SOLITARY *ASPERGILLUS* GRANULOMA OF THE BRAIN

REPORT OF 2 CASES

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Fungal infections of the central nervous system caused by *Aspergillus* are quite unusual. We were able to find a dozen reports of these lesions in the literature. However, only 7 occurred as solitary intracranial granulomatous tumors. Therefore we believe that the addition of 2 such cases of a single space-occupying mass may be of interest.

*Aspergillus* is a microscopic fungus consisting of nonseptate, elongate hyphae which originate in mycelial foot cells and bear conidiophores of characteristic structure. There are over 350 authenticated strains.10,12 The fungus is a regular inhabitant of the soil, occurring predominantly in warm damp climates. It is frequently isolated from cereal products, unmilled grain, hay, and other stock feeds. The fungus is generally found as a laboratory contaminant. *Aspergillus fumigatus* is perhaps the most common species producing disease in man but it is likely that this situation results from factors other than its being most pathogenic, such as frequency of effective exposure.

The infection usually involves the lungs, skin, external ears, paranasal sinuses, orbit, and occasionally the bone and meninges.4 The common pathological picture is one of necrosis and acute inflammation.1 However, the central nervous system is not only a rare site for this fungus, but also may present the pathological features of chronicity.

In 1897 Rénon14 observed pulmonary *Aspergillus* as an occupational disease in wig makers and pigeon feeders. It was not until almost 50 years later that Coe3 reported such a case which was brought to trial before the industrial accident board and judged to be an occupational disease. The literature reveals in general two different types of central nervous system affection. The commoner is that of a systemic infection with cerebral metastasis, and the other is intracranial lesions with or without an adjacent portal of entry. Moniz and Loff11 in 1931 reported the necropsy findings of a left frontal lobe abscess in which the etiological agent was not cultured but was morphologically compatible with *Aspergillus*. Since the patient had a history of a corneal ulcer, the authors postulated that the orbit was the portal of entry for the fungus. In the same year Just9 recorded a case of right frontal lobe abscess and granuloma in which the *Aspergillus* fungus was cultured from the aspirated surgical fluid. At autopsy, only the frontal lobe lesion was present and the surgeon felt that the mode of entrance intracranially was via the nose and frontal sinus. Several years later Guillian et al.7 presented the necropsy findings of a patient with a right frontal lobe abscess and localized basilar meningitis which appeared to have been caused by *Aspergillus* although no culture was obtained. They, too, were of the opinion the fungus entered through the orbit. Oppe12 as early as 1897 reported a case of *Aspergillus* of the brain in which the primary infection was in the sphenoid sinuses. Wät-
jen\(^t\) in 1928 told of such a cerebral extension with the primary infection arising in the ethmoid cells.

We were able to find only two reports, one being questionable, in which the patient benefited by surgical intervention. Peet\(^15\) presented before the American Neurological Association in 1946 the case of a 7½ year-old child who did quite well following the removal of a large dense fibrotic mass containing many small abscesses from the cerebellum. A pure culture of *Aspergillus* was obtained. There is no note as to the length of the followup. However, Cawley's\(^2\) report a year later from the same institution describes the case study of a patient which appears to be the same that Peet had presented. This patient died 9 months after admission to the hospital despite intensive and protracted treatment, including surgical intervention, with a downhill course. The other possible surgical success was reported by David *et al.*\(^5\) in 1951 in which an encapsulated temporal lobe abscess was removed containing *Aspergillus amstelodami*. Their patient did well following surgery, but there was no notation as to the length of the followup.

Cawley's account in 1947 was probably the first report of a case of generalized *Aspergillus* infection with involvement of the central nervous system. He reported another such situation several years later, but the pathological studies are not too convincing regarding the central nervous system involvement.\(^6\) Several other reports in the literature deal mainly with *Aspergillus* meningitis.\(^5\)

**CASE REPORTS**

*Case 1.* JSH #88041. S.D., a 36-year-old colored male, was admitted on July 10, 1953 to the Neurosurgical Service of the John Sealy Hospital because of visual loss. About 16 months previously he began to have some frontal headaches. A month before admission a rapid loss in visual acuity occurred.

He had come to the Out-Patient Clinic a year before complaining of "sinus trouble" of about 8 years' duration. The otolaryngologists felt the patient had a chronic sinusitis and nasal polyps. They removed the nasal polyps and lavaged his antrums. A considerable amount of pus was present on the right but none on the left side. The right side continued to drain for several months. He did not return to the Out-Patient Clinic until almost a year later when he presented himself because of failing vision.

He stated that 15 years previously he had been struck over the right eye and since then had no visual perception in that eye.

