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Fungal Cerebritis from Intravenous Drug Abuse

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ABSTRACT: Three intravenous drug abusers (predominantly cocaine) developed a fulminant fungal cerebritis without any other identifiable predisposing factor. Two died and one survived with a severe neurologic deficit. Zygomycetes (nonseptated fungi) were identified in the brain tissue of two victims and *Acremonium alabamensis* was cultured from the brain tissue of the third. Fulminant fungal cerebritis in intravenous drug abusers (in the absence of any predisposing illness) may represent a unique variant of the acquired immunodeficiency syndrome (AIDS). Future surviving patients should be evaluated for the possibility of a cellular immune deficiency state in order to confirm this impression.

KEYWORDS: toxicology, cerebritis, acquired immunodeficiency syndrome (AIDS), cocaine, drug abuse, fungal cerebritis

Intravenous drug abusers are susceptible to a variety of localized and systemic infections. Infections of the central nervous system, however, are rare in the absence of an underlying endocarditis or pneumonitis. Fungal infections of the brain are even more unusual and, in general, are associated with patients who are immunosuppressed for a variety of reasons.

This communication describes three intravenous drug abusers who developed fulminant fungal cerebritis without any other identifiable predisposition. *Acremonium alabemensis* and *Rhizopus species* were cultured from the brain tissue of two victims. Immunofluorescent staining of brain tissue in the third case was positive for *Rhizopus* or *Absidia species*.

Clinical Summaries

Case 1

A 20-year-old black male was admitted to the hospital from the local jail where he had been incarcerated for 23 days. He complained of a continuous temporal and frontal head-

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ache of one-week duration, dizziness and an unsteady gait for three days, and blurred and double vision the day before admission. He was an intravenous drug abuser (cocaine and amphetamines) for five years. A year earlier he had been treated in a clinic for a toothache and also for minor lacerations of his fingers and the dorsum of his left foot, but had no other previous illnesses.

Physical examination disclosed a blood pressure of 150/100 mm Hg, a temperature of 38°C, a pulse of 96/min, and respirations of 18/min. Except for the presence of needle "tracks" in the left antecubital fossa and posterior cervical lymphadenopathy, the only significant findings were discovered in the neurological examination. These included an agitated and confused sensorium, right sixth nerve palsy, nuchal rigidity to anterior flexion, a right Babinski's sign, and finger-to-nose ataxia. Initial laboratory data revealed a white blood count of 6600/mm^3 with 10% neotrophilic bands, 56% mature neutrophils, 27% lymphocytes (1782/mm^3), and 7% monocytes. The erythrocyte sedimentation rate was 80 mm/h. Tests for systemic lupus erythematosis and syphilis were negative, and other routine tests were unremarkable. A lumbar spinal puncture revealed an opening pressure of 230-mm water. The cerebrospinal fluid contained 360 red blood cells (RBC)/mm^3 and 1654 white blood cells (WBC)/mm^3 with a differential of 60% monocytes and 40% neutrophils. The cerebrospinal fluid (CSF) protein was 90 mg/dL and the glucose 57 mg/dL (with a blood glucose of 115 mg/dL). Smears and cultures for bacteria, amoeba, and acid-fast organisms were negative. An india ink preparation was negative as were tests for cryptococcal antigen and syphilis.

Radiographs of the chest, skull, and paranasal sinuses were interpreted as normal. A computerized tomographic (CT) scan of the head revealed mild ventricular asymmetry with mild compression of the right frontal horn.

The initial clinical impression was a basilar meningitis, most likely of tuberculous origin and less likely of fungal origin. Accordingly, treatment with isoniazid and rifampin was begun. The hospital course was marked by progressive neurologic deterioration and by the fourth day he was responsive only to deep pain. A repeat CT scan at that time revealed low density areas in the right frontal lobe and right cerebellar hemisphere. An angiogram revealed a deep right frontal avascular mass. Treatment with Decadron®, mannitol, and antibiotics were futile, and the patient died on the seventh hospital day.

