Cranial zygomycosis caused by *Saksenaea vasiformis*

Case report

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A previously healthy youth who had sustained severe head trauma and had received steroids and broad-spectrum antimicrobial agents developed a cranial zygomycotic infection with *Saksenaea vasiformis*. This is the first time this zygomycete has been implicated as a disease agent. Early identification of the fungal infection and subsequent vigorous medical and surgical therapy led to recovery.

**KEY WORDS**
- zygomycete
- skull fracture
- brain abscess
- head injury
- meningitis
- fungus infection

The wide variety of fungi formerly in the class Phycomycetes have been re-grouped into six new classes of fungi. The old class “Phycomycetes” has thus been discarded and the obsolete term “phycomycosis” replaced by the new and more appropriate “zygomycosis.”

Most commonly, zygomycosis is an opportunistic infection developing in hosts with impaired defense mechanisms. The etiologic agents incriminated in this disease have been species of the five genera *Absidia*, *Basidobolus*, *Entomophthora*, *Mucor*, and *Rhizopus*. Our recent experience in identifying and successfully treating a cranial infection caused by a member of a sixth genus of zygomycetes, *Saksenaea*, prompted this report.

**Case Report**

This 19-year-old man suffered severe head trauma in an automobile accident and was admitted to the Keesler Medical Center. At first he was unresponsive to all commands, then he gradually aroused to a combative, confused state, moving all extremities.

**Examination.** The patient’s blood pressure was 140/70, pulse 104, and respiration rate 24. His left ear was almost detached and he had extensive lacerations across the left orbital ridge avulsing off the lateral aspect of the ridge so that the upper eyelid had to be gingerly lifted with its attached bone to reveal the left eye. He had several irregular lacerations through the scalp over the left zygoma as well. Brain tissue and blood were...
FIG. 1. Lateral skull x-ray film showing left frontal orbital fractures and pneumocephalus.

exuding from the right external ear canal. The left canal was filled with blood. The right pupil reacted briskly to light and accommodation and the right extraocular movements appeared to be intact. The left pupil did not react to direct light, but did react consensually. Left extraocular movements were not observed. The patient's left zygoma was depressed. His nose, palate, and mandible were intact, as was the right maxilla. The remainder of the general physical examination was normal.

On neurological examination the patient was stuporous; he responded to painful stimuli with purposeful movements of all extremities and occasionally to voice command. Corneal reflexes were intact, and the fifth and seventh cranial nerves were normal. The palate and tongue were midline and the patient gagged and swallowed normally. Motor function was judged to be good bilaterally and the patient had intact right oculocephalic reflexes and no right nystagmus. Deep tendon reflexes were hypactive and symmetrical. The right great toe dorsiflexed on plantar stimulation.

After the patient's condition had been stabilized, multiple x-ray films were taken of the skull. They showed that the roof of the patient's left orbit projected into the frontal fossa. In addition, a comminuted fracture of the left frontotemporal bone, a depressed left zygomatic arch, and an opacified left maxillary sinus were noted (Fig. 1).

First Operation. In the operating room the patient was intubated and light general anesthesia established. Indirect ophthalmoscopy demonstrated that the left retina and retinal blood vessels were intact. The external ear canals were suctioned free of blood and examined with a Zeiss operating microscope. The patient's facial wounds were debrided following Betadine soap and saline washing and irrigation. The surgical team of neurosurgeon, otolaryngologist, and ophthalmologist first turned a left frontal osteoplastic flap and explored the patient's left frontal fossa. They then performed an internal fixation of the patient's fracture fragments and sutured his lacerations. The craniotomy disclosed lacerated left orbital gyri, a small epidural hematoma, and a subdural hematoma over the frontal fossa and left temporal tip. The left frontal and temporal tips also had multiple small lacerations and contusions. The brain lacerations were debrided and the hematomas removed. A pericranial graft was used to reapproximate the orbital dura and multiple small pieces of the orbital roof were removed. Laceration of the left optic nerve was not noted. After the craniotomy the orbit was explored and a Silastic graft was placed in the floor of the left orbit. Bone fragments were wired together and the patient's left ear was reapproximated to the scalp and the bone flap and orbital ridge wired back in place. During the operation, 1.5 liters of whole blood were administered to the patient.