*Examination.* He was an afebrile, well developed colored male who did not appear acutely or chronically ill. The neuropsychiatrists felt that he exhibited no abnormal mental signs. His sense of smell was absent bilaterally. There was no light perception nor reaction to light in the right eye. Vision in the left eye was 3/200. Visual fields revealed a concentric constriction of the left field. There was optic atrophy on the left. The right fundus was not visualized as there was a partial dislocation of the right lens with capsular opacity.

Roentgenograms of the skull showed slight separation of the coronal sutures, erosion of the right petrous ridge, and a calcified pineal gland displaced posteriorly and down. X-rays of the chest, urinalysis, and blood and spinal serology revealed no abnormalities. Findings on peripheral blood studies were normal except the eosinophilic count ranged between 7 and 24 per cent on several occasions. The spinal fluid pressure was 280 mm. of water with 288 WBC/c.mmm., 148 mg. per cent of protein and a Lange curve of 00000000.

A bilateral carotid arteriogram was done on July 14, 1953 which revealed a large expanding lesion in the right anterior fossa (Fig. 1A).

Ten days later a pneumoencephalogram demonstrated a definite displacement to the left of the lateral and third ventricles (Fig. 1B).

*Operation.* A right frontal craniotomy (I.J.J.) was done on July 24, 1953 under general anesthesia. The entire frontal lobe was almost completely replaced by a hard mass of tumor
tissue leaving only a rim of frontal cortex. The tumor extended over the entire floor of the anterior fossa and posteriorly to the chiasmal region and sphenoid ridge. It had grown over to the left side of the chiasm. This mass was so hard that it was even difficult to cut with a
cauterity knife. It was exceptionally avascular but firmly adherent to the floor of the anterior fossa. In no area of the removal was there any softening, discoloration, or cyst formation. The entire frontal lobe with a great part of the mass was removed, leaving the attachment to the floor of the anterior fossa intact.

Postoperative Course. The patient’s course was progressively downhill. He expired on Sept. 12, 1953, about 7 weeks after operation. During the postoperative period a multitude of laboratory studies were carried out. Skin tests for blastomycosis, coccidioidomycosis and histoplasmosis were negative. Tuberculin skin test was negative at a dilution of 1:1000 but positive at 1:100 after 48 hours. During the very early postoperative period an infection developed beneath the operative skin flap from which Staphylococcus aureus was cultured. This organism was also obtained from the spinal fluid on three occasions. His temperature ranged for the most part between 99° and 101°. There were only several occasions on which it went to 102°. He was given antibiotics to no avail. A great many lumbar punctures were done and the spinal fluid continued to show several hundred white cells and an elevated protein of over 100 mg. per cent. The Lange test exhibited a meningitic curve and on two occasions the Kolmer test was positive. Repeated examinations of the fluid failed to reveal acid-fast organisms and fungi. His demise was attended with a pulmonary embolus.

Pathological Findings. (1) Surgical (S-41130). The surgical specimen, weighing 10 gm., consisted of multiple irregular pieces of rubbery gray tissue and softer cerebral tissue. Frozen sections revealed chronic granulomatous inflammation. Some of the tissue was submitted to the Bacteriology Department for cultures.

Permanent histological sections disclosed large areas of dense fibrous and collagenous connective tissue infiltrated with collections of lymphocytes, mononuclear cells, scattered eosinophiles, and multinucleated giant cells (Fig. 1C). Portions of adjacent brain tissue manifested an intense reactive gliosis. Ziehl-Neelsen, Gram and Giemsa stains failed to reveal specific organisms. The first attempt to stain organisms by the periodic acid-Schiff method failed. On second attempt, however, organisms were found which consisted of a septate fungus showing occasional spores (Fig. 1D). These organisms were found within giant cells and deep within the tumor tissue and could not possibly be considered to be a contaminant.

Unfortunately, cultures were negative for fungi, but the organisms were considered to be morphologically compatible with Aspergillus.

A late review of microscopic specimens of the nasal polyps did not reveal a lesion as described above.

(2) Necropsy (P.M. 8997). At autopsy part of the right frontal lobe had been surgically removed. A large, firm, irregular, gray tumor mass was firmly attached to the orbital gyri of both frontal lobes anteriorly and to the lesser wing of the sphenoid bone posteriorly. This mass was larger on the right and measured 8×6×3 cm. Part of the tumor was torn away during removal because of the firm attachment to bone. Granulomatous tumor tissue obscured the optic chiasm and involved cranial nerves I, II, III, IV and ophthalmic division of V on the right side (Fig. 2).

Horizontal sections of the brain revealed invasion and destruction of frontal cortex and granulomatous inflammation extending 2 cm. into the frontal centrum. In addition there was evidence of recent bilateral softening of the centrum ovale. This was apparently the result of vascular obstruction by the granuloma. Sections of the tumor mass revealed a dull yellow surface with areas of gray and pink, tough, rubbery tissue. A thick, gray exudate covered the basilar pons to the region of the bifurcation of the vertebral arteries, but there was none elsewhere.