The postmortem examination was significant in that there was no evidence of peripheral or pulmonary infection, and there was no endocarditis. A sample of the brain was submitted for fungal, bacterial, and mycobacterial cultures. The brain (Fig. 1) was soft and swollen, with massive subfalcial herniation of the right cingulate gyrus and subtentorial herniation of the right medial temporal lobe. In the right frontoparietal white matter was a 6-cm central zone of hemorrhagic encephalomalacia which extended across the corpus callosum into the deep left parietal and temporal areas with involvement of the basal ganglia (particularly the lenticular nucleus and claustrum). In the white matter of the right cerebellar hemisphere was a 1.8-cm cavity. A diffuse cerebritis with occasional perivascular accumulations of lymphoid cells was observed microscopically. Large branching and budding septate hyphae (Fig. 2) were easily observed with periodic acid-Schiff (PAS) and methenamine silver stains, but could not be visualized with hematoxylin-eosin staining. A culture of the brain tissue eventually grew the fungus, *Acremonium alabamensis*. (Identification was made by Michael R. McGinnis, Ph.D., at North Carolina Memorial Hospital, Chapel Hill, NC.)

Case 2

A 23-year-old black female complained of the sudden onset of a severe generalized throbbing headache the day before admission to a local hospital. Left-sided weakness and blurred vision developed during the next 24 h. She had experienced similar symptoms four months

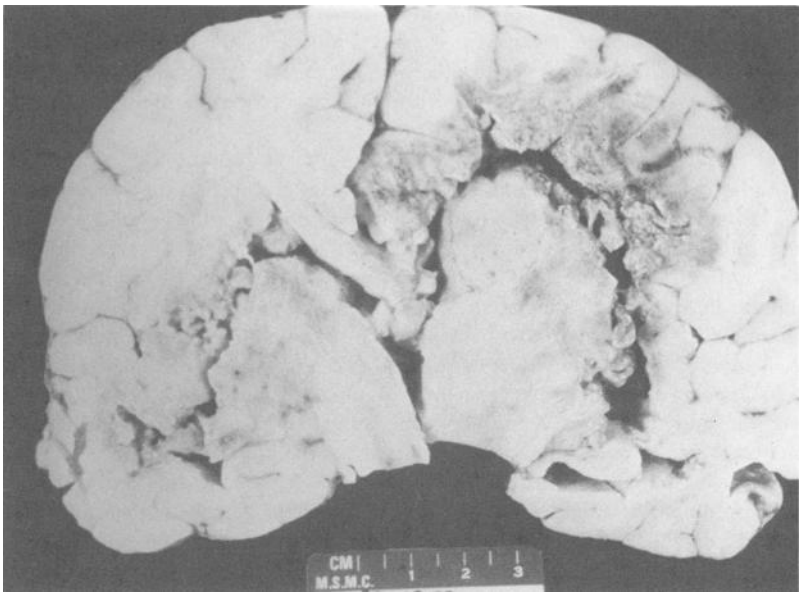

FIG. 1—*Case 1—Coronal section of brain with massive fungal cerebritis most pronounced in the right cerebral hemisphere along with herniation of the right cingulate gyrus.*

