Mucormycosis

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The clinical picture of cerebral mucormycosis is well defined, usually involving a diabetic adult in acidosis who develops rhinitis, headache, unilateral ptosis, lid oedema, total ophthalmoplegia, proptosis, and loss of vision. Death generally follows disorientation and coma in 2 weeks. In many cases, diagnosis is made *post mortem* after the characteristic fungus has been found in the involved tissues. The disease may involve the orbit, nose, paranasal sinuses, oral cavity, soft tissues of the cheek, and central nervous system. Baum (1967) suggested that the term rhino-orbital mucormycosis should be employed in cases in which the patient presents the symptoms mentioned above.

Approximately 50 per cent. of patients with cerebral mucormycosis have diabetes mellitus and most of these patients have acidosis (McBride, Corson, and Darnmin, 1960). In patients who do not have diabetes, this disease has been associated with many other conditions, including multiple myeloma, thermal burns, carcinoma, anaemia, congenital heart disease, leukaemia, enteritis, hepatitis, cirrhosis, diarrhoea, renal disease, septicaemia, and alveolar proteinosis. Craig and Farber (1953) stressed the association of this fungus disease with the use of steroids, ACTH, antibiotics, ionizing radiation, and folic acid antagonists.

McBride and others (1960) noted that cerebral involvement occurred more frequently in diabetics. The pulmonary form is usually found in a patient with leukaemia or lymphoma, and the disseminated form in a patient with neither diabetes nor lymphoma.

Cerebral mucormycosis begins in the nose or nasopharynx, extends to the paranasal sinuses, and may involve the orbit either by direct extension or by haematogenous spread. Organisms may also reach the orbit through the nasolacrimal duct. Involvement of the brain and meninges may occur by direct extension from any of the above-mentioned sites, via blood vessels or cranial nerves (Bauer, Flanagan, and Sheldon, 1955). The organisms cause thromboses of the ophthalmic artery or the internal carotid artery or both, and less often of the cavernous sinus. The clinical manifestations and pathological changes are due to arterial thromboses by the organisms causing infarction, necrosis, and acute inflammation, direct tissue invasion by the organisms, or toxic inflammatory response due to the hyphae.

Over sixty cases of cerebral mucormycosis have been reported and the majority of these have been tabulated in review articles (McBride and others, 1960; Bauer, Ajello, Adams, and Hernandez, 1955; Ferry, 1961; Gass, 1961a; Straatsma, Zimmerman, and Gass, 1962). Only seventeen patients surviving this disease have been reported (Table, opposite).

The present report adds two cases to the relatively small number who have survived cerebral mucormycosis. They have been described elsewhere (Battock, Grausz, Bobrowsky, and Littman, 1968) and are presented here with special regard to the ocular findings.

Table Seventeen patients reported as surviving by various authors in order of date

Harris (1955)	Wasserman, Shiels, and Sporn (1961)
Baker (1957)	Bank, Shibolet, Gilat, Altmann, and Heller (1962)
McCall and Strobos (1957)	Landau and Newcomer (1962)
Faillo, Sube, and Anderson (1959)	Burrow, Salmon, and Nolan (1963)
Muresan (1960)	Taylor, Shklar, Budson, and Hackett (1964)
Gass (1961b)	DeWeese, Schleuning, and Robinson (1965)
Heller (1961)	Baum (1967)
Hoagland, Sube, Bishop, and Holding (1961)	Prockop and Silva-Hutner (1967)

Case reports

(1) **A 37-year-old white female** was admitted to hospital on April 22, 1966, because of lethargy and dyspnoea. She had a 2-year history of diabetes mellitus and was taking 500 mg. tolbutamide daily but had never had acidosis or renal disease. One week before admission she developed a productive cough but denied any history of sinusitis; 3 days before admission she developed polydipsia and polyuria.

Examination

She was a moderately obese woman, alert, and well orientated. Blood pressure 110/70 mm. Hg, pulse 130/min. and regular, respiration 40/min., temperature 98°F. Ocular examination, including extraocular movements and fundi, was reported as normal. No nasal discharge was present. The neck was supple and the lungs clear. All other findings of the routine physical and neurological examination were normal.

