July 17 revealed a decrease in number of white cells to 23 per c.mm., an increase in total protein to 70 mg. per cent, but the total sugar content was unchanged.

The clinical impression was probable tuberculous meningitis. Headaches, nausea and vomiting persisted. Hemiparesis developed on her left side, beginning in the face.

On July 23, aspiration of the clavicular tumor yielded yeast-like organisms identified tentatively as Cryptococcus neoformans and later confirmed by cultures. There was weakness of the left arm, leg and lower face. The left leg was slightly spastic; the left arm and hand were flaccid. Meningitis caused by Cryptococcus neoformans was entertained as a likely possibility.

On July 24, spinal fluid analysis revealed 44 white blood cells per c.mm. Although no yeast organisms were found on microscopy, the culture was positive for Cryptococcus neoformans on August 13.

Pneumoencephalography was performed July 27. There was poor filling of the right lateral ventricle, particularly of the frontal horn, but without displacement. A right cerebral arteriogram was done immediately afterward. While this revealed no displacement of the anterior or middle cerebral vessels, a faint tumor shadow was noted in the right midfrontal region.

Clinical Diagnosis. The preoperative diagnosis was tumor of the right frontal lobe, possibly caused by Cryptococcus neoformans.

Operation. On July 27, 1953, immediately following arteriography, a right frontal bone
flap was turned down. A circumscribed nodule, 1 cm. in diameter, was found in the center of the surgical field, attached to the arachnoid but involving the cerebral cortex as well. The main mass of tumor was probed at a depth of 3 cm. in the mid-portion of the right frontal lobe. It was approached by removing a circular cap of cortex in the prefrontal region. The tumor was very hard, granular, nodular and sharply demarcated from the surrounding white matter.

Pathological Report. The tumor was $5 \times 4 \times 4$ cm. in size (Fig. 1). The external surface was glistening, pale, yellowish-pink and somewhat bosselated. The cut surface was glistening, and mucoid in appearance. The central portion of the mass was a distinct yellow, while the outer narrow rim was gray-pink. India-ink preparations made from scrapings of the freshly cut surface revealed typical encapsulated yeast organisms, consistent with Cryptococcus neoformans, irregularly distributed between bands of hyalinizing fibrous connective tissue.

Fig. 1. Cross section of tumor removed from the right frontal lobe. Cut surface shown on the right.

Schiff's periodic acid stains were positive, as were cultures from the tumor. Sections of cerebral cortex revealed a granulomatous meningitis.

Subsequent Course. She had a complete flaccid hemiplegia on the left but was relieved of headache. On August 6, the medial half of the right clavicle was resected by Dr. Nels Ahnlund, consultant in orthopedic surgery. The mass over the clavicle measured $8 \times 3$ cm., was dark red in color, firm to palpation and contained a great deal of gelatinous mucoid material.

On August 31, Cryptococcus neoformans was cultured from the sputum. Motor function had returned to approximately 50 per cent of normal in the left leg, but the arm remained completely paralyzed.

Actidione therapy was started Sept. 1, 1953. Initial doses of 20 mg. intramuscularly once daily were given. However, dosages larger than 5 mg. were not tolerated because of vomiting, and this medication was discontinued after 1 week. Spinal fluid on September 9 contained 1 white blood cell per c.mm.; total protein was $52$ mg. per cent. On September 4 the guinea pig that was inoculated with spinal fluid on July 13 was sacrificed. No acid-fast bacilli were found but there were numerous organisms identified as Cryptococcus neoformans in the mesenteric lymph nodes.

During October and November, 1953 there was little change in her condition. In December, 1953 she had a severe generalized seizure. She became drowsy and depressed, with loss of appetite. Her headaches returned.

On May 10, 1954, the spinal fluid was xanthochromic with a total protein of $600$ mg. per cent; total sugar was $12$ mg. per cent; there were $54$ white cells per c.mm., and culture was negative for Cryptococcus neoformans.

In August 1954 she was no longer able to take nourishment by mouth. Frequent convul-
CEREBRAL GRANULOMA CAUSED BY CRYPTOCOCCUS NEOFORMANS

Sions developed, predominating on the right side. She expired suddenly on August 14, 1954.

Autopsy. Gross findings. There was patchy consolidation of both lungs. The cut surface of the lungs presented a somewhat spongy, cystic appearance in all lobes. Some of these cavities were filled with a yellowish-gray caseous material. The brain weighed 1,350 gm. There was a large, healed surgical defect 5×5 cm. in diameter. There was extensive necrosis of the cerebral peduncles and mesencephalon. The ventricles were small and the right lateral ventricle was partially obliterated by fibrous adhesions. The surgical defect extended into the internal capsule. The cortex and meninges revealed only minimal thickening. The spinal cord was not remarkable.