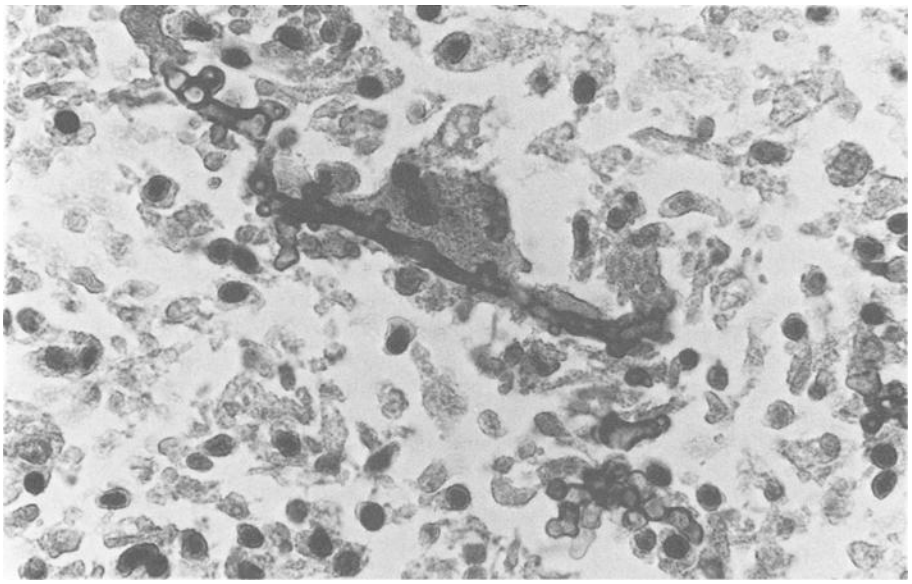

FIG. 2—*Case 1—Budding, septate, hyphae of* Acremonium alabamensis *in necrotic brain tissue. (Gomori methenamine silver stain, ×520).*

earlier, and five months prior to this admission had been treated with antibiotics for an infection of her hand. She admitted to intravenous cocaine use for five years.

Initial examination revealed a blood pressure of 130/90 mm Hg, a heart rate of 100, respiratory rate of 24, and a temperature of 39°C. Physical examination was otherwise within normal limits except for a left deviation of the protruded tongue. Initial laboratory tests were unremarkable except for a white blood cell count of 14 100/mm^3 with 89% polymorphonuclear leukocytes, 9% lymphocytes (1269/mm^3), and 2% monocytes. A CT scan of the brain revealed two ring-enhancing lesions of the right putamen, consistent with brain abscesses. The following day she developed a left hemiparesis with a Babinski's sign, and subsequently lost consciousness. The neurologic deterioration continued despite antibiotics and efforts to reduce cerebral edema. She died on the sixth day after admission. During the hospital course, multiple blood cultures were negative for microorganisms. Antibodies to the hepatitis B surface antigen were demonstrated. Clinical evidence of cerebral edema contraindicated examination of the cerebrospinal fluid.

The postmortem examination revealed scars and needle tracks of both forearms, carious dentition, mild chronic pelvic inflammatory disease, and patchy bronchopneumonia in a hypostatic distribution. No endocarditis or extracerebral focus of primary infection, including the pelvic inflammatory disease, was observed. Microscopic examination of the tissues was confirmatory except for a solitary granuloma in the vertebral marrow (no organisms were identified with special stains).

The 1200-g brain (Fig. 3) was pale, soft, and friable. In the right cerebral hemisphere was a 3-cm abscess which destroyed much of the basal ganglia and extended into the ventricular system. Surrounding brain tissue was extensively necrotic. The process extended across the corpus callosum into the left centrum semiovale, the midbrain, and the pons. The histopathologic features were those of extensive necrosis with frequent microabscesses. The polymorphous, predominantly neutrophilic, inflammatory infiltrate tended to be perivascular and often permeated vascular walls. Broad, branching, nonseptate fungal hyphae were visual-

