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MAJOR ARTICLE

Isolated Cerebral Mucormycosis in Immunocompetent Adults who Inject Drugs: Case Reports and Systematic Review of the Literature

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Background. Mucormycosis involves life-threatening rapidly progressive angioinvasion with infiltration across tissue planes, resulting in necrosis and thrombosis, most commonly seen in the setting of immunocompromised states. We describe 2 cases of isolated cerebral mucormycosis in immunocompetent adults and describe this syndrome in detail in the context of a systemic literature review.

Methods. Using the criteria (1) isolated cerebral disease, (2) mucormycosis (by polymerase chain reaction, culture, or pathology), and (3) affected an immunocompetent individual, we identified 53 additional cases from 1969 to 2020.

Results. Of these 55 cases, ~60% occurred in men, >70% were in patients under age 35, 92% were associated with intravenous drug use, and >85% had infection centered in the basal ganglia. Many presented with cranial nerve deficits, headache, focal weakness, or altered mental status.

Conclusions. No patient survived without amphotericin, and steroid administration was associated with worse outcomes. Given the current opioid crisis, this syndrome may be seen more frequently.

Keywords. basal ganglia abscess; isolated cerebral mucormycosis; IVDU.

Rhizopus, *Rhizomucor*, *Mucor*, and *Absidia* belong to the Mucorales order of environmental fungi and are identified by their characteristic broad-based aseptate hyphae. Although Mucorales can often be cultured from the oropharynx and stool of healthy individuals, they can also cause rapidly progressive angioinvasion with infiltration across tissue planes that results in necrosis and thrombosis and is life-threatening [1].

Mucormycosis most commonly occurs in the context of acute myeloid leukemia (or other hematologic malignancies), severe neutropenia, graft-vs-host disease, diabetes, or end-stage renal disease on dialysis and use of iron chelators (eg, deferoxamine). The various mucormycosis syndromes (disseminated, rhinocerebral, pulmonary, cutaneous, gastrointestinal, and isolated cerebral disease) differ in predisposing conditions and prognosis.

We define isolated cerebral disease in immunocompetent adults as a syndrome fulfilling 3 criteria: (1) isolated cerebral localization (infection in cerebellum, cerebral hemispheres, or brainstem, without direct extension to sinuses or cranial bones and without involvement of other organ systems); (2) Mucorales identified as pathogen by positive culture, polymerase chain reaction (PCR), or characteristic broad-based aseptate hyphae on pathology from brain biopsy or autopsy sample; and (3) host is immunocompetent without hematologic malignancy or rheumatologic disease, diabetics in DKA, or receiving immunosuppressing medications, including chronic steroids.

In individuals with diabetes, particularly in the presence of ketoacidosis, disease due to mucormycosis is most commonly the rhinocerebral form, due to direct invasion of the central nervous system (CNS) through the sinuses [2]. Individuals with no underlying condition are most likely to present with cutaneous mucormycosis, often following trauma, but can present with cerebral disease, including rhinocerebral, sinus/sino-orbital, or isolated cerebral disease [2]. Isolated cerebral disease, with a focus most commonly in the basal ganglia, is due to hematogenous seeding following intravenous inoculation and, among immunocompetent individuals, is an important presentation. The vast majority of the published cases of isolated cerebral mucormycosis are associated with injection drug use, making this a critical component of the social history, particularly given the current opioid crisis.

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We describe 2 cases of isolated cerebral mucormycosis in immunocompetent patients and perform a systematic review, identifying 53 cases in the published literature. We present a thorough synopsis of this syndrome, focusing on associated risk factors, presentation, diagnosis, microbiology, treatment, and outcomes.

CASE REPORTS

Case 1

A 53-year-old man with a long history of intermittent intravenous drug use who had been treated for poorly differentiated squamous cell carcinoma of the neck presented with acute mental status alteration, confusion, agitation, and tonic-clonic movements, without headaches.

The patient was febrile to 38.5°C and hemodynamically stable. He was alert but unable to follow commands and had left-sided ptosis and intermittent involuntary movements of his left arm. Initial laboratory studies showed a mild leukocytosis and normal serum creatinine, electrolytes, and liver transaminases, and negative HIV test (Table 1). Toxicology was positive for cocaine, opiates, and benzodiazepines. Brain imaging showed an infiltrative mass involving the right basal ganglia (Figure 1A, B). Cerebral spinal fluid (CSF) examination showed 83 nucleated cells (reference range, 0–5/μL) with 31% neutrophils, 47% lymphocytes, and 22% mononuclear cells, normal glucose, and elevated protein (81 mg/dL; reference range, 5–55 mg/dL). CSF nucleic acid–based testing for herpes simplex virus 1 and 2 and other viruses was negative.

Given a high concern for metastasis of the prior cancer, dexamethasone was started. Simultaneously, out of concern for an infectious process, acyclovir, ceftriaxone, metronidazole, and vancomycin were also initiated.

Over the next few days, the patient's mental status declined, and he required intubation for airway protection. New bradycardia raised concern for increasing intracranial pressure, and mannitol was provided. Interval imaging showed progression of the basal ganglia lesion now involving the contralateral side (Figure 1A, B). A stereotactic brain biopsy revealed aseptate hyphal organisms consistent with Mucorales spp. by calcofluor and histopathology (Figure 1C, D). Liposomal amphotericin B (LAmB) was started; however, given worsening episodes of hypertension and bradycardia, the family transitioned the patient to comfort measures, and the patient passed quickly. Culture of the brain biopsy subsequently grew *Rhizopus* species.

