Orbitofacial mucormycosis with unusual pathological features*

DANIEL M. ALBERT,¹ ROBERT L. LESSER,² ROBERT C. CYKIERT,² AND Z. NICHOLAS ZAKOV¹

From the ¹Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, and ²Yale University School of Medicine, New Haven, Connecticut, USA

SUMMARY A 52-year-old man with mild diabetes and acute stem cell leukaemia developed an orbitofacial mucormycosis. Cultures showed the fungus to be *Rhizopus oryzae*. Vigorous treatment with amphotericin B and with other bactericidal and bacteriostatic antibiotics for a concurrent sepsis failed to suppress the infections, and the patient died. On post-mortem examination characteristic haematoxylin-staining, broad, aseptate fungal hyphae were found in the right eye, orbit, and lung. A striking and unusual feature of this case is the presence of brightly birefringent crystals within the severely degenerated eye. These were found by histochemical staining and x-ray diffraction studies to be calcium salts of fatty acids, apparently liberated from necrotic adipose tissue of the orbit.

Mucormycosis, or phycomycosis, is an infection caused by one of a variety of fungi belonging to the class *Phycomycetes*. Although these fungi are usually saprophytic and ubiquitous in nature, they can cause serious and rapidly fatal infections in man. Usually the patients who manifest this infection have a predisposing debilitating condition, among the most common of which are diabetes with acidosis, diarrhoea and dehydration, renal failure, cirrhosis, leukaemia or other lymphoproliferative disorders, and severe burns. In addition steroids, antibiotics, and cytotoxic agents have been strongly implicated both clinically and experimentally as predisposing agents for this infection. Excellent reviews of this subject are available (Hutter, 1959; McBride *et al.*, 1960; Ferry, 1960; Gass, 1961a; Gass, 1961b; Straatsma *et al.*, 1962; François and Rysselaere, 1972; Schwartz, 1977).

Case report

A 52-year-old white male with acute stem cell leukaemia developed a small, dark, gangrenous-

looking lesion in his right superior gingiva. One month prior to this admission he had been admitted to another hospital for evaluation of severe low back pain, the onset of which followed lifting a heavy load. Medical and neurological examinations at that time were within normal limits. Laboratory studies including complete and differential blood count, serum electrolytes, liver function tests, and acid phosphatase were within normal limits. A diagnosis of diabetes mellitus was made on the basis of raised fasting serum glucose and abnormal glucose tolerance test. Radiological examinations at the time of the first admission were within normal limits, with the exception of a possible ruptured lumbar disc. The diabetes was controlled by diet alone, and the patient was discharged on analgesics 1 week after admission.

At the time of the second admission the patient complained of persistent low back pain, loss of appetite, weight loss, and general malaise. Positive findings on physical examination included a palpable spleen, mild abdominal distension, and highly tympanic bowel sounds. A complete blood count revealed haemoglobin of 11.2 g/dl, a white blood count of $22 \times 10^9/l$ composed almost entirely of blast cells of stem cell or myeloblastic origin, and a platelet count of $98 \times 10^9/l$. A diagnosis of acute stem cell leukaemia was made. Other laboratory studies and radiological examinations were within normal limits.

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Correspondence to Dr Daniel M. Albert, Howe Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114, USA

Fig. 1 Appearance of the patient with right orbitofacial mucormycosis

The patient was kept in isolation and was followed up with frequent peripheral and bone marrow smears. Treatment with a combination of thioguanine and cytosine arabinoside eventually led to anaplastic marrow and necessitated platelet and white blood cell transfusions.

Three weeks after the second admission the gingival lesion developed; within days it had spread to the cheek and soon involved the entire right side of the face (Fig. 1). Numerous attempts at bacterial culture from this widespread lesion were negative. Biopsy of the lesion showed numerous fungi with broad septate hyphae embedded in a matrix of chronic inflammatory cells and necrotic tissue. A culture of the fungus from the facial lesion was identified as *Rhizopus oryzae*. Treatment with intravenous amphotericin B was begun.