Microscopic Examination. Some of the spaces in the lung were lined by caseating granulomatous inflammatory tissue with many multinucleated Langhan’s cells. Schiff’s periodic acid stain failed to reveal the presence of fungi. An acid-fast stain was also negative. Elsewhere there were extensive residuals of chronic inflammation with edema and patchy confluent bronchopneumonia. A few of many sections of the central nervous system stained with Schiff’s periodic acid technique showed only an occasional organism consistent with Cryptococcus neoformans.

Comment. The onset of symptoms in this case was typical of pulmonary tuberculosis. When signs of meningeal complications appeared, these were attributed to tuberculous meningitis. When Cryptococcus neoformans was isolated from the clavicular mass, the possibility that the entire clinical picture was caused by cryptococcosis seemed very likely.

When the signs of a focal cerebral lesion appeared, the diagnosis of cerebral granuloma caused by Cryptococcus neoformans was made presumptively because the organisms had been identified in smears from the clavicular mass. The postoperative survival period was far longer than predicted in view of the advanced degree of both diseases (tuberculosis and cryptococcosis). The association of pulmonary tuberculosis with systemic cryptococcosis has been reported but rarely. This unusual feature will be discussed separately in a subsequent report.

DISCUSSION

In further study of the 18 cases reported in Table 1, it was observed that although various operative procedures were performed in many instances, there were only 11 cases in which granulomas of the brain caused by Cryptococcus neoformans were actually removed surgically (Table 2).

The case reported by Gáspár in 1929 was that of a 52-year-old blacksmith who had headaches and pain in the neck for 2 months. Vertical nystagmus, nuchal

**TABLE 2**

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Author</th>
<th>Location</th>
<th>Size of Granuloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1929</td>
<td>Gáspár²</td>
<td>L. frontal</td>
<td>6 cm.</td>
</tr>
<tr>
<td>2</td>
<td>1930</td>
<td>Freeman³</td>
<td>R. cerebellum</td>
<td>3 mm.</td>
</tr>
<tr>
<td>3</td>
<td>1936</td>
<td>Mook &amp; Moore¹⁹</td>
<td>R. frontal</td>
<td>“pea size”</td>
</tr>
<tr>
<td>4</td>
<td>1942</td>
<td>Dickmann et al.⁵</td>
<td>L. cerebellum</td>
<td>6 cm.</td>
</tr>
<tr>
<td>5</td>
<td>1944</td>
<td>Swanson &amp; Smith²⁰</td>
<td>R. cerebellum</td>
<td>4×5 cm. (Case 2)</td>
</tr>
<tr>
<td>6</td>
<td>1946</td>
<td>Krainer et al.¹¹</td>
<td>L. frontal</td>
<td>“size of tennis ball”</td>
</tr>
<tr>
<td>7</td>
<td>1949</td>
<td>Daniel et al.²</td>
<td>L. cerebellum</td>
<td>4.5×3.5 cm.</td>
</tr>
<tr>
<td>8</td>
<td>1952</td>
<td>Balakrishna Rao &amp; Lilauwala¹</td>
<td>R. parietal</td>
<td>1.2×1.2 cm.</td>
</tr>
<tr>
<td>9</td>
<td>1952</td>
<td>Beeson²</td>
<td>R. temporal</td>
<td>miliary lesion</td>
</tr>
<tr>
<td>10</td>
<td>1953</td>
<td>Liu¹⁴</td>
<td>R. frontal</td>
<td>miliary lesion “size of mothballs”</td>
</tr>
<tr>
<td>11</td>
<td>1955</td>
<td>Manganiello &amp; Nichols¹⁷</td>
<td>R. ventricle</td>
<td>6×5×4 cm.</td>
</tr>
</tbody>
</table>
tenderness, unsteadiness of gait, pleocytosis and papilledema were the chief findings. After an unsuccessful attempt at ventriculography, a subtemporal decompression was done. Temporary improvement was interrupted by severe jacksonian seizures 3 months later. A tumor 6 cm. in size was removed from the "motor area on the left." Although the postoperative hemiplegia improved considerably, the patient then deteriorated and died a few weeks later. *Cryptococcus neoformans* was demonstrated in the surgical specimen as well as in the brain at autopsy. This was the first reported case of surgical removal of this type of granuloma from the brain.

Dickmann et al. in 1942 reported a case in which a large cerebellar tumor caused by *Cryptococcus neoformans* was removed. The patient progressed remarkably well postoperatively but left the hospital 1 month later against advice. At that time there was no evidence of activity of the disease elsewhere but contact with the patient was lost.