First Postoperative Course. Intramuscular injections of Dilantin (100 mg every 6 hours), Kantrex (0.5 gm every 12 hours), and Decadron (4.0 mg every 6 hours) were given postoperatively; ampicillin was given intravenously (2.0 gm every 4 hours). The patient's postoperative mental status was characterized by agitated cursing, occasional sexual exhibitionistic behavior, and alternate periods of somnolence and gross confusion. During the seventh postoperative day his temperature increased to 38.6° C. The periorbital swelling and erythema, which had been improving, began to worsen and a wound infection was suspected. On the ninth postoperative day his
fever reached 39.4° C. At this time all the sutures were removed from the wounds. Exudate was Gram stained and cultured; the Gram stains showed neutrophils without organisms, and cultures did not grow bacteria. Prior antimicrobial therapy was discontinued and intravenous therapy with gentamicin (80 mg every 6 hours) and methicillin (1 gm every 2 hours) was begun. On the tenth postoperative day, the Silastic floor implant was removed and the wounds were drained and cultured. The left eye had appeared progressively less viable. The patient continued spiking temperatures to 39.4° C. Lumbar puncture had demonstrated clear cerebrospinal fluid (CSF) with only four lymphocytes; CSF cultures were negative. Seropurulent material was now draining from the left orbital wound. At this time the Gram-stained smears of this drainage revealed the presence of broad aseptate hyphae and the first cultures gave rise within 3 days to a luxuriant growth of a zygomycetous fungus. Smears of a deep orbital probe showed the same type of fungal forms in necrotic tissue and a diagnosis of zygomycosis was thus established.

Second Operation. On the twelfth postoperative day all bone fragments were removed from the lesion. The left eye was enucleated and the orbit exenterated. The wound was markedly avascular, rather dry, grayish-black in areas, and appeared necrotic. The left eye and muscle cone were excised with minimal bleeding. The subgaleal space had areas of black clot and bled minimally. Histological examination of tissue removed from the orbit, as well as pieces of herniating brain, demonstrated the characteristic aseptate hyphae of a zygomycete (Fig. 2 left). Necrotic areas with vascular thrombosis and perivascular infarction were also revealed. The muscle cone around the globe demonstrated infarcted muscle with broad aseptate hyphae (4 to 6 µ in diameter) invading the muscle as well as an arteritis (Fig. 2 right). Sinus x-ray films, left maxillary antrostomy, and biopsy of sinus mucosa did not disclose any evidence of zygomycete infection.

Second Postoperative Course. Following extensive surgical debridement and enucleation, methicillin, gentamicin, and Decadron were discontinued and treatment with intravenous amphotericin B was initiated. After noting that the patient tolerated an initial 1-mg test dose, 5 mg was infused over 6 hours in 500 ml of 5% dextrose and water. Because of the severity of our patient's infection, the recommended dose for zygomycotic infection was reached in 4 days by the following increments: 25 mg the second day, 50 mg the third, and 75 mg the fourth. For 1 week, 75 mg infusions were given daily, and then every other day. Each infusion included 25 mg of hydrocortisone plus 5000 units of heparin,
and was preceded by a 10-mg intramuscular injection of Compazine. Vigorous surgical debridement of the remaining orbital tissue was performed daily. With this regimen the patient's mental status progressively brightened.

The debrided tissue was fixed in 10% buffered formalin, standard sections were made and stained with hematoxylin and eosin. Histological examination of the debrided tissue over the next 2 months disclosed the presence of the zygomycete. Attempts to grow the fungus retrieved from the wound once amphotericin was begun were unrewarding.

Evaluations to uncover any factor that would have predisposed our patient to a zygomycotic infection were negative. Numerous blood sugar tests and the patient's family history were negative for diabetes mellitus. Serum protein electrophoresis and immunoglobulin levels were normal and a mumps skin test was positive. In addition, white blood counts and differential cell counts were always appropriate to the patient's clinical situation.
Cranial zygomycotic infection

**Third Operation.** Because of his deep tissue injury and what appeared to be brain tissue lying in the left orbit, the patient was returned to the operating room for further debridement of the orbit and closure of the dural rent. Since cultures from the orbit grew *Staphylococcus aureus*, prophylactic methicillin was given. Exploration, debridement, and dural closure were carried out.

**Third Postoperative Course.** The patient developed an *Escherichia coli* meningitis within a week. Once again debried tissue disclosed the presence of the zygomycete. The meningitis responded to ampicillin. A sudden epidural hematoma followed an intracranial aspiration attempt 6 days following the dural closure. A repeat acute epidural and subdural hematoma occurred 2 days later and was removed. With these complications the patient lapsed into a coma and developed a profound right hemiplegia, both of which completely resolved.

Four months following his initial accident the patient developed an *E. coli* left frontal lobe abscess that was treated with intravenous Chloromycetin for 3 weeks, by tapping and draining, and then by a 4-week course of intravenous ampicillin therapy. The onset of the *E. coli* abscess occurred 1 month after the cessation of the amphotericin.

The patient received a total of 3.2 gm of amphotericin B over 80 days. Therapy was continued until mycelium was no longer observed in tissue from two consecutive debridements. Figure 3 shows the effect of amphotericin B on the blood urea nitrogen (BUN) and hematocrit levels; Fig. 4 shows the cumulative dosage of amphotericin B related to the highest daily temperatures over the 82-day treatment period. At the present time the patient has survived this terrible sequence of events with a current IQ of 108. He has no paresis and is caring for all of his affairs.