An ophthalmological examination was done about 2 weeks after the development of facial mucormycosis. It showed that vision in the right eye was of no light perception and in the left eye was 6/12 (20/40) with best correction. The right periorbital area was necrotic and indurated. The right eye was proptosed 6 mm, and no extraocular movements could be elicited. Manipulation of the right lids was done with difficulty because of pain and caused some bleeding. The cornea was ulcerated; the conjunctiva of the right eye showed severe injection. The right eye was softer to palpation than the left. On slit-lamp biomicroscopy of the right eye corneal ulceration was evident; the anterior chamber was deep, and no hypopyon was seen. Findings on slit-lamp biomicroscopy of the left eye were within

normal limits. The iris, lens, and anterior vitreous body appeared normal on the right. The view of the right fundus was hazy, but no discrete vitreous or retinal lesions were seen. The overall impression was that of a right eye with no light perception owing to a phycomycosis of the right face and orbit. A right cavernous sinus thrombosis was highly suspected. Results of examination of the left eye were within normal limits.

Although treatment with amphotericin B seemed to prevent further extension of the facial lesion, the patient soon developed a partial atelectasis of the right lung, intestinal obstruction, and became septic, with *Escherichia coli* and a *Bacteroides* species being cultured from the blood. Treatment with gentamicin and cephalothin in addition to the amphotericin B did not lead to improvement of the patient's condition. The patient died in septic shock 6 weeks after admission to the hospital and approximately 3 weeks after developing the orbitofacial phycomycosis.

PATHOLOGY

Necropsy revealed a septicaemia, stem cell leukaemia, small bowel perforation with peritonitis and abscess formation, gastric mucosal petechiae, haemorrhagic pyelitis, splenic abscesses, and widespread mucormycosis, with fungi present in the entire right face, orbit, and eye as well as the lung.

Eye pathology (AFIP Accession No. 1546176). The right eye was found to be a necrotic grey-black mass measuring 21×27 mm. It had no identifiable external landmarks and did not transilluminate light. The cornea and pupil could not be identified. The optic nerve was 14 mm long and appeared normal. The globe was opened anteroposteriorly. The ciliary body and lens were not distinguishable. The vitreous was replaced by viscid, mottled material. The retina, choroid, and optic disc could not be identified on gross examination. The sclera was largely absent, but where present, was thickened.

Microscopically the right eye was found to be extremely disorganised, with marked degeneration of all layers (Fig. 2). Only small sections of sclera and optic nerve were intact. The remainder of the globe resembled fibrous and fatty tissues with a diffuse infiltration of strongly hematoxylin-staining long, broad, non-septate hyphae, consistent with a fungus belonging to the class *Phycomycetes* (Fig. 3). Within the globe were many crystals which stained intensely with alizarin red (Fig. 4), and were brightly birefringent when observed under polarised light. These crystals did not stain with hematoxylin and eosin, periodic acid-Schiff (PAS), Gomori methenamine silver (GMS), or von Kossa stain. Johnson's 'bubble test' for calcium oxalate was negative

Fig. 2 Low-power view of right eye, showing extreme destruction (H and E $\times 3.7$)

Fig. 3 Appearance of aseptate fungi typical of *Phycomycetes* (H and E $\times 410$)

(Johnson, 1956). There were a number of foci of chronic inflammation composed of lymphocytes, plasma cells, macrophages, and scarce eosinophils, interspersed with hyphae. Occasional arterioles could be identified which were completely thrombosed by fungi and debris (Fig. 5). The optic nerve was atrophic and free of fungi. A diagnosis of *Rhizopus oryzae* panophthalmitis with degeneration of the globe and deposition of calcium salts of fatty acids was made.

The patient's left eye was grossly normal but microscopically showed early cataractous changes, peripheral retinal cystoid degeneration with schisis, and questionable early optic atrophy.

