*Marc S. Micozzi,*[1] *M.D. and Charles V. Wetli,*[2] *M.D.*

# Intravenous Amphetamine Abuse, Primary Cerebral Mucormycosis, and Acquired Immunodeficiency

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**ABSTRACT:** Two intravenous amphetamine abusers had fatal, rapidly progressive cerebral mucormycosis with abscess formation in the presence of absolute lymphopenia. Postmortem examination confirmed the primary nature of the fungal cerebritis, documented by postmortem culture and histology. The clinical and pathologic features of these cases are compared to previously reported occurrences of primary fungal cerebritis (and abscess) among intravenous drug abusers, including cocaine users. Primary fungal cerebritis associated with intravenous abuse of stimulant drugs is discussed as a possible variant of the acquired immunodeficiency syndrome.

**KEYWORDS:** toxicology, acquired immunodeficiency syndrome, amphetamine, fungal cerebritis, intravenous drug abuse, mucormycosis

Fatal fulminant fungal cerebritis (mucormycosis) with cerebral abscess was observed in association with intravenous amphetamine abuse and acquired immunodeficiency (absolute lymphopenia). There was no gross, microscopic, or mycologic evidence of peripheral infection, pulmonary involvement, or endocarditis in these cases at autopsy. Although intravenous drug abusers are susceptible to a number of infections, isolated primary fungal cerebritis is an extremely rare complication. Intravenous drug abusers are also at risk for development of acquired immunodeficiency syndrome.

Immunodeficiency may contribute to the unusual presentation of isolated primary fungal cerebritis arising in intravenous amphetamine abusers without any other identifiable predisposition.

## Case Histories

Fatal fulminant fungal cerebritis (mucormycosis) with cerebral abscess was observed in association with intravenous amphetamine abuse and marked immunodeficiency (absolute lymphopenia) in two cases.

### *Case 1*

A 38-year-old white woman was admitted to the hospital with the sudden onset of lethargy, dysphagia, and right-sided weakness. Eleven days before admission, the patient had seen a

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[1]Formerly, associate medical examiner, Dade County, FL and clinical assistant professor of pathology, University of Miami School of Medicine, Miami, FL; presently, senior investigator, National Institutes of Health, Bethesda, MD.

[2]Deputy chief medical examiner, Dade County, FL and clinical associate professor of pathology, University of Miami School of Medicine, Miami, Fl.

neurologist and related a history of approximately five episodes of transient speech hesitancy/arrest (lasting 5 to 10 min each) during the preceding nine months. She admitted to intravenous amphetamine abuse during that time, but denied any drug abuse for the past two months. She sought consultation because of a recurrence of these episodes, but the neurological exam was normal at that time.

On the evening before admission, she developed persistent dysarthria and right-sided weakness. She gradually became obtunded and was brought to the hospital by her family the following morning. The patient's family and friends indicated that intermittent intravenous self-administration of amphetamine-like drugs had continued to the present.

Physical examination revealed a blood pressure of 120/70 mm Hg, a temperature of 38.3°C (101°F) (rectal), a pulse rate of 70/min and respirations of 16/min. The physical examination was normal except for the findings on neurologic examination, including right facial weakness, mild nuchal rigidity, right-sided hemiplegia, depressed reflexes, and a right Babinski sign. The presence or absence of needle puncture marks from intravenous drug abuse was not noted clinically, and could not clearly be distinguished from evidence of medical therapy at autopsy.

Initial laboratory examinations included a white blood cell count of 15 500/$mm^3$ with 92% mature neutrophils, 7% lymphocytes (1085/$mm^3$), and 1% monocytes. The erythrocyte sedimentation rate was 15 mm/h. Other routine laboratory tests were unremarkable. A lumbar spinal puncture revealed an opening pressure of 170 mm of water, and the cerebrospinal fluid appeared cloudy. The cerebrospinal fluid contained no red blood cells, and 590 white blood cells (WBS)/$mm^3$ with a differential of 98% neutrophils and 2% monocytes. The cerebrospinal fluid (CSF) protein was 148 mg/dL and the glucose 59 mg/dL (with a blood glucose of 119 mg/dL). Smears and cultures for bacteria, amoeba, and acid-fast organisms were negative. An india ink preparation was negative. Multiple blood cultures and urine cultures remained negative. Amphetamine and methamphetamine were detected in blood and urine. A small plastic vial of methamphetamine was found in the patient's home and presumably used for intravenous self-injection.