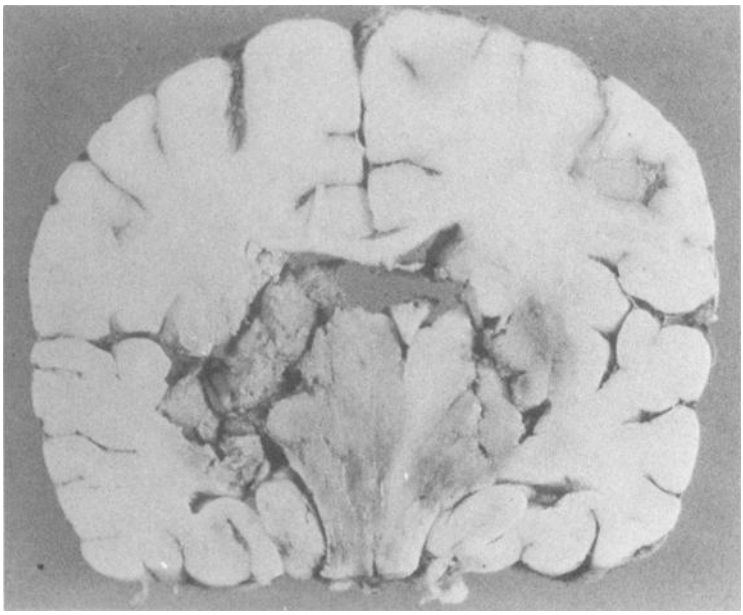

FIG. 3—*Case 2—Coronal section of brain with fungal cerebritis.*

ized with hematoxylin-eosin staining. Although the fungal hyphae were distributed randomly in the necrotic cerebral tissue, they also were frequently observed in the walls and lumens of the cerebral blood vessels and accompanied by an intense inflammatory response (Fig. 4). Occasionally, the fungal elements were associated with multinucleated giant cells. Immunofluorescent staining of paraffin-embedded tissue identified the organism as a *Rhizopus* or *Absidia species*. Immunofluorescent staining for *Mucor species* was negative. (Identification was performed by the Centers for Disease Control, Atlanta, GA.)

Case 3

A 32-year-old white male was admitted to the hospital with fever, chills, lethargy, slurred speech, and a right hemiparesis of three days' duration. He was an intravenous abuser of heroin and cocaine for six or seven years. Family members said they believed he was off these drugs for some of this time but resumed the habit about 18 months earlier. Except for an episode of infectious hepatitis at age 20, he had been previously healthy. His temperature on admission was 37.7°C. Physical examination diclosed a right deviation of the tongue and uvula, dysarthria, lethargy, and right-sided weakness. The gag reflex was absent, he had a snout reflex, and a Babinski's sign bilaterally. Intravenous "track marks" were on both upper extremities and herpetic vesicles were on the glans penis. Initial laboratory values were within normal limits exept for a total leukocyte count of 11 500/mm^3 with 11% lymphocytes (1265/mm^3). A lumbar spinal tap was considered contraindicated. A CT scan of the brain disclosed a low density area near the left anterior caudate nucleus. Three days later the area had progressed to a ring-enhancing lesion, and a low density area had appeared on the right. During this time his lethargy worsened. The clinical evaluation coupled with the CT brain scan results strongly suggested the presence of a fungal brain abscess. A brain biopsy was performed and subsequently the patient became comatose. Hematoxylin-eosin stained mate-

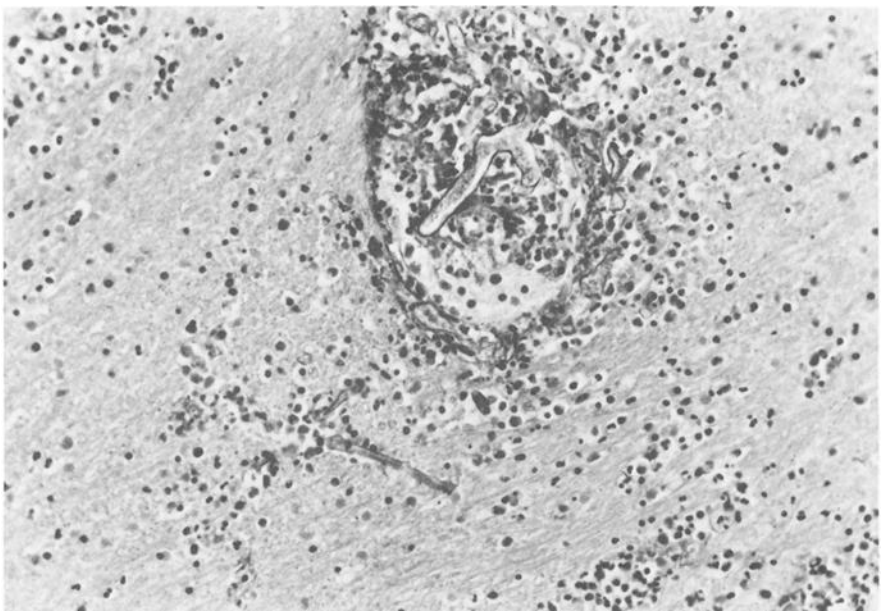

FIG. 4—*Case 2—Nonseptate fungal hyphae invading wall of cerebral blood vessel. Note the intense inflammatory response. (Hematoxylin-eosin stain ×520).*

rial obtained from the biopsy contained broad nonseptate fungal hyphae (Fig. 5) and cultures grew *Rhizopus species*. (Identification by T. J. C.).