Laboratory studies

WBC 31,000/mm.³ with 64 per cent. polymorphonuclear cells, 24 per cent. bands, 10 per cent. lymphocytes, and 2 per cent. monocytes. Blood sugar was 425 mg./100 ml., blood urea nitrogen 13 mg./100 ml., and CO₂ combining power 14 mEq./litre. Urine analysis revealed grade* 4 sugar, grade* 4 acetone, grade* 2 protein, occasional WBC clumps, 10 to 15 RBC/HPF, and 2 to 3 granular casts. Gram stain of the urine showed a few Gram-negative rods in the uncentrifuged specimen. Acetone test of the undiluted serum was grade* 4. Electrocardiogram showed a sinus tachycardia but was otherwise normal.

Hospital course

30 minutes after admission, her blood pressure dropped to 70/0 mm. Hg. She was treated with 100 units regular insulin intravenously and 700 ml. 0.45 N saline solution. She developed acute pulmonary oedema and was treated with 0.75 mg. digitalis lanata and 10 mg. morphine sulphate intravenously. Within one hour the pulmonary oedema subsided. During the next 12 hours she received 200 units regular insulin and 132 mEq. sodium bicarbonate intravenously.

On the second hospital day she became semicomatose. Acetone test of the undiluted serum was negative, blood sugar was 180 mg./100 ml., and the temperature rose to 103°F. Lumbar puncture revealed normal cerebrospinal fluid under a normal pressure of 120 mm. H₂O. Chest x ray was normal.

She was treated daily with 12 g. sodium cephalothin intravenously and 100 mg. methylprednisolone sodium succinate for what was thought to be Gram-negative bacterial septicaemia. On the third hospital day urinary output decreased to 100 ml./24 hours and serum and urine osmolality were 404 mOsm., suggesting acute tubular necrosis. Peritoneal dialysis was started and continued for 7 days. Blood sugar ranged from 200 to 400 mg./100 ml. during dialysis, but serum acetone was negative. Temperature ranged from 100°F to 101.4°F and she remained comatose.

On the eighth day she had a grand mal seizure and 400 mg./day diphenylhydantoin was started. A second lumbar puncture revealed xanthochromic spinal fluid. On the ninth day she regained consciousness at which time ptosis of the left eyelid was noted. Examination on the following day showed total ophthalmoplegia of the left eye, a 6-mm. fixed pupil, corneal anaesthesia, and a left seventh-nerve palsy. By the thirteenth day she had no perception of light in the left eye and fundus-

Graded 1 to 4 as follows: 1 mild, 2 fair, 3 moderate, 4 severe

scopy revealed occlusion of the central retinal artery. Over the next 2 days she developed periorbital oedema and proptosis of the left eye. Carotid angiogram was normal.

Diagnosis

Because of the occurrence of ophthalmoplegia and proptosis in a diabetic patient, a diagnosis of mucormycosis was considered. A left ethmoiditis was noted. X rays revealed sinusitis involving the left ethmoid, maxillary, and frontal sinuses. Smear of the ethmoidal discharge revealed non-septate branching hyphae. Culture produced *Rhizopus oryzae*. Growth and physical characteristics were typical for the organism.

Treatment included an intravenous infusion of amphotericin B, intermittent irrigation of the involved sinuses with amphotericin B aqueous solution (1 mg./ml.), 30 units NPH insulin daily, and 30 ml. hyperimmune gamma globulin intramuscularly for 10 days. A left maxillary antrotomy was performed on day 30, and ethmoidectomy and Caldwell-Luc procedure on day 44, with incisional debridement of necrotic bone and drainage of purulent discharge from the left maxillary sinus. The initial daily dose of 5 mg. amphotericin B was increased over a 4-day period to 25 mg./day. It was then increased in increments of 0.2 mg./kg. every other day until a peak dose of 1.2 mg./kg. was reached. This dose was then administered every second day until a total dose of 2 g. was reached. The amphotericin B was administered over an 8-hour period in 500 ml. 5 per cent. glucose in distilled water containing 10 mg. sodium heparin. Aside from initial fever, chills, and thrombosis of veins at the sites of intravenous infusions, the patient tolerated therapy well.

During the fourth week she had transient right hemiplegia and grand mal seizures. The haematocrit dropped from 30 to 21 per cent. and blood transfusions were given. The electroencephalogram was compatible with bilateral cortical infarction but reverted to normal at the end of therapy.