Discussion

This patient, like almost all patients who develop mucormycosis, was debilitated before infection. He had diabetes and leukaemia, and was being treated with cytotoxic agents for the latter. Thus there were 3 factors strongly predisposing to subsequent mucormycosis infection. His course was unusual in the fact that, although in most cases an orbitofacial mucormycosis originates in the nasal mucosa or paranasal sinuses, our patient had his infection originate in the gingival mucosa. Further, while

Fig. 4 Calcium crystal found within right eye (Alizarin red $\times 400$)

Fig. 5 Blood vessel thrombosed by fungi and debris, right eye (H and E $\times 365$)

most cases of orbital mucormycosis go on to involve the meninges and brain, our patient had no clinical or histological evidence of intracranial involvement.

From an ophthalmological viewpoint the most common feature in mucormycosis is an orbital cellulitis. Many cases of this have been reported (Gregory *et al.*, 1943; LeCompte and Meissner, 1947; Stone, 1950; Martin *et al.*, 1954; Bauer *et al.*, 1955; Harris, 1955; Foushee and Beck, 1956; Johnson, 1956; Baker, 1957; McCall and Strobos, 1957; Bryan *et al.*, 1958; Dwyer and Changus, 1958; Borland, 1959; Burns, 1959; Dolman and Herd, 1959; Faillo *et al.*, 1959; Hutter, 1959; Long and Weiss, 1959; Berk, 1961; Ferry, 1961; Gass, 1961a; Gass, 1961b; Hoagland *et al.*, 1961; Rabin *et al.*, 1961; Wasserman *et al.*, 1961; Bank *et al.*, 1962; Straatsma *et al.*, 1962; Lubbe, 1964; Lincoff *et al.*, 1965; Parmentier *et al.*, 1965; Ginsberg *et al.*, 1966; Tomiyasu and Baker, 1966; Baum, 1967; Blodi *et al.*, 1969; Fleckner and Ginsberg, 1969; Anco and Iriya, 1970; Best *et al.*, 1971; Vergez *et al.*, 1971; Georgiades *et al.*, 1972; Bullock *et al.*, 1974). Intraocular involvement in mucormycosis, diagnosed by the presence of fungi within the globe, is less common but has been reported (Gregory *et al.*, 1943; Martin *et al.*, 1954; Viers and Davis, 1958; Borland, 1959; Smith and Kirchner, 1958; Ferry, 1961; Wasserman *et al.*, 1961; Ginsberg *et al.*, 1966; Tomiyasu and Baker, 1966; Best *et al.*, 1971). From our own experience as well as from a review of the literature this appears to be an extreme case of destruction of the eye by mucormycosis. One possible sequence of events in this diabetic patient

may have been severe ketosis on terminal illness with deviation of metabolism to deposit fatty acids with subsequent calcification in this deposit. However, the rapid course which our patient had makes this an unlikely possibility.

It should be noted that 1 week before the patient's death an ophthalmological examination of the affected eye revealed corneal ulceration but an essentially normal anterior chamber, iris, and lens. No lesions of the vitreous and retina were noted. One week later pathological examination of the same eye after the patient's death showed these structures to be completely destroyed and unrecognisable. This demonstrates the rapidity of ocular destruction by this fungus even while the patient was treated by systemic amphotericin B. The question might be raised whether amphotericin B would have been of value in preventing intraocular damage if given intracamerally and intravitreously as well as intravenously.

Of note in the histological findings was the presence of birefringent crystals within the degenerated eye. These crystals were not found elsewhere at necropsy. No similar report of such crystals occurring in a similar case could be found in our review of the literature. Possibly this finding was overlooked in previously reported cases, and we would recommend examining any tissue infected by this fungus with polarised light. Although Wadsworth (1951) mentioned that 'numerous cholesterol crystals' were embedded in a fibrous tissue scar behind the macula in an eye destroyed by mucormycosis, a careful review of his tissue sections by Straatsma *et al.* (1962) revealed that what were initially thought to be fungi within the eye were probably mineralised retinal capillaries.

Finally, it should be noted that the fungi in our patient are seen more easily with haematoxylin than with GMS, the stain usually used to demonstrate fungus. This confirms the previous finding of Straatsma *et al.* (1962) that these fungi had a greater affinity for haematoxylin than for PAS, GMS, or Grindley's stain.

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