Treatment with amphotericin B was begun on the sixth hospital day. The clinical course was complicated by a *Pseudomonas* urinary tract infection and by a *Klebsiella* pneumonia. Both infections were successfully treated. Generalized tonic-clonic seizures were controlled with phenytoin. He was discharged to a nursing home nine weeks after admission. The patient is now aphasic, spastic, and has only the ability to follow simple commands.

No evidence for endocarditis or other source for the fungal brain abscess was obtained clinically. An initial echocardiogram was suggestive of some mitral valve thickening but a repeat examination a week later failed to confirm this. Except for the episode of *Klebsiella* pneumonia, blood cultures were consistently negative.

Discussion

Intravenous drug abusers have always been regarded as susceptible to a variety of infections, particularly peripheral abscesses, endocarditis, pneumonitis, and hepatitis [*1, 2*]. This is partly attributable to their overall disregard for hygiene, the materials injected, and immunologic aberrations [*3, 4*]. Complications involving the central nervous system are considered unusual [*1-3, 5, 6*] and where present are regarded as noncharacteristic isolated findings [*7*]. Bacterial infections of the central nervous system are usually associated with an underlying pneumonitis or endocarditis [*1, 7*], although abscesses and mycotic aneurysms may be primary in these individuals [*8*].

Even more unusual is the development of primary fungal infections of the brain. Generally, deep mycotic infections such as zygomycosis (nonseptated fungi) are associated with identifiable predisposing factors such as lympho-reticular neoplasms, immuno-compromised patients, and diabetes mellitus [*9-11*]. Rarely, like bacterial infections of the central nervous system, they may occur without any such apparent predisposition [*12-16*], although

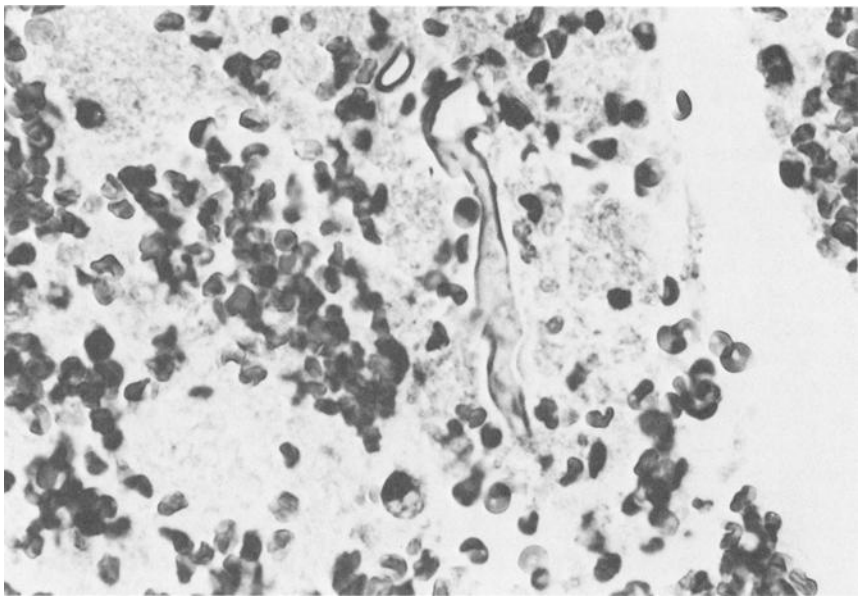

FIG. 5—*Case 3—Nonseptate fungal hyphae in necrotic brain tissue obtained by biopsy. Culture grew* Rhizopus species. *(Hematoxylin-eosin stain. ×520).*

several cases of fungal cerebritis (and abscess) have been reported in association with parenteral drug abuse [*11,12,17-20*]. Three of the reported cases were noted to use narcotics [*17-19*] and three others were simply classified as parenteral drug abusers [*12,20*]. Zygomycetes were most commonly isolated [*17-20*], and *Cladosporium species* was isolated once [*12*]. The three cases reported here are similar to previously reported cases but differ in that all three abused cocaine intravenously and two did not use narcotics (Case 1 used cocaine and amphetamines and Case 2 used only cocaine).