A computerized tomographic (CT) scan of the brain showed an ill-defined area of decreased density in the region of the left basal ganglia and hypothalamus. The initial clinical impression was infarction of the left cerebral hemisphere with consideration of septic emboli secondary to bacterial endocarditis, brain abscess, focal viral encephalitis, and angitis secondary to amphetamine abuse.

Treatment was initiated with intravenous gentamycin, nafcillin, chloramphenicol, cytosine arabinoside, and intravenous Decadron®. The patient manifested some initial improvement on this regimen, but subsequently continued to deteriorate neurologically, and she developed diabetes insipidus. Signs of cerebral brain death were apparent on the fifth day after admission and she was pronounced dead on the seventh day after admission.

The postmortem examination revealed no evidence of peripheral or pulmonary infection, and there was no endocarditis. The brain was congested, soft, and friable. There was massive necrosis of the basal ganglia and midline structures of the cerebral hemispheres with focal hemorrhage of the left thalamus, punctate hemorrhages in the midbrain and pons, and diffuse softening of the cerebellum. Microscopic examination revealed focal meningitis, diffuse cerebritis, and septic vasculitis with large, branched, nonseptate fungal hyphae growing in the walls and luminae of blood vessels on hematoxylin-eosin (Fig. 1), and Gomori methenamine-silver stains. A culture of brain tissue eventually grew *Mucor sp.*

*Case 2*

A 30-year-old right-handed black man was admitted to the hospital with sudden onset of lethargy, aphasia, and right-sided weakness. The history was obtained primarily from family members. He had been in good health until two days before admission when his wife noted that he became somnolent and began walking with a limp. The next day he was noted by other family

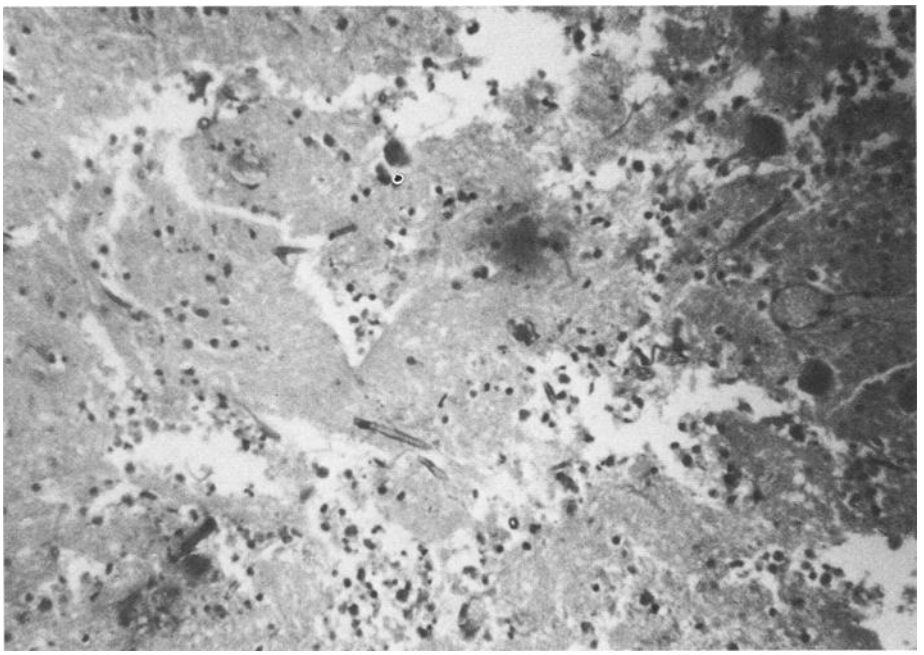

FIG. 1—*Case 1: Branched, nonseptate hyphae of* Mucor sp. *in necrotic brain tissue (Hematoxylin-eosin stain ×100).*

members to display a "twisted face" and garbled speech patterns. Later that evening, he became unable to walk at all and was admitted to the hospital. Emergency cerebral arteriogram and computerized tomographic (CT) scan of the head revealed a left hemispheric mass effect.

He had a history of smoking, "binge" ethanol abuse, and "recreational" use of cocaine and amphetamines. He was reported to have been on a "recreational binge" of intravenous amphetamine abuse three days before admission.

Physical examination revealed a blood pressure of 140/80 mm Hg, a temperature of 38.1°C (100.6°F) (rectal), a pulse range of 60 to 80/min, and respirations of 22/min. Examinations of the ears, eyes, nose, and throat were negative. There was hyperpigmentation on the dorsum of the right hand. Neurologic examination revealed somnolence, intermittent restlessness, and obvious right-sided neglect. The cranial nerves showed a left gaze preference, anhydrosis of the left face, diminished right corneal reflex, right central facial paresis, and paresis of the right trapezius muscle. The right lower extremity was paralyzed with hypalgesia of the right face, arm, leg, and trunk. Reflexes were increased on the right. The presence or absence of needle puncture marks from intravenous drug abuse was not noted clinically, and could not clearly be distinguished from evidence of medical therapy at autopsy.