Table 1. Initial Laboratory Values

Initial Lab Investigations	Case 1	Case 2
White blood cell count (ref range, 4.5–11.0 K/μL), K/μL	15.51	15.44
% neutrophils	91.7	87.6
Hematocrit (ref range, 41.0–53.0%), %	35.8	22.5
Platelets (ref range, 150–400 K/μL), K/μL	389	403
Serum sodium (ref range, 136–145 mmol/L), mmol/L	133	140
Serum bicarbonate (ref range, 20–31 mmol/L), mmol/L	26	10
Serum creatinine (ref range, 0.50–1.30 mg/dL), mg/dL	0.60	15.04
Venous pH (ref range, 7.32–7.42)	N/A	7.14
HIV 1/2 Ab/Ag	Negative	Negative
CSF RBC count (ref range, 0–5 /μL), /μL	4	61
CSF WBC count and differential (ref range, 0–5/μL), /μL	83 (31% PMNs, 47% lymphs)	1 (61% lymphs)
CSF glucose (ref range, 50–75 mg/dL), mg/dL	50	71
CSF protein (ref range, 5–55 mg/dL), mg/dL	81	30
CSF HSV 1/2 PCR	Negative	Negative
CSF VZV PCR	Negative	Negative
CSF adenovirus PCR	Negative	Negative
CSF enterovirus PCR	Negative	Negative
CSF culture	Negative	Negative

Abbreviations: Ab, antibody; Ag, antigen; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell; VZV, varicella zoster virus.

Case 2

A 37-year-old man with a history of intravenous fentanyl use presented with 1 week of right-sided hemiparesis, dysarthria, and right facial droop, without headaches or fevers. He was initially afebrile and hemodynamically stable. His labs showed a mild leukocytosis, with markedly elevated BUN (120 mg/dL; reference range, 9–23 mg/dL) and serum creatinine (15.04 mg/dL; reference range, 0.50–1.30 mg/dL), a markedly low serum bicarbonate (10 mmol/L; reference range, 20–31 mmol/L), and normal liver function tests (Table 1). A venous blood gas showed a pH of 7.14, confirming acidemia. Urine analysis showed nephrotic range proteinuria.

Brain imaging showed a left basal ganglia mass with restricted diffusion and surrounding edema. CSF examination revealed 61 red blood cells/mL, 1 nucleated cell (61% lymphs), and normal glucose and protein (Table 1). Initial treatment was vancomycin, cefepime, and metronidazole for presumed bacterial brain abscess and a bicarbonate drip for acidemia. On day 3, repeat brain magnetic resonance imaging (MRI) showed features of probable microhemorrhage within the lesion (Figure 1E), raising concern for mucormycosis. The patient developed progressive word-finding difficulty, lethargy, dysarthria, and seizures. Antifungal agents (LAmB, micafungin, and posaconazole) were added to the regimen, and stereotactic brain biopsy revealed broad-based aseptate hyphae consistent with Mucorales spp. (Figure 1F, G). Fungal cultures did not isolate fungi, but PCR-based analysis of the biopsy (University of Washington) was positive for *Rhizopus oryzae*.

A kidney biopsy showed systemic amyloid A amyloidosis, thought to be related to longstanding injection drug use [3].

The patient completed 4 weeks of 3-drug therapy with posaconazole, LAmB, and micafungin, followed by 3 weeks

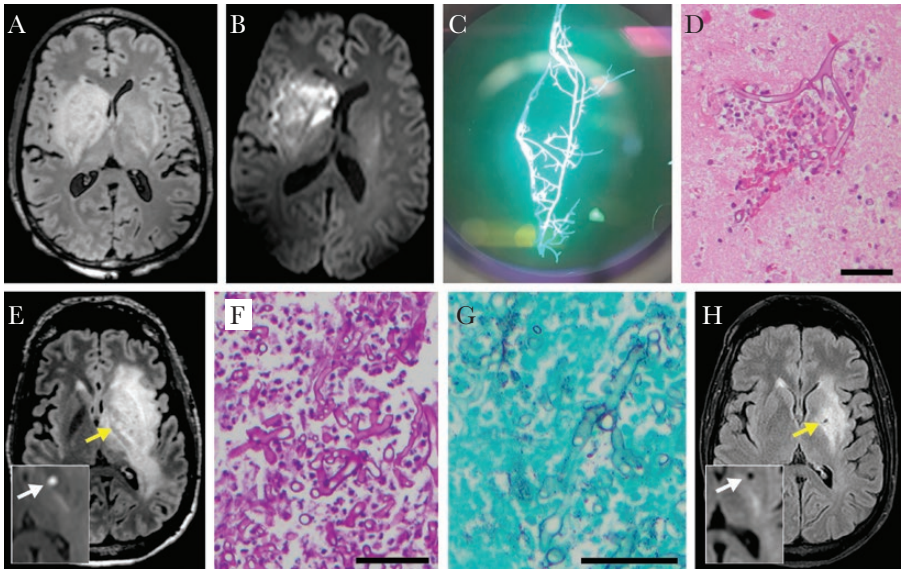

Figure 1. Diagnostic data. A–D, Case 1. Day 2 brain MRI axial FLAIR (A) and diffusion-weighted (B) images. Fungal forms seen on media by calcofluor-white stain (C) and hematoxylin and eosin–stained histology (D) from brain biopsy. E–H, Case 2. Day 3 (E) or 1 month later (H) brain MRI axial FLAIR images; insets, diffusion-weighted images; arrows, micro-abscess. Fungal forms on periodic acid-Schiff-stained (F) and silver-stained (G) histology from brain biopsy. Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery. Size bars, 50 μm.

of 2-drug therapy with posaconazole and intravenous (IV) LAmB then de-escalation to posaconazole alone, which he continues currently, 15 months after diagnosis. Serial brain MRIs have shown gradual improvement over time, with decreased T2 intensity and reduced edema and mass effect (Figure 1H). Residual neurologic deficits are a slight right facial droop and mild right-hand weakness.