Renal function throughout amphotericin B therapy was impaired but returned to normal 2 weeks after therapy was discontinued. A biopsy of ethmoid bone taken on day 65 revealed fragments of necrotic fungi but cultures were negative. Sinus x rays on day 75 were normal.

Discharge

The patient was discharged 91 days after admission having received 2,244 mg. amphotericin B over a 65-day period. There were no signs of sinus discharge, periorbital oedema, facial palsy, or hemiplegia. Ocular findings included total ophthalmoplegia, blindness, ptosis, and proptosis of the left eye.

Follow-up

16 months after discharge there was no evidence of recurrence of the disease. Renal function had been normal and the patient's diabetes was controlled by 40 units of NPH insulin daily.

The patient had been disturbed by the cosmetic appearance of the ptotic left eyelid (Fig. 1). An attempt was made to keep the left eyelid raised by attaching a ptosis crutch to the patient's spectacles but its use was discontinued when episodes of exposure keratitis developed.

The left eye was then fitted with a scleral contact lens with horizontal ridges superiorly and inferiorly on the anterior surface to keep the eye open (Fig. 2). She has tolerated this well and is pleased with the cosmetic result.

FIG. 1 Case 1, showing complete ptosis of left lid

FIG. 2 Case 1, showing position of left upper lid using a ridged contact lens

(2) **A 55-year-old diabetic Negro female** was admitted to hospital on July 14, 1966, with a febrile illness of 4 days' duration. She complained of headache, stiff neck, double vision, and protrusion of the left eye. She had had diabetes mellitus for 7 years and was on 60 units NPH insulin daily which she had neglected to take for several weeks before admission. She had noted polydipsia, polyuria, and loss of weight. There was no history of sinusitis. In 1957, she had had a sub-total thyroidectomy for hyperthyroidism.

Examination

She was disorientated, and showed ptosis of the left eyelid and proptosis of the left eye. Blood pressure 120/80 mg. Hg, pulse 100/min., temperature 102°F, respiration 45/min. The left infraorbital area was hot, tender, and fluctuant. The right eye was normal. The visual acuity in the left eye without correction was 20/200. In addition to ptosis, proptosis, and lid oedema, the patient had total ophthalmoplegia, chemosis, loss of corneal reflex, and a 5-mm. pupil which reacted more briskly consensually than directly. The fundi were normal. There was left facial palsy and hemianaesthesia. The left portion of the hard palate was tender and swollen and the left nasal cavity revealed a black eschar and purulent discharge. There was slight nuchal rigidity. All other findings of the physical examination were normal.

Laboratory studies

WBC-16,800/mm.³ with 75 per cent. polymorphonuclear cells, 16 per cent. lymphocytes and 6 per cent. monocytes; haematocrit 31 per cent.; blood sugar 250 mg./100 ml.; blood urea nitrogen 18 mg./100 ml. Urine analysis revealed 4 sugar, 4 acetone, 1 protein, 8-10 WBC/HPF and a specific gravity of 1.024. Spinal fluid was slightly cloudy with a normal opening pressure of 90 mm./H₂O and contained 350 WBC/mm.³, of which 85 per cent. were neutrophils. Cultures for bacteria and fungi were negative. Fungus mycelia were not found in the nasal scrapings. X rays revealed clouding of the left maxillary and ethmoid sinuses.

Hospital course

Mucormycosis was strongly suspected but antifungus therapy was withheld pending culture studies. 40 million units penicillin G daily were started intravenously because of possible pyogenic infection. 300 units regular insulin and infusion of 500 ml. 0.45 N saline solution were given over an 8-hour period. The patient subsequently required 60 units NPH insulin daily to control the diabetes.

Left maxillary antrotomy was performed the day after admission and culture and microscopical examination of the biopsy specimen were negative for fungi. Repeat lumbar puncture showed xanthochromic cerebrospinal fluid and 250 WBC/mm.³. The temperature remained at 102°F. After 4 days without improvement, it was decided to treat the patient on the basis of a clinical diagnosis of mucormycosis. Penicillin was discontinued, and amphotericin B, 0.4 mg./kg. in 500 ml. 5 per cent. glucose and distilled water containing 10 mg. sodium heparin were started. The dose was increased by 0.2 mg./kg. every second day until a peak dose of 1.2 mg./kg. was reached. This dose was given on alternate days until a total dose of 2 g. was reached. The drug was administered over an 8-hour period. 10 gr. aspirin and 40 mg. diphenhydramine were given orally 30 minutes before the infusion. The patient tolerated therapy well except for initial fever and chills. The haematocrit fell to 22 per cent. on day 30 and she was given blood transfusions.