**Mycological Studies**

The fungus recovered from the patient's initial surgical excisions and drainage first grew on 5% sheep's blood agar and freshly boiled thioglycollate broth. These cultures were sent to the Mycology Division of the Center for Disease Control (CDC) in Atlanta, Georgia. Examination showed that the fungus colonies were made up of hyaline, broad aseptate mycelium typical of a zygomycete. However, careful search failed to reveal the

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**Fig. 4.** Graph shows effect of amphotericin B administration related to highest daily temperatures over the 82-day course of therapy.
FIG. 5. Photomicrograph of characteristic flask-shaped sporangium of Saksenaea vasiformis. Growth was induced by transferring mycelium obtained on hay infusion agar to a plate of sterile distilled water. Lactophenol cotton blue mounts, × 640.

development of sporangiophores and sporangia, by which classification of genera and species is made.

The isolate was subcultured on tubes of Sabouraud dextrose agar and corn meal agar and incubated at 25° C. Growth was sparse and remained so over a period of 4 weeks. The fungus again failed to produce spores. The isolate was sent to an authority on the zygomycetes, Dr. John J. Ellis of the U.S. Department of Agriculture, Northern Regional Research Laboratory, Peoria, Illinois. By growing it on Czapek's agar and on hay infusion agar, sporulation was induced. On the basis of the striking long-necked, flask-shaped sporangia produced on these media, the isolate was identified as Saksenaea vasiformis, a fungus first described by Saksena in 1953.10 Once these conditions required to induce sporulation were learned, the fungus was grown on plates of hay infusion agar at the CDC. Although growth was luxuriant on this dilute medium, sporangia failed to develop. However, their production was induced by placing blocks of agar growth in plates of sterile distilled water. Under these conditions the distinctive sporangia were produced (Fig. 5). The diagnostic features of S. vasiformis and the complex etiology of zygomycosis are to be reported elsewhere.

Discussion

The case of a previously healthy youth who developed an unusual mycotic infection following massive head trauma has been presented. Early identification of the fungal infection and subsequent vigorous medical and surgical treatments led to recovery and deserve further comment.

In a diabetic or immunosuppressed patient, periorbital and perinasal swelling progressing to induration and discoloration, blood-tinged dark nasal discharge, facial pain, ptosis, proptosis, limitation of eye mobility, pupil fixation and loss of vision, loss of corneal reflexes, progressive lethargy, and black necrotic turbinates have been suggested as strongly indicative of rhinocerebral zygomycosis caused by Rhizopus arrhizus or R. oryzae.8,9,11,12 However, since many of these findings are also seen after cranio-cerebral trauma, the diagnosis may not be considered in that setting. Routine, compulsive, and thorough microbiological and histological surveillance in these cases may be the only way to make the diagnosis. Such was the case in our patient. Cultures of the seropurulent material suggested the presence of a zygomycotic infection and smears of a deep orbital probe confirmed it. It was necessary to observe the fungal forms in tissue to establish the diagnosis and rule out laboratory contamination since zygomycete spores are ubiquitous. Only after surgical reexploration were the hallmarks of zygomycotic infection (vascular thrombosis and infarction) appreciated.

Man has a strong natural resistance to the zygomycetes.8 When such fungi have caused disease, there usually has been a complex interplay of predisposing factors that included a susceptible host, tissue trauma that served as a portal of entry, and disturbance of the normal microbiological-ecological balance.4,7
Cranial zygomycotic infection

Since some of the zygomycetes are common laboratory and household contaminants and are not ordinarily pathogenic, why did our previously healthy patient become infected? Even though he was not debilitated and did not have diabetes mellitus or a malignancy, his resistance had been altered as a result of the trauma and treatment with antibiotics and steroids. Consequently, we believe that the antibiotics and steroids caused him to become a susceptible host in a clinical setting that was not common for development of a zygomycotic infection. The unusual feature of this infection is that it represents the first time that Saksenaea vasiformis has been implicated as a disease agent. Since zygomycetes are found in soil, dung, and vegetable material, and since multiple pieces of glass, car paint, sand, and gravel were debrided from his wound, the fungus was probably introduced into the orbit at the time of the accident. One previous fatal case of head trauma infected with a Zygomycetes mucor has been reported.

Cerebral zygomycotic infections in general are rapidly fatal. In the few cases that have been cured, successful treatment has depended on the combination of early diagnosis, control of the host's underlying disease, surgical removal of involved tissues, and administration of amphotericin B. We believe that the successful outcome in our case also can be attributed to such an approach. After identifying the presence of a zygomycotic infection, steroids and antibiotics were discontinued and extensive debridement of the left orbit followed enucleation of the left globe. Amphotericin B therapy was also begun and the dosage was increased to the recommended alternate day dose of 1.2 mg/kg. Because of the fulminant nature of our patient's disease, amphotericin B was rapidly increased in 4 days to this dose without untoward effects. Daily debridements served two purposes: they not only kept the wound clean but also determined the duration of amphotericin B therapy. When mycelium was no longer seen histologically, we were confident that the infection had been cured and amphotericin B was discontinued. A final contributing factor that might have influenced our patient's survival was the absence of a CSF fistula. When this has been present in patients with fungal infected war wounds from Vietnam, the outcome has been fatal.

References

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