METHODS

A systematic review the literature was performed using key words "isolated cerebral mucormycosis," "brain mucor," "isolated cerebral phycomycosis," "basal ganglia zygomycosis," "cerebral phycomycosis heroin," "cerebral mucormycosis IV drug use," and a conditional search of [("mucormycosis" or "zygomycosis" or "Mucor" or "Absidia" or "Rhizopus" or "Rhizomucor") and either ("primary" or "isolated")] in PubMed. Additional studies were identified by reviewing the reference lists of the papers identified in PubMed.

Cases were defined as adults meeting all 3 of the following criteria: (1) isolated cerebral disease, (2) mucormycosis, and (3) affecting an immunocompetent host. Patients were considered to have "isolated cerebral" disease when the infection only involved the brain tissue (cerebellum, cerebral hemispheres, or brainstem), without direct extension from the sinuses or other cranial bones or related to trauma or prior cranial surgery and without infection of other body sites (lungs, kidneys, skin, etc.). Mucormycosis was defined as a culture, molecular, or histopathologic diagnosis identifying an organism from the Mucorales order of fungi. Molecular diagnosis included PCR and next-generation sequencing. Histopathology that showed characteristic broad-based aseptate hyphae was also considered diagnostic.

Patients were considered immunocompetent if they were not on immunosuppressing medications (including long-term steroids), did not have diabetes, and did not have a history of hematologic malignancy or rheumatologic disease. Accordingly, patients with these conditions or who were on immunosuppressive medications, including long-term steroids, were excluded from our analysis even if they were included in other reports. Patients with HIV were included regardless of CD4 cell count, as HIV infection is not considered a risk factor for mucormycosis [4]. One small series of potential cases was excluded due to insufficient detail on the presentation, diagnosis, and treatment course of the patients. Papers not written in English were also excluded.

Details about each of the cases that met the inclusion criteria were collected and tabulated (Tables 2–4). Specifically, we sought to describe the presenting syndrome including the duration and type of symptoms and whether cranial nerve deficits were present. We detail how the diagnosis was made and whether the patient had HIV infection, and we list the treatments the patients received, including antifungal agents, steroids, and surgical procedures. Finally, we describe the clinical outcomes and, where possible, the duration of survival and the long-term functional status of the survivors at the time of the publication using language from the reports.

RESULTS

We identified and reviewed 790 publications. The most common reasons for exclusion from this review were (1) cases did not

represent isolated cerebral disease (384); (2) duplicate studies (102); (3) a host that did not meet the study criteria, either immunosuppressed including due to diabetes or animal studies (101); or (4) not written in English [39]. Some studies were excluded for multiple reasons. Six studies were excluded because the subjects were children. One study was excluded because it lacked sufficient detail about the clinical course, treatment, or diagnosis. Initially included were 32 papers; after reviewing the reference lists of these 32 papers, an additional 11 papers were identified. From these 43 papers, 53 cases of isolated cerebral mucormycosis in immunocompetent adults were identified. With the 2 cases presented here, a total of 55 distinct cases of isolated cerebral mucormycosis in immunocompetent adults were analyzed.

Among the 55 individuals, 34 (61.8%) were men (Table 2). Age ranged from 20 to 53 (mean, 31.1) years old, with 38 of 54 (70.4%) under age 35 (note 1 individual was listed as "young" without an age indicated). The most commonly reported presenting symptoms were headache (29/55, 52.7%), fever (26/55, 47.3%), focal weakness (18/55, 32.7%), and altered mental status (14/55, 25.5%). Cranial nerve deficits were present in at least 28/55 (50.9%) individuals.

Injection drug use was common, reported in 92% of cases where drug use was queried (46/50 cases for which IV drug use history was assessed) (Table 3). Five cases were in individuals who were HIV positive, although 12 cases were reported before 1986, the year testing became widely available.

In 47 cases (85.5%), basal ganglia involvement was explicitly stated, and 4 cases (7.3%) involved ventricular infection, generally with obstructing hydrocephalus. In 31 cases (56.4%), diagnosis was made by biopsy, most often stereotactic; in 4 cases, diagnosis was made on samples obtained at the time of ventricular drain placement; in 18 cases, diagnosis was made at autopsy. In 37 cases (67.3%), diagnosis was made by histopathological finding of aseptate hyphae. In several cases, culture, PCR, and next-generation sequencing were used.

The survival rate for patients receiving AmB was 54.1% (20/37), and for patients not receiving AmB it was 0% (0/18) (Table 4). The survival rate for those receiving AmB and steroids was 46.2% (6/13), and for those receiving AmB without steroids it was 58.3% (14/24). The clinical course in those who died tended to be more fulminant, with shorter presentation-to-diagnosis rates. Among those who died, 29/35 presented with less than a week of symptoms, whereas among those who survived, approximately half had symptoms for a week or longer before diagnosis.