Microscopically the same type of granulomatous inflammation was found as described for the surgical specimens. Periodic acid-Schiff stains revealed the same septate fungus within foreign body giant cells in most areas. In addition, there was microscopic evidence of a chronic, granulomatous meningitis of the base of the pons. The centrum ovale of both frontal lobes showed recent softening, as was evident on gross examination.

Although 8 hours had elapsed between death and autopsy, and the brain had inadvertently been placed in formalin, a section was taken deep within the tumor mass for a second
attempt to culture this fungus. However, this effort also proved fruitless. It was considered that failure to culture the organism before and after death could have been attributable to the very dense type of tissue within which the organisms were found.

The tumor was considered to be a chronic granuloma caused by a septate fungus morphologically compatible with *Aspergillus*.

**Case 2.** JSH #38283. A white female was first admitted to John Sealy Hospital at the age of 10 on June 8, 1932 under the care of the late Dr. A. O. Singleton, Sr. She had a 2 months' progressive history of a left painless nonpulsating exophthalmus. A decompression of the orbital cavity was performed on June 12, 1932. A very hard tumor was found lying on the floor of the orbital cavity, adherent to the periosteum extending to the medial wall. It was felt that this growth arose from the periosteum and not the nerve.

**Pathological Report** (SP 5573). The tissue taken from biopsy was described as follows: "The tumor represents an inflammatory process in the orbital cavity. There are numerous giant cells in the sections and a fair number of eosinophiles. There is old inflammatory tissue along with new connective tissue which probably represents the periosteum of the orbital cavity." The diagnosis of nonspecific inflammatory tissue was made.

**2nd Admission.** The patient was readmitted on July 19, 1932 for further studies. The peripheral blood, serology, sputum, basal metabolic rate, and EKG were normal.

**Pathological Report.** The diagnosis of the tissue described above (SP 5573) was changed, for a reason unknown to us, to benign giant cell tumor of the orbit.

*Fig. 2. Case 1. Autopsy specimen (9397) showing the large *Aspergillus* granuloma attached to the inferior frontal region of the brain. The tumor is outlined by dotted line.*
Fig. 3. Case 2. (A) Hematoxylin and phloxine stain of granuloma. Note clear spaces in foreign body giant cells. These spaces contain unstained fungi. ×531. (B) Periodic acid-Schiff stain of another section from the same block of tissue, showing a septate fungus morphologically compatible with Aspergillus. ×531.
3rd Admission. She was readmitted on March 27, 1933 because of progression of the exophthalmus. On the following day a Krönlein operation with enucleation of the eye and removal of the growth was done. The tumor had penetrated the lateral wall of the orbit, invading the ethmoid cells. Twenty-five mg. of radium was implanted for 8 hours.

Pathological Report (SP 5936). There were many giant cells of the benign giant cell tumor type. There were areas of marked fibrosis and some increase in the number of blood vessels. The diagnosis of a giant cell tumor was again made.

Course. The patient was seen again in 1935 and 1936 with no appreciable change in her condition.

4th Admission. Twelve years after the 1st admission she was readmitted on May 8, 1944 at the age of 22. About a year before she began to complain of severe left temporal headaches associated with vomiting and fever of 104° to 105°F. Shortly preceding this admission she became aware of weakness of her right hand and some difficulty in speech.

Examination revealed a suggestion of a right facial palsy, aphasia, right upper extremity incoordination, right hyperactive deep tendon reflexes, right positive Babinski sign, and papilledema of the right fundus. While in the hospital, her headaches became more severe, with development of lethargy, mental confusion, right hemiplegia, and bilateral choked disc.

On May 25, 1944, Dr. S. R. Snodgrass carried out a left frontoparietotemporal osteoplastic craniotomy. The dura mater was under extreme pressure. About 1 to 2 cm. below the surface of the cortex a huge solid tumor was encountered. An incomplete removal was carried out, leaving a cavity about the size of a medicine glass. Tumor was still present on the floor of the anterior fossa, medially and posteriorly.

Pathological diagnosis (S 14114) was malignant giant cell tumor with cerebral metastasis.

Course. She improved considerably after this operation and was given 11 deep X-ray treatments. Her improvement continued to where she was able to walk and talk. During the following year she received several small courses of deep X-ray therapy because of recurrent headache and a bulging operative defect. With each treatment she had some improvement but of a less degree each time. She finally succumbed Nov. 9, 1945 of increased intracranial pressure, 18 months postoperatively. As the patient died at home in another city no postmortem examination was obtained.