Initial laboratory examinations included a white blood cell count of 19 400/$mm^3$ with 84% mature neutrophils, 1% neutrophilic bands, 4% lymphocytes (776/$mm^3$), and 11% monocytes. The erythrocyte sedimentation rate was 35 mm/h. Serologic tests for systemic lupus erythematosis, antinuclear antibody, syphilis, *Candida*, *Aspergillus*, and hepatitis were negative, and other routine tests were unremarkable. A lumbar spinal puncture revealed a normal opening pressure, and the cerebrospinal fluid contained 5 red blood cells (RBC)/$mm^3$ and 48 white blood cells (WBC)/$mm^3$, 100% neutrophils. The cerebrospinal (CFS) protein was 37 mg/dL and the glucose 116 mg/dL (with a fasting blood glucose of 153 mg/dL). Smears and cultures for bacteria, amoeba, and acid-fast organisms were negative. An india ink prepara-

tion and tests for crytococcal antigen were negative. Amphetamines were detected in the urine and a diagnosis of amphetamine angiitis was rendered.

The patient was placed immediately on high dose dexamethasone with some initial improvement. His temperature remained 37.8 to 38.3°C (100 to 101°F) rectally, and multiple blood and urine cultures (including Castaneda medium) remained negative. No source of infection was found. Phenytoin and mannitol were added to the regimen without improvement. Neurologic deterioration progressed rapidly until the patient was entirely without brainstem reflexes. He was pronounced dead early on the ninth hospital day.

The postmortem examination revealed acute hemorrhagic gastritis and nodular goiter. No endocarditis or extracerebral focus of infection was found. Microscopic examination of the tissues revealed only focal subpleural interstitial fibrosis of the lung and a microscopic pulmonary embolus of foreign material, consistent with intravenous drug abuse.

The 1325-g brain was swollen, soft, and flattened. Approximately 25 cm of thick serosanguineous fluid drained from the base. There was bilateral uncal herniation with compression of the brainstem and cerebellum. A single midline coronal section in the fresh brain showed massive bilateral necrosis of the basal ganglia (Fig. 2).

Fresh brain tissue aspirated from the abscesses in the basal ganglia grew *Mucor sp.* in postmortem cultures. Microscopic examination of multiple sections of brain tissue, after fixation, revealed extensive cerebritis, focal meningitis and septic vasculitis (Fig. 3). *Mucor* organisms were seen growing in brain tissue and blood vessels with hematoxylin-eosin stain (Fig. 4), as well as with periodic acid-Schiff (PAS) and Gomori methanamine silver (GMS) stains.

There was no gross, microscopic, or mycologic evidence of peripheral infection, pulmonary involvement, or endocarditis at autopsy in either of these two cases.