Although excluded for the purposes of this review, it should be noted that similar presentations were seen in other hosts, including individuals with diabetes [49]. One case was reported in an individual with poorly controlled diabetes and severe Crohn's disease who was receiving infliximab and injecting drugs [50]. One additional case in the literature that deserves mention describes a strikingly similar clinical syndrome due to *Acremonium alabamensis* (a non-Mucorales fungus) [6].

DISCUSSION

Isolated cerebral mucormycosis in immunocompetent adults, defined as infection with Mucorales species (demonstrated by pathology, culture, or molecular testing), isolated from the brain only, in an immunocompetent host without diabetes, is a rare entity. In our review of 53 previously reported cases in the literature and 2 new cases described here, injection drug use was a prominent feature, present in 92% of cases for which it was assessed. The strong association with injection drug use is almost certainly because it facilitates hematogenous introduction of the mold. The increasing prevalence of people who inject drugs is associated with significantly higher rates of hospitalizations for infections related to injection drug use [51–53]. In the context of the current opioid epidemic, we anticipate that many more cases of cerebral mucormycosis will be recognized in the years ahead. An epidemic curve showing the reported cases plotted over time (Figure 2) suggests increased numbers of cases between 1980 and 1995 and again since 2005, although reporting bias limits conclusions that can be drawn from this.

The disease appears to be one primarily of young adults, with >70% of individuals reviewed here under age 35 at the time of diagnosis. Headache, fever, focal weakness, and altered mental status were all commonly reported. More than half had cranial nerve deficits reported at the time of presentation.

That more than 85% had infection centered in the basal ganglia is quite notable. Basal ganglia brain abscesses are unusual; in a meta-analysis of nearly 10 000 cases of brain abscesses, basal ganglia localization occurred in only 3% [54]. Moreover, fungal etiologies account for only 1% of all brain abscesses [54]. The observed association of Mucorales spp. with the basal ganglia may result from the predilection of the organism for the brain; as early as 48 hours after injection of *Absidia ramosa* spores into the tail vein of mice, hyphae were seen in the brain and kidney [55]. This predilection for the basal ganglia has been hypothesized to be due to the high iron content of this tissue, as germination of *Rhizopus* spp. spores requires free iron [50, 56]. Brain abscesses due to *Listeria monocytogenes*, another organism that requires iron for virulence, are also commonly found in the basal ganglia [57, 58]. In addition to the basal ganglia, localization of Mucorales infection to the ventricles, with associated obstructive hydrocephalus, was reported in several cases. Whereas the differential diagnosis for inflammatory lesions of the basal ganglia is broad, aggressive Mucorales spp. infection should be considered.

Approximately half of those who survived presented subacutely, reporting symptoms for at least a week or more, whereas among those who died, the vast majority (>80%)

Table 2. Clinical Presentation

Case No.	Age/Sex	Presenting Symptoms	Time From Onset of Symptoms to Diagnosis	Cranial Neuropathy	Source/Year
1	37/F	Alerted mental status, headache, fever	Several weeks	None reported	[5]/1980
2	32/M	Positional vertigo, nystagmus, vomiting	Days	12th nerve	[6]/1984
3	24/F	Fever, chills, slurred speech	Diagnosed on hospital day 24	6th and 3rd nerves	[7]/1986
4	20/F	Headache, fever	Days	None reported	[8]/1988
5	24/M	Parkinsonian symptoms	>3 wk of symptoms	Dysarthria/dysphagia	[9]/1989
6	28/M	Headache, right-sided weakness	2 wk	Multiple	[10]/1992
7	28/M	Right-sided weakness, slurred speech, headache, unsteady gait	2 wk	7th nerve	[11]/1994
8	30/F	Dysarthria, left-sided weakness	Days	7th nerve	[12]/1996
9	24/F	Alerted mental status, fever	Days	None reported	[13]/2007
10	42/F	Headache, fever, left-sided weakness	>2 wk	None reported	[14]/2008
11	43/M	Worsening balance	Possibly 9–12 mo	7th nerve	[15][c]/2010
12	40/M	Unresponsive	Diagnosed >4 wk after admission	None reported	[16]/2017
13	23/F	Headache, confusion	Days	None	[17]/2019
14	37/M	Right-sided weakness and facial droop, dysarthria	Days	Dysarthria + 7th nerve	(This study)/2020
15	44/M	Altered mental status, fever, flu-like illness	Days	None reported	[18]/1989
16	26/M	Headache, vomiting, fever	Days	None reported	[19]/1990
17	31/F	Headache, speech change	1 wk	7th and 12th nerves	[20]/1990
18	34/M	Ataxia, fever	Unknown (disoriented on admission)	None	[21][d]/1991
19	53/F	Confusion, right-sided weakness	Diagnosed >3 mo after admission	7th nerve	[22]/1992
20	29/F	Fever, headache, confusion	Days	None reported	[23]/1994
21	28/M	Lethargy, severe headache, vomiting	Hours	None reported	[24]/1982
22	21/M	Fever, disorientation	Unclear prodrome as patient altered on arrival	None reported	[25]/1988
23	23/F	Unconscious, fever	Unclear prodrome as comatose on arrival	None reported	[25]/1988
24	25/M	"Comatose"	Days	None reported	[26][e]/1988
25	33/F	Right-sided weakness, lethargy, headache, fever	Acute onset	None	[27]/2000
26	"Young"/M	Headache, fever, chills	1 day	None	[28]/2005
27	24/M	Headache, confusion, left-sided weakness	Days	None reported	[29]/2007
28	22/M	Severe headache, difficulty walking	Hours	7th nerve	[30]/2011
29	43/M	Altered mental status	Last seen normal 4 days before brought in altered	None reported	[31]/2016
30	27/M	Fever, headache, nausea, vomiting	Days	7th nerve	[32]/2020
31	26/F	Fever, headache, nausea, vomiting	Days	6th and 7th nerves	[33]/1985
32	27/F	Tonic-clonic movements, headache, vomiting	Days	7th nerve	[34]/1994
33	37/M	Aches, fever, chills, headache	Hours	7th nerve	[34]/1994
34	32/F	Headache, right-sided weakness, dysarthria	Days	Multiple	[34]/1994
35	49/M	Tonic-clonic movements, fever	Days	None	[35]/2006
36	22/F	"Fever and neurologic deficits"	Prodrome unclear based on information in report	N/A	[36]/2007
37	24/M	Left-sided weakness, headache	"New onset"	Facial droop	[37]/2018
38	24/M	Dead on arrival	Unclear prodrome as dead on arrival	Deceased on arrival	[38]/1969
39	32/M	Altered mental status, unable to swallow, fever	1 day	Multiple	[39]/1970
40	27/M	Sudden left-sided weakness and headache	Days	Multiple	[40]/1982
41	27/M	Lethargy, severe headache, left-sided weakness	Days	Dysarthria	[24][f]/1982
42	23/F	Headache	1 wk	12th nerve	[6]/1984