Swanson and Smith in 1944 reported 2 cases of cerebellar tumor caused by *Cryptococcus neoformans*. In their first case, surgery was not performed because the patient expired suddenly while in the hospital undergoing diagnostic study. In their second case the pre-operative diagnosis was cerebellar tumor probably caused by *Cryptococcus neoformans*. The patient, aged 36, had been rejected from the Army 2 years earlier with a pulmonary lesion regarded as tuberculous. However, *Cryptococcus neoformans* was isolated from the sputum and gastric contents. Because of headaches, pain in the neck, vomiting, ataxia, papilledema and a right abducens paresis, ventriculography was done. The tumor measured 3X3 cm. and involved the right cerebellar tonsil. After 4 months of marked improvement, there were signs of recurrence. At the second operation the mass measured 4X5 cm. Five days later the patient lapsed into coma and expired.

Krainer et al. in 1946 described the case of a Sikh, aged 32 years, who had a draining supraorbital mass, a swelling in the right hip and a pulmonary lesion. *Cryptococcus neoformans* was isolated from the mass over the hip. Orbital exploration revealed the inflammatory mass extended to the dura mater. Three months later, after a convulsive seizure, signs of increased intracranial pressure and a left frontal lobe lesion appeared. At craniotomy, a mass, "the size of a tennis ball," was removed. An excellent recovery was made. At the last follow-up examination, 11 months later, the only residual finding was increased reflexes in the right leg.

Daniel et al. in 1949 described the case of a miner, aged 50 (Case 2), who had a clinical history of 2 years, beginning with consumptive symptoms, later complicated by the features of subacute meningitis. Although the radiographic appearance of the lung fields was said to be typical of tuberculosis, tubercle bacilli were never found in samples of the sputum. Neurological findings indicated a left cerebellar lesion. At operation, a gelatinous mass measuring 4X3X3 cm. was removed from the left cerebellar hemisphere. After a brief period of considerable improvement, his condition deteriorated and he expired 6 months after operation. No autopsy was performed.

Balakrishna Rao and Lilauwala in 1952 reported removal of a cerebral granuloma caused by *Cryptococcus neoformans*. Convulsions were the patient's only symptom. Pneumoencephalography revealed a mass in the right parietal region. The patient was apparently cured at the time their paper was published.

Liu in 1953 reported the case of a man, aged 35, who collapsed at work and had several seizures. Examination when he recovered from this episode revealed increased patellar reflex on the left, positive Babinski sign on the left, and absent
abdominal reflex on the left. Roentgenograms of the skull revealed a cluster of 5 small calcifications resembling mothballs in the right frontal region. Air studies revealed slight blunting of the right frontal horn. The lesions were excised. An excellent postoperative course followed. One year later he was asymptomatic and no abnormal findings were noted on examination.

In the case described by Manganiello and Nichols in 1955 the tumor was found in the right lateral ventricle. The patient, a 61-year-old male, had a 2-week history of headaches, blurring of vision and one "blackout spell." There were clinical signs of a right hemispheral lesion without papilledema. While undergoing studies to determine the exact cause of the pleocytosis found at spinal tap, the patient’s condition became much worse. Ventriculography demonstrated a mass obliterating the right lateral ventricle. This measured 4×5×6 cm. when removed at operation and was attached to the choroid plexus. A downhill course followed and the patient died 10 days later.

In spite of the rather large size of the lesions, papilledema was present in but 4 of the 11 cases summarized. Of this group of 11 patients, all but 3 died within a few weeks following operation. One patient (Daniel et al.) left the hospital against advice 1 month postoperatively. Only 2 patients were alive and apparently well for as long as 1 year after surgery (cases of Krainer et al. and Liu). In spite of this long period of apparent recovery, the prognosis in such cases must remain guarded because this disease may become indolent for many years and ultimately be fatal. The case reported by Beeson, followed for 16 years, is a remarkable example of this aspect of cryptococcosis.

It is the opinion of the authors that when a patient with suspected or proven cryptococcosis shows signs of a localized intracranial lesion, with or without increased intracranial pressure, cerebral contrast studies should be undertaken and the tumor, if found, be removed; for in spite of the generally poor prognosis of such cases, surgical treatment can be rendered with relief of distressing symptoms and in some instances apparent cure, although it is doubtful that permanent cures can be obtained with present methods.

SUMMARY

A case of large cerebral granuloma caused by Cryptococcus neoformans, treated surgically with 13 months’ survival, is reported. Review of the literature revealed only 8 similar cases. The lesion measured 5×4×4 cm. in size, was located in the right frontal lobe and was associated with cryptococcosis of meninges, bone and lungs, and pulmonary tuberculosis.

The authors wish to express their appreciation to Dr. Walter Freeman for his kind suggestions in the preparation of this manuscript.

REFERENCES