On the 8th day after admission, the patient had no perception of light in the left eye. The left pupil was fixed at 5 mm. and the fundus examination showed occlusion of the central retinal artery.

On the 10th day, a left ethmoidectomy, a sphenoidectomy, and a Caldwell-Luc procedure were performed. Histological section of the tissue now showed fragmented, non-septate hyphae, consistent with a diagnosis of mucormycosis. Culture for fungi on Sabouraud's media was again negative.

Skull x rays, electroencephalogram, brain scan, cerebrospinal fluid, and intravenous pyelogram were normal at this time. Additional treatment included daily local irrigation of the sinuses with 1 mg./mm. amphotericin B.

Throughout the remainder of her stay in hospital she remained afebrile and the neurological findings remained unchanged. Culture of the sinus drainage failed to demonstrate fungi. She received a total dose of 1,960 mg. amphotericin B in 80 days, during which renal function was depressed but returned to pre-treatment levels after cessation of therapy.

Follow-up

13 months after her discharge from hospital, the patient showed no evidence of recurrence of the disease. Ocular findings included proptosis, ptosis, and blindness of the left eye (Fig. 3). The facial palsy cleared up and she regained slight function of the inferior rectus muscle. The diabetes is controlled by 40 units NPH insulin daily.

FIG. 3 Case 2, showing complete ptosis of left lid

Discussion

Mucormycosis should be suspected in any diabetic patient with ophthalmoplegia, ptosis, proptosis, and neurological signs and symptoms of meningoencephalitis. A biopsy should be taken of any accessible lesion and a search made for the hyphae. Cultures of scraping or biopsy material on Sabouraud's media should be done. The fungus produces a luxuriant, fluffy, white filamentary colony growth in 2 to 3 days which turns dark tan a few days later. Blood may be cultured for fungi although this has been of little value in the past. A positive skin test to autogenous *Rhizopus* has been reported in mucormycosis (Miller, Giddens, and Foster, 1957).

Treatment is directed towards control of diabetes mellitus or other underlying disease. The continued use of steroids and antibiotics should be re-evaluated. While the majority of fatal cases were not treated with anti-fungal drugs, all but three (Baker, 1957; Muresan, 1960; Wasserman, Sheils, and Sporn, 1961) of the seventeen reported survivors did receive these agents. Thus the various antimycotic drugs and autogenous vaccine desensitization are potentially valuable when given early in the disease. Drugs may fail to reach the organisms because of vascular thrombosis in the lesions and anticoagulants and topical drug administration have therefore been suggested. Excision of localized lesions when evident and surgical debridement must be considered.

Ginsberg, Spaulding, and Laing (1966) have noted that cerebro-mucormycosis involves the left side more frequently than the right; this observation is interesting but as yet unexplained. As noted, both patients presented in this paper had involvement of the left eye.

Forced duction tests were performed on the affected eyes of both patients reported in this paper. In each case, the globe moved easily and with no resistance, in all directions (Fig. 4, opposite). This suggests that the limitation of eye movement was due not to mechanical restriction within the orbit but rather to neurological involvement.

FIG. 4 Case 2, showing limitation of elevation. Insert, showing negative forced duction test

A satisfactory cosmetic result was achieved in Case 1 with the use of a scleral contact lens with ridges which provided support to the upper lid. In Case 2, it is interesting to note that a slight amount of function of the inferior rectus muscle has returned. This has proved to be a disadvantage since the downward rotation of the eye makes the fitting of a scleral lens more difficult.

Summary

Two cases of cerebro-mucormycosis in diabetic patients are presented. Both were treated with systemic and local amphotericin B resulting in eradication of the infection and survival of the patient. Only seventeen cases of survival from this disease have previously been reported. Ocular findings in the course of the disease and on long-term follow-up are described.

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