Table 2. Continued

Case No.	Age/Sex	Presenting Symptoms	Time From Onset of Symptoms to Diagnosis	Cranial Neuropathy	Source/Year
43	28/M	Fever, headache, vomiting, seizure	1 wk	Facial weakness	[41]/1987
44	40/M	Fever, headache, right-sided weakness	Days	Dysarthria	[41]/1987
45	25/M	"Acute neurologic deficit"	Acute	Not assessed	[36]/2007
46	28/M	Lethargy, confusion, fever	Days	None reported	[42]/2013
47	50/M	Garbled speech, confusion, right arm and facial weakness	Acute	Dysarthria	[43]/2015
48	38/F	Fever, lethargy, dysphagia, right-sided weakness	2 wk	Dysarthria	[44]/1985
49	30/M	Lethargy, aphasia, right-sided weakness, fever	Days	Multiple	[44]/1985
50	22/F	Seizures, vomiting, headache	3 mo	Diplopia	[45]/1985
51	47/F	Severe headache	3 mo	None	[46][9]/1986
52	41/M	Right-sided weakness, headache, fever	2 day	None reported	[47]/1987
53	25/M	Confusion, left-sided weakness, headache, chills	2 wk	None reported	[48]/1988
54	31/F	"Acute neurologic deficit"	Acute	N/A	[36]/2007
55	53/M	Altered mental status, tonic-clonic movements, fever	Days	Dysarthria	(This study)/2020

Abbreviations: F, female; M, male; wk, week(s); mo, month(s).

Table 3. Risk Factors and Diagnosis

Case No.	Age/Sex	IV Drug Type	Localization of Infection	HIV Ab	Diagnosis (Method)/Manner Obtained	Source
1	37/F	Drug use history not stated	Ventricular infection causing obstructive hydrocephalus	N/A[a]	Aseptate hyphae/CSF exam after drain placed	[5]
2	32/M	Heroin and cocaine	Right basal ganglia	N/A	*Rhizopus/Absidia* (immunostains)/biopsy	[6]
3	24/F	Pentazocine and tripelennamine	Brain stem	N/A	Aseptate hyphae/brain biopsy	[7]
4	20/F	Drug use history not stated	Left basal ganglia	N/A	Aseptate hyphae/brain biopsy	[8]
5	24/M	Heroin and cocaine	Bilateral basal ganglia	Neg	Aseptate hyphae/biopsy	[9]
6	28/M	IVDU, not further specified	Left basal ganglia	N/A	*Rhizopus* spp. (culture)/stereotactic biopsy	[10]
7	28/M	IVDU, not further specified	Left basal ganglia	Neg	Aseptate hyphae/stereotactic brain biopsy	[11]
8	30/F	IVDU, not further specified	Left basal ganglia	Pos	Aseptate hyphae/stereotactic brain biopsy	[12]
9	24/F	Heroin	Right basal ganglia	Neg	*Rhizopus arrhizus* (PCR)/stereotactic brain biopsy	[13]
10	42/F	IVDU, not further specified	Right basal ganglia	Neg	Aseptate hyphae/stereotactic biopsy	[14]
11	43/M	IVDU, not further specified	Left cerebellar hemisphere	Neg	Aseptate hyphae/open biopsy	[15]
12	40/M	IVDU, not further specified	Left basal ganglia	Neg	*Rhizopus oryzae* (PCR)/stereotactic brain biopsy	[16]
13	23/F	Methamphetamine	Bilateral basal ganglia	Neg	*Rhizopus* spp. (culture)/brain biopsy	[17]
14	37/M	Fentanyl	Left basal ganglia	Neg	*Rhizopus oryzae* (PCR)/stereotactic brain biopsy	(This study)
15	44/M	Cocaine and opioids	Bilateral basal ganglia	Neg	Aseptate hyphae/stereotactic biopsy	[18]
16	26/M	Amphetamines	Right basal ganglia	Neg	*Rhizopus oryzae* (culture)/aspiration	[19]
17	31/F	Cocaine	Left basal ganglia	Pos	Aseptate hyphae/stereotactic biopsy	[20]
18	34/M	Heroin	Left basal ganglia	Neg	*Rhizopus arrhizus* (culture)/biopsy	[21]