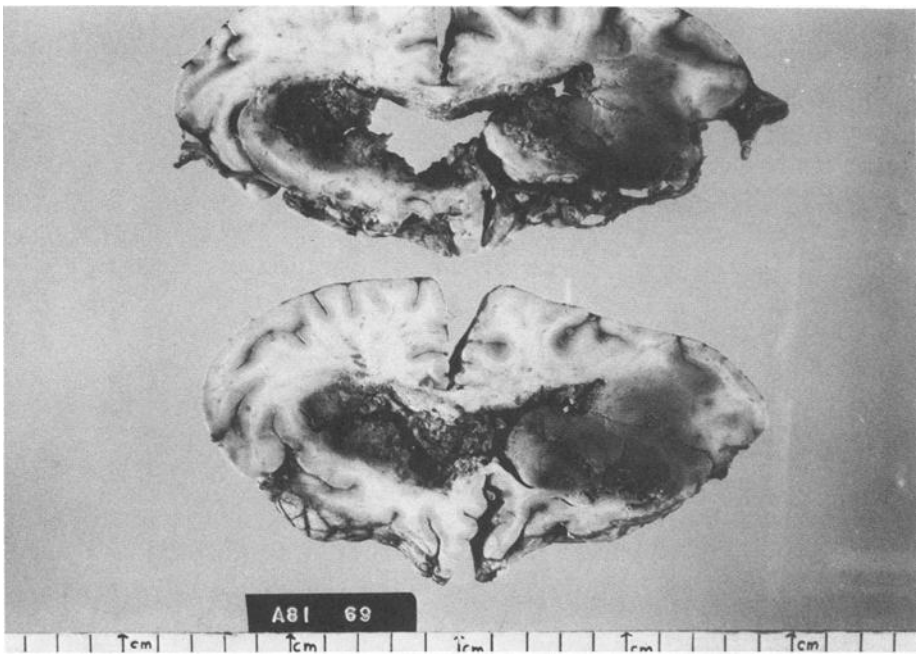


FIG. 2—*Case 2: Coronal sections of fixed brain with massive fungal cerebritis and necrosis of basal ganglia.*

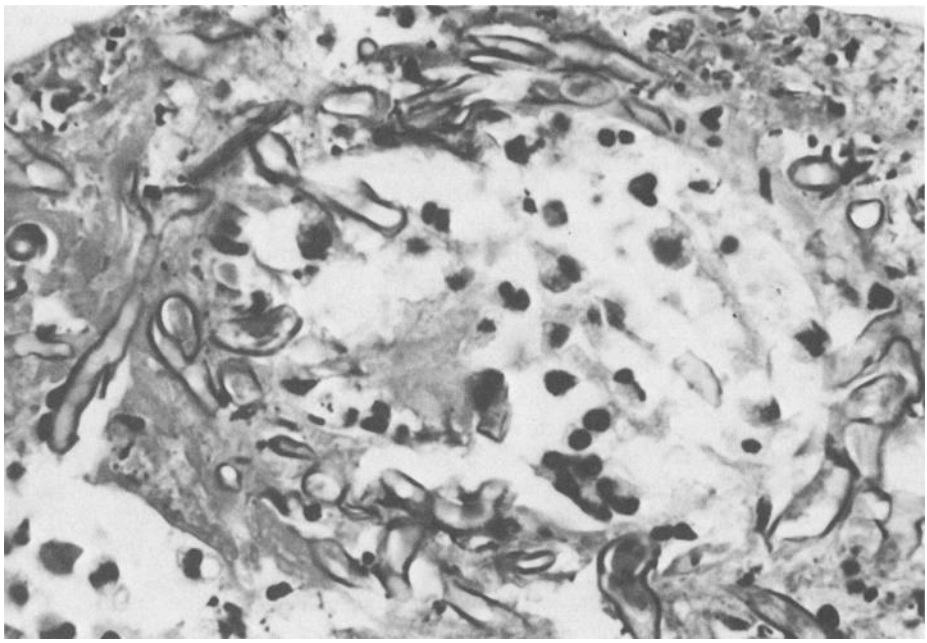

FIG. 3—*Case 2: Branched, nonseptate hyphae growing in wall of cerebral blood vessel, with intense inflammatory response (Hematoxylin-eosin stain ×400).*

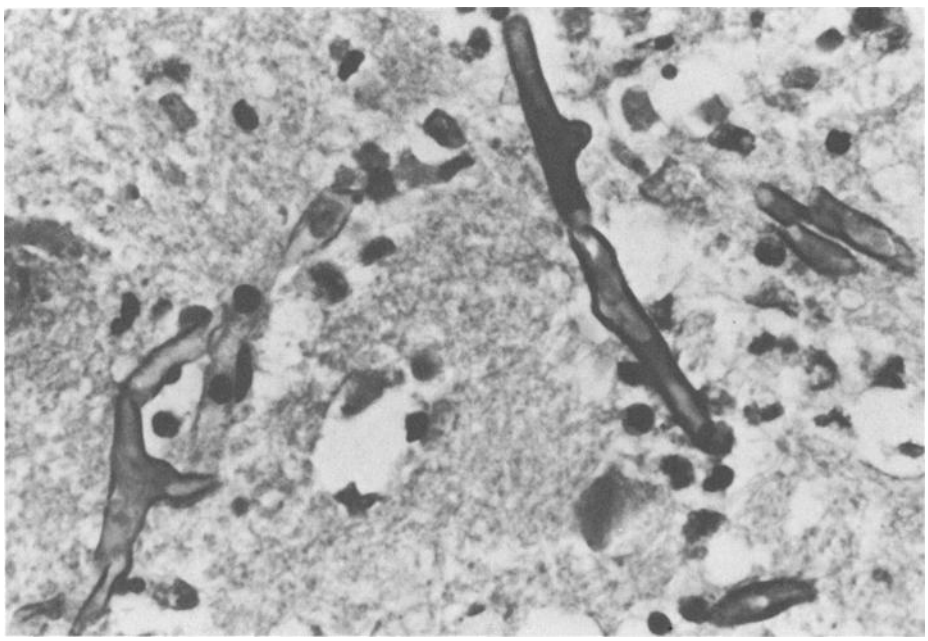

FIG. 4—*Case 2: Branched, nonseptate hyphae representative of Mucor sp. (Hematoxylin-eosin stain ×400).*

## Discussion

The diagnosis of deep mycosis is reliable when appropriate special stains are used, even if cultures are not available [*1*].