Microscopic Findings. When the slides in this case were reviewed in 1954 by one of us (K.E.) in the process of re-evaluating all cerebral neoplasms at this institution it was noted that there was considerable inflammatory and dense collagenous tissue forming a stroma between large foreign body types of giant cells. In some areas this did have the appearance of a giant cell tumor, but there was an immense inflammatory reaction and an unusual amount of collagenous tissue. Clear, elongated, oval spaces were seen within some of the foreign body giant cells. These clear spaces showed no evidence of staining with hematoxylin and phloxine (Fig. 3A). The sections were stained by the periodic acid-Schiff reaction. This stain revealed a septate fungus within many of the giant cells and in the stroma (Fig. 3B). In some areas the fungus seemed to be forming small bulbous endings. This fungus had the morphological appearance of Aspergillus. Therefore a 12-year-old pathological diagnosis was changed from a giant cell tumor to Aspergillus granuloma.

DISCUSSION

Within the past few years there has been an increase in the literature on fungous infections of the central nervous system. This relationship to the current administration of antibiotics has been noted by Wybel. He felt that in his patient the administration of penicillin enhanced the growth of the fungus and cited some references in the literature to support this claim. However, antibiotics played no role whatsoever in our 2 patients. Anamnesis of both patients obviously occurred in pre-antibiotic days. It would appear more likely that the paucity of previous reports is ascribable to the fact that the pathological diagnosis had been misinterpreted and special stains and cultures were not employed.
There would seem to be little question that this is a very slow-growing lesion as evidenced by the anamnesis, surgical lesion and the microscopic picture. With such strong features of chronicity one would anticipate more evidence of calcium deposits either in the roentgenograms or the pathological specimens. This is apparently not so since there has been only one such reported case. The most frequent site of *Aspergillus* as a solitary intracranial mass is the frontal lobe, as occurred in our 2 patients. The clinical features seem to fall into two groups. One is that of a slow-growing tumor and the other a chronic meningitis becoming acute. All have met with fatality. Death has been caused by either acute increased intracranial pressure or acute sepsis of the central nervous system.

It is possible that in our first patient the ocular injury 15 years before admission might well have been the portal of entry. However, the history and objective evidence of "sinusitis" should be taken into consideration as the possible portal of entry. Even though the microscopic studies of the nasal polyps were noncontributory, special studies of the pus were not made and this well could have been an *Aspergillus* sinusitis. These possible portals of entry together with our second patient's orbital granuloma certainly coincide with similar cases in the literature, adding further evidence that this fungus gains access to the brain by means of direct extension. The frequent involvement of the frontal lobe favors the portal of entry through the orbit or nasal passageway.

Our second patient offers considerable speculation regarding granulomas. Fungus granulomas involving the cranium and brain may be mistaken for unusual giant cell tumors of bone. The pathologists who had previously studied these microscopic sections were impressed with the degree of inflammatory reaction. It is interesting to note that the original pathological report in 1932 called this a nonspecific inflammatory tissue, but for some reason not known to the authors this was changed to a benign giant cell tumor. One might suppose that the change was made because they readmitted the patient for superficial laboratory studies and since the findings were normal the diagnosis of inflammation was not compatible. The final diagnosis in 1944 was a giant cell tumor of the bone arising in the orbit and invading the brain secondarily. Organisms had not been previously observed and no cultures were made.

The fact that some fungi do not stain with the ordinary stains in some laboratories makes it easy to see how this could well have been mistaken for an unusual giant cell tumor with secondary inflammation. However, the cells of the stroma are definitely inflammatory and not of the neoplastic type seen in giant cell tumors. The fungi stain particularly well with the periodic acid-Schiff stain. This of course brings up the question as to whether these granulomas are as rare as the literature seems to indicate and whether other previously diagnosed giant cell tumors are not actually granulomas. The fungus stain should be done on all atypical giant cell tumors, especially those that show considerable inflammatory reaction. Whenever the stromal cells of a tumor of this sort are definitely inflammatory and not actual neoplastic cells, one should be suspicious of a granuloma and attempts should be made to find the etiological agent by culture and special stains. Any tissue must be ground to a smooth, preferably pipettable suspension, before reliable bacteriological work can be undertaken. Failure to do this in our first case probably accounts for our negative culture.
SOLITARY ASPERGILLUS GRANULOMA OF BRAIN

SUMMARY

Two patients are presented with large single granulomatous tumor masses in the frontal lobes. The histological examination of the surgical and necropsy material revealed a septate fungus morphologically compatible with Aspergillus. Special stains are needed to confirm the diagnosis. The possibility of these granulomas being misdiagnosed as giant cell tumors without the special stains is brought out. The portal of entry in one case was probably either the nasal sinuses or orbit and the other the orbit. The clinical history is slow and progressive. The present day therapy, being surgical, is only palliative.

REFERENCES