Table 3. Continued

Case No.	Age/Sex	IV Drug Type	Localization of Infection	HIV Ab	Diagnosis (Method)/Manner Obtained	Source
19	53/F	Heroin and cocaine	Multiple abscesses including in left basal ganglia	Neg	Aseptate hyphae/brain biopsy	[22]
20	29/F	Opioids	Left basal ganglia	Neg	Aseptate hyphae/biopsy	[23]
21	28/M	IVDU, not further specified	Left basal ganglia	N/A	*Rhizopus oryzae* (culture)/open brain biopsy	[24]
22	21/M	Heroin	Bilateral basal ganglia	Pos	Aseptate hyphae/brain biopsy	[25]
23	23/F	IVDU, not further specified	Bilateral basal ganglia	Pos	Aseptate hyphae/brain biopsy	[25]
24	25/M	IVDU, not further specified	Right temporal lobe	Neg	*Rhizopus arrhizus* (culture)/aspiration	[26]
25	33/F	IVDU, not further specified	Left basal ganglia	Neg	Ventriculostomy culture with aseptate branching hyphae	[27]
26	"Young"/M	Heroin	Bilateral basal ganglia	Neg	Fungi with aseptate hyphae/autopsy	[28]
27	24/M	Drug use history not stated	Bilateral basal ganglia	Neg	*Rhizomucor* (culture)/biopsy	[29]
28	22/M	Heroin and cocaine	Right basal ganglia	Neg	Hyphal elements from autopsy	[30]
29	43/M	IVDU presumed but not confirmed	Ventricular disease with a left basal ganglia mass	Neg	Aseptate hyphae/ventricular biopsy	[31]
30	27/M	Drug use history not stated	Right basal ganglia	Neg	*Rhizopus* spp. (next-generation sequencing)/CSF exam from time of drain placement	[32]/2020
31	26/F	Drug use history not stated	Bilateral basal ganglia	N/A	Aseptate hyphae/brain biopsy	[33]
32	27/F	Cocaine and opioids	Right basal ganglia	Neg	Aseptate hyphae/stereotactic brain biopsy	[34]
33	37/M	Heroin and cocaine	Left basal ganglia	Neg	Aseptate hyphae/autopsy	[34]
34	32/F	Heroin and cocaine	Left basal ganglia	Neg	Aseptate hyphae/autopsy	[34]
35	49/M	No history of IVDU	Left frontal lesion progressed to involve right frontal and right basal ganglia	Neg	Aseptate hyphae/autopsy	[35]
36	22/F	IVDU, not further specified	Bilateral basal ganglia	Neg	Aseptate hyphae/stereotactic brain biopsy	[36]
37	24/M	IVDU, not further specified	Bilateral basal ganglia	N/A	Aseptate hyphae from culture from ventriculostomy	[37]
38	24/M	Heroin	Right basal ganglia	N/A	Aseptate hyphae/autopsy	[38]
39	32/M	Heroin	Left basal ganglia	N/A	Aseptate hyphae/autopsy	[39]
40	27/M	Heroin	Bilateral basal ganglia	N/A	Aseptate hyphae/autopsy	[40]
41	27/M	IVDU, not further specified	Multiple bilateral cerebral abscesses	N/A	Aseptate hyphae/autopsy	[24]
42	23/F	IVDU, not further specified	Right basal ganglia	N/A	Aseptate hyphae/autopsy	[6]
43	28/M	Heroin	Ventricular infection causing obstructive hydrocephalus	N/A	Aspirate during craniotomy with aseptate hyphae	[41]
44	40/M	Heroin	Left basal ganglia	N/A	Autopsy with aseptate hyphae	[41]
45	25/M	IVDU, not further specified	Right basal ganglia	Neg	Not stated	[36]
46	28/M	Heroin	Bilateral basal ganglia	Neg	Aseptate hyphae/autopsy	[42]
47	50/M	Heroin and cocaine	Bilateral basal ganglia	Neg	Aseptate hyphae/autopsy	[43]
48	38/F	Amphetamines	Left basal ganglia	N/A	*Mucor* spp. (culture)/autopsy	[44]
49	30/M	Cocaine and amphetamines	Bilateral basal ganglia	N/A	*Mucor* spp. (culture)/autopsy	[44]
50	22/F	No history of IVDU	Ventricular infection causing obstructive hydrocephalus and basilar meningitis	N/A	Autopsy with aseptate hyphae	[45]
51	47/F	No history of IVDU	Right frontal lobe	N/A	Culture from abscess drainage	[46]
52	41/M	Heroin and amphetamines	Left basal ganglia	N/A	Aseptate hyphae seen at autopsy	[47]
53	25/M	IVDU, not further specified	Right basal ganglia	Neg	*Rhizopus oryzae* (culture)/autopsy	[48]
54	31/F	IVDU, not further specified	Bilateral basal ganglia	Pos	Not stated	[36]
55	53/M	Heroin and cocaine	Bilateral basal ganglia	Neg	*Rhizopus* spp. (culture)/stereotactic brain biopsy	(This study)

Abbreviations: Ab, antibody; CSF, cerebrospinal fluid; F, female, M, male; IV, intravenous; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; IVDU, intravenous drug use; spp, species.

[a]N/A, HIV status not explicitly stated.