Fungi belonging to the taxonomic order Mucorales (*Rhizopus, Absidia, Mortierella*, and *Mucor*) are ubiquitous in the environment, subsisting on decaying vegetation and diverse organic material. Mucorales participates in the processes of postmortem decay and transformation of human and animal remains [*2*]. Mucormycosis is well known to occur in immunosuppressed individuals as an opportunistic infection, and may be manifest as rhinocerebral mucormycosis in ketoacidotic diabetics, or as pulmonary or disseminated infection in patients with leukemia or lymphoma [*3*]. In a recent review of cases from Mt. Sinai Hospital, New York City, from 1958 to 1978, no cases of cerebral mucormycosis were seen in the absence of palatal, paranasal, or orbital involvement or both [*4*].

As a ubiquitous environmental organism, *Mucor sp.* may also be introduced into the human host through the parenteral route by contaminated needles, and take root in individuals who may be immunosuppressed as a result of drug abuse. The first case of isolated cerebral phycomycosis was reported in a heroin addict in 1970 [5]. Although intravenous drug abusers are susceptible to a variety of infections, primary complications involving the central nervous system in general [*6*], and isolated cerebral mucormycosis in particular [*7*], are extremely rare. Among 50 cases of phycomycosis reviewed at the Armed Forces Institute of Pathology (AFIP) in 1962, a single case of primary cerebral mucormycosis had arisen in a young hypertensive woman for no apparent reason [*8*]. Intravenous drug abuse was not considered in this case.[3] Isolated phaeohyphomycosis of the brain was more recently observed in a young immunologically competent black woman without evidence of underlying disease [*9*]. Again, drug abuse was not considered.

As stimulant drugs, amphetamines cause vasoconstriction and may sensitize the microvasculature to injury. In animal experimental models, intravenous amphetamines are observed to cause cerebral angiitis and microvascular injury, which may be responsible for central nervous system damage [*10*]. At the same time, *Mucor* and related fungi have a propensity for invading blood vessel walls, resulting in inflammation, contributing to microvascular injury, and causing CNS damage [*8*]. A synergistic effect between amphetamines and *Mucor sp.* may be responsible for the unusual pattern of pathology produced in the cerebral microvasculature in these cases. Furthermore, intravenous drug abusers are also at risk for development of acquired immunodeficiency syndrome (AIDS) [*11*]. While absolute lymphopenia is not absolutely specific or sensitive for AIDS, immunodeficiency may contribute to the unusual presentation of isolated primary fungal cerebritis in intravenous amphetamine abusers without any other identifiable predisposition. The cerebral microvasculature may be the likely site for involvement by opportunistic infection as a result of the effects of amphetamines.

Wetli et al [*12*], have recently reported three cases of isolated fungal cerebritis in intravenous cocaine abusers, which may represent a variant of the acquired immunodeficiency syndrome. As a stimulant drug, cocaine may have effects on the cerebal microvasculature similar to those of amphetamines. An association of intravenous abuse of cocaine and amphetamine stimulants with isolated fungal cerebritis has now been observed. The etiologic relationship to microvascular injury, as well as acquired immunodeficiency, merits further investigation.

[3]The case history is here summarized because of the similarity to our Cases 1 and 2:

AFIP Case 27. Lesions of phycomycosis were found in a young woman with hypertension, but not other associated disease. There was acute onset of right temporal headache with slurring of speech and left hemiparesis. Cerebrospinal fluid showed pleocytosis and moderately elevated total protein. On a rice diet, her blood pressure returned to normal, and neurologic impairment diminished. However, she suffered a relapse and died two weeks after the onset of illness. Autopsy revealed multiple areas of softening and excavation in the basal ganglia and internal capsule, with associated marked enlargement of the right cerebral hemisphere. The abscesses contained hyphae of phyconycetes (Straatsma, Zimmerman & Gass, 1962).

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Address requests for reprints or additional information to
Marc S. Micozzi, M.D.
Senior Investigator
National Institutes of Health
P.O. Box 8217
Silver Spring, MD 20907