Neither the source of the organisms nor the factors predisposing to a primary fungal cerebritis and abscess in these cases is known. It is possible that the organisms may be introduced during an intravenous injection [*8,12,20*], and disseminate after passing through the pulmonary vasculature [*3,21,22*]. However, these are low virulence organisms and one would therefore expect the combination of a large innoculum along with an identifiable state of debilitation. Also, cultures of illicit drug paraphernalia and of illicit drugs have failed to grow organisms implicated in infectious complications of intravenous drug abuse [*4,20*]. Furthermore, it has been demonstrated with staphylococcal endocarditis among parenteral drug abusers that the source of the organisms is from the skin or upper respiratory tract, not the drug paraphernalia [*23*].

Another possibility is that the central nervous system may have been seeded from a peripheral abscess which resolved sometime earlier and which may or may not have come to medical attention. In this regard note our Case 2 was treated with antibiotics for an infected hand five months earlier.

Since amphetamines have been shown to cause central nervous system (CNS) damage by their effect on the CNS microvasculaure [*24,25*] it is conceivable that this could predispose to opportunistic infection. The question is then raised as to whether drug-induced vascular damage in the brain is unique to amphetamines or is a property shared by other stimulant drugs, such as cocaine.

Immunologic aberrations associated with chronic intravenous narcotism [*3,4*] may provide some predisposition to opportunistic infection. Although intravenous cocaine abusers, as with two of the cases presented here, do not have evidence of reticuloendothelial stimulation [*26*] characteristic of narcotic abusers [*3*], this does not exclude the possibility of an acquired immunodeficiency syndrome (AIDS). The Centers for Disease Control defines AIDS as a disease at least moderately predictive of a defect in cellular immunity occurring in a person with no known cause for diminished resistance to that disease [*27*]. Our cases seem to fit that definition. In addition, it has been reported that about 13% of all AIDS cases have a history of intravenous drug abuse, and about 60% of the heterosexual cases of AIDS have a history of intravenous drug abuse [*27*]. Also, neurological complications may characterize many AIDS victims [*28*]. It is therefore possible that the three cases of fungal cerebritis reported here and the six reported previously [*12,17-20*] may represent a distinctive subset of AIDS. All nine cases have in common a history of intravenous drug abuse, were previously healthy, and had a fulminant, rapidly fatal, fungal cerebritis and cerebral abscess. Unfortunately, the fulminant nature of the cases discussed here prevented any evaluation of their cellular immunity. Such an evaluation could give a better indication as to whether or not they are examples of the acquired immunodeficiency syndrome.

The fulminant course of the cases discussed in this report underscore the necessity for aggressive diagnosis and treatment. Hence, it is recommended that intravenous drug abusers who present with rapidly progressive CNS deterioration (in the absence of an underlying endocarditis or other focus of infection) be subjected to a diagnostic brain biopsy, particularly if ring-enhancing lesions are observed on a CT scan of the brain [*29,30*]. This procedure seems justified not only because of the rapid clinical course but because cerebral edema may preclude examination of the spinal fluid, as in two of our three cases. Also, if the spinal fluid is examined, the organism may not be identified unless the abscess ruptures into the ventricular system [*31*].

Future patients, should they survive, should be evaluated for the possibility of a cellular immune deficiency state. In particular it would be of interest to learn if these patients have an inverted ratio of helper (inducer) and suppressor T-lymphocytes characteristic of AIDS [*28*]. Finally, it should be determined whether it is the parenteral use of illicit drugs in general that predisposes these individuals to opportunistic fungal cerebritis or whether specific drugs or drug combinations are involved.

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