Table 4. Treatment and Outcomes

Case No.	Age/Sex	Outcome	Antifungal Therapy & Duration[a] of Treatment (if Survived)	Steroids[b]	Survival Duration at Time Case Reported	Functional Status After Treatment	Source
1	37/F	Survived	AmB,[c] duration not stated	No	Not stated	"Patient returned to normal health"	[5]
2	32/M	Survived	AmB for "weeks"	No	At least months	"Now aphasic, spastic and has only the ability to follow simple commands"	[6]
3	24/F	Survived	AmB for "over a four-month period"	No	>5 mo	"Functioning normally"	[7]
4	20/F	Survived	AmB for weeks to months	No	>4 mo	"Only minimal weakness in the right extremities"	[8]
5	24/M	Survived	AmB for "8 weeks"	No	Months	"Enjoying gradual but steady improvement"	[9]
6	28/M	Survived	AmB for "12 days"	No	Unclear	"Symptoms improved"	[10]
7	28/M	Survived	AmB for weeks to months	No	At least months	"Returned to employment"; symptoms resolved	[11]
8	30/F	Survived	AmB for 6 mo	No	At least months	"Recovered from her left hemiparesis and regained ability to walk" independently	[12]
9	24/F	Survived	AmB, duration not stated	No	Not specifically stated	"Alert and able to follow commands, but she remained mute"	[13]
10	42/F	Survived	LAmB[d] for 6 mo with 80 day of IT AmB and some debridement	No	>3 years	"Completely recovered from left leg but only partially from left arm paralysis"	[14]
11	43/M	Survived	AmB for 2 wk following surgical resection (AmB stopped due to renal failure)	No	Months	"Continues to be ambulatory"	[15]
12	40/M	Survived	LAmB followed by isavuconazole after acute renal injury, duration not stated, some debridement	No	At least months	Clinical improvement "initially with his speech, followed by improved wakefulness and awareness"	[16]
13	23/F	Survived	LAmB and posaconazole for 45 d followed by posaconazole suppression	No	>25 mo	"Able to ambulate without assistance" and "severely dysarthric" and "mild spasticity and discoordination"	[17]
14	37/M	Survived	LAmB, posaconazole, and micafungin for 4 wk, followed by LAmB and posaconazole for 3 wk, followed by >1 y of ongoing posaconazole suppression	No	>6 mo	"Remarkable neurologic recovery with only a faint right facial droop and mild residual right-hand weakness"	(This study)
15	44/M	Survived	AmB for 10 wk	Yes	Not specifically stated, at least months	"Able to ambulate without assistance, can verbally communicate, and is oriented to person, place, and time"	[18]
16	26/M	Survived	AmB, including intrathecal AmB for several months	Yes	>20 mo	"Continued disability in the form of partial weakness of his left leg and complete weakness of his left arm"	[19]
17	31/F	Survived	AmB for months	Yes	>5.5 mo	"Alive and well, with minimal neurologic deficits"	[20]
18	34/M	Survived	AmB for months	Yes	>6 mo	"Able to ambulate with assistance"	[21]
19	53/F	Survived	AmB, including intrathecal AmB, for months	Yes	>7 mo	"Mental status and hemiparesis improved"; "alive and well" after completion of AmB	[22]
20	29/F	Survived	AmB for months plus intrathecal AmB for 18 d	Yes	At least 3 mo	"Alert and able to follow simple commands, but she had a persistent dense left hemiplegia"	[23]
21	28/M	Deceased	AmB	No	—	—	[24]
22	21/M	Deceased	AmB	No	—	—	[25]
23	23/F	Deceased	AmB	No	—	—	[25]
24	25/M	Deceased	AmB	No	—	—	[26]
25	33/F	Deceased	AmB	No	—	—	[27]

Table 4. Continued

Case No.	Age/Sex	Outcome	Antifungal Therapy & Duration[a] of Treatment (if Survived)	Steroids[b]	Survival Duration at Time Case Reported	Functional Status After Treatment	Source
26	"Young"/M	Deceased	LAmB	No	—	—	[28]
27	24/M	Deceased	AmB	No	—	—	[29]
28	22/M	Deceased	AmB	No	—	—	[30]
29	43/M	Deceased	IV and IT AmB and posaconazole	No	—	—	[31]
30	27/M	Deceased	AmB and posaconazole	No	—	—	[32]
31	26/F	Deceased	AmB	Yes	—	—	[33]
32	27/F	Deceased	AmB	Yes	—	—	[34]
33	37/M	Deceased	AmB	Yes	—	—	[34]
34	32/F	Deceased	AmB	Yes	—	—	[34]
35	49/M	Deceased	AmB	Yes	—	—	[35]
36	22/F	Deceased	AmB	Yes	—	—	[36]
37	24/M	Deceased	IV LAmB, IT AmB, isavuconazole	Yes	—	—	[37]
38	24/M	Deceased	None	No	—	—	[38]
39	32/M	Deceased	None	No	—	—	[39]
40	27/M	Deceased	None	No	—	—	[40]
41	27/M	Deceased	None	No	—	—	[24]
42	23/F	Deceased	None	No	—	—	[6]
43	28/M	Deceased	None	No	—	—	[41]
44	40/M	Deceased	None	No	—	—	[41]
45	25/M	Deceased	None	No	—	—	[36]
46	28/M	Deceased	None	No	—	—	[42]
47	50/M	Deceased	None	No	—	—	[43]
48	38/F	Deceased	None	Yes	—	—	[44]
49	30/M	Deceased	None	Yes	—	—	[44]
50	22/F	Deceased	None	Yes	—	—	[45]
51	47/F	Deceased	None	Yes	—	—	[46]
52	41/M	Deceased	None	Yes	—	—	[47]
53	25/M	Deceased	None	Yes	—	—	[48]
54	31/F	Deceased	None	Yes	—	—	[36]
55	53/M	Deceased	None[e]	Yes	—	—	(This study)

Abbreviations: AmB, amphotericin B; F, female, IT, intrathecal; IV, intravenous; M, male; mo, month(s); wk, week(s).

[a]Duration reported directly when described in case report. In some cases, duration calculated from total dose of AmB reported.

[b]If not mentioned as administered in the case report, steroids were presumed not given.

[c]AmB, amphotericin B, formulation not specified.

[d]LAmB, liposomal amphotericin B.

[e]This patient received only 1 dose of LAmB within hours of dying.

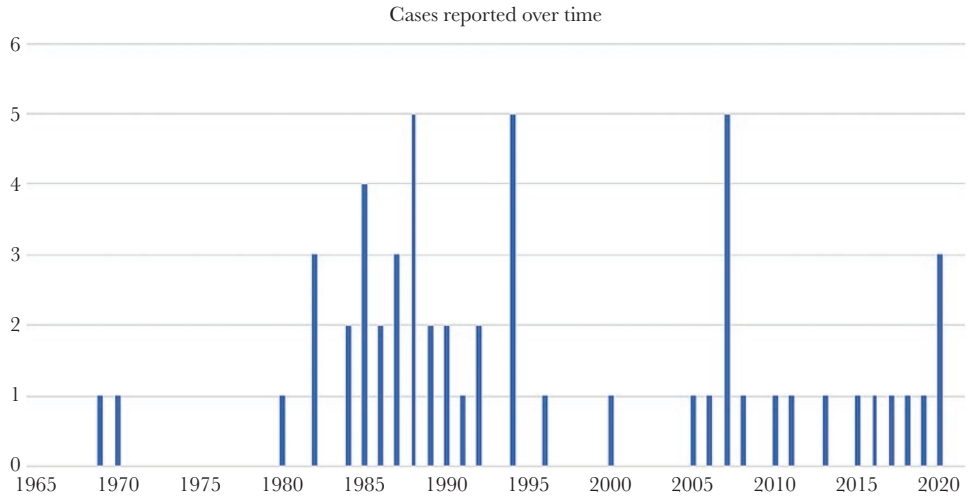

Figure 2. Epidemic curve of reported cases since 1965, plotted as a function of year of presentation.

presented with less than a week of symptoms, most reporting hours to days of symptoms. The observed differences in duration of symptoms could be explained by an inoculum effect, wherein individuals whose brains were seeded with small numbers of Mucorales spores of vegetative cells have a more indolent course than individuals whose brains were seeded with greater numbers of Mucorales spores. Alternatively, more effective host immune function, including neutrophil activity, might allow better control of the infection, slowing the angioinvasive and necrotizing processes. Also possible is that another initial inciting event that predisposes to secondary superinfection by Mucorales, such as focal ischemia, may modulate the duration of symptoms. Further study of this syndrome in an animal model could help shed light on these aspects of the syndrome.

Diagnosis requires tissue, which should be sent for culture and pathology to look for characteristic broad-based aseptate hyphae (Figure 1). Even when visible on histopathology, the organisms do not always grow in culture, potentially because they are nonviable. This is particularly likely if antifungals are administered before sample collection, highlighting the utility of PCR-based testing. The imaging modality of choice is brain MRI with special sequences, including gradient echo and susceptibility weighting, to assess for microhemorrhage, which suggests a potentially invasive process.

There are several important treatment considerations for this syndrome. Amphotericin is essential to treatment, as no patients survived without amphotericin B (AmB). In patients with underlying hematologic malignancy, survival from mucormycosis is significantly increased with early treatment with AmB [59]. These findings are consistent with our retrospective observations herein, together strongly suggesting that early diagnosis and early initiation of AmB improve survival in immunocompetent patients with mucormycosis. Whether to add additional agents for combination therapy is controversial, with no benefit shown for combination therapy in the context of hematologic malignancy [60]. However, some providers may prefer adding a triazole with anti-Mucorales activity, such as posaconazole or isavuconazole, to initial treatment, as was done in Case 2 in this series [61, 62]. Because of potentially better CNS penetration [63], isavuconazole is preferred to posaconazole by some clinicians, but both triazoles demonstrate good clinical outcomes in CNS infections [64–67]. Echinocandins show in vitro synergy with AmB against *Rhizopus oryzae* but display poor CNS penetration [68]. In addition, treatment failures with echinocandins when used as monotherapy for susceptible fungal brain abscesses are documented [69].

We found that steroid use was associated with worse outcomes, raising the possibility that they are harmful in this setting. As steroids are frequently administered for the treatment of edema associated with brain lesions, early diagnosis is particularly important in isolated cerebral mucormycosis, so that inappropriate steroid administration can be avoided. Additionally, as acidemia promotes Mucorales growth and binding to endothelial cells, thereby accelerating angioinvasion, control of hyperglycemia and acidemia are critical [70].

CONCLUSIONS

Isolated cerebral mucormycosis in immunocompetent adults is a rare and possibly underrecognized syndrome that requires a high index of suspicion for diagnosis and prompt treatment. Many patients present with headaches and cranial nerve deficits, and some with fevers or altered mental status. The vast majority of cases involve the basal ganglia. Tissue from a biopsy is important for establishing the diagnosis. Treatment should include amphotericin B. Good outcomes are possible. Given the current opioid crisis, the frequency of cases may increase.

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