POST-OPERATIVE MYCOTIC ENDOPHTHALMITIS DIAGNOSED CLINICALLY AND VERIFIED HISTOPATHOLOGICALLY*†

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THE clinical and histopathological features of exogenous intra-ocular fungus infections have recently been the subject of a review (Fine and Zimmerman, 1959) based upon cases filed in the Registry of Ophthalmic Pathology, special attention being directed to those which appeared as complications of intra-ocular surgery. As a result there emerged a rather distinctive clinico-pathological picture: in contrast with other post-traumatic infections, mycotic endophthalmitis develops not immediately, but after a latent period of several days to many months. Its initial symptoms may appear suddenly but the subsequent evolution of the endophthalmitis is slowly progressive. Typically there is a relatively well-localized abscess in the anterior segment and light projection remains good for many weeks. Treatment with corticosteroid and antibacterial preparations often seems to be beneficial, but only for brief periods, after which symptoms return, the disease progresses, and enucleation is required. The ocular pain which this disease produces is believed to be the result of the inflammatory reaction itself for there is rarely a secondary glaucoma.

As our review of the Registry cases was being completed and the distinctive clinical features of this infection were becoming apparent, an opportunity presented itself to observe a patient with the characteristic clinical picture. This provided an occasion to put to a test the diagnostic significance of the distinctive features just described. It is the purpose of this presentation to report the clinical and pathological observations made in this case.

Case Report

An adult white woman was found to have a visual acuity of 20/70 in the right eye and a mature cataract with good light projection in the left eye. Examination 4 months later showed a decrease in the visual acuity in the right eye to 5/400 with sustained good light projection in the left eye.

A round-pupil intracapsular extraction of the left lens was done under local anaesthesia. There were no operative complications and the early post-operative course was uneventful. Furacin ophthalmic ointment had been used twice daily for one week before surgery. No steroids were used. Examination 18 days later revealed an excellent result. Visual acuity in the aphakic eye with a temporary lens (+13 D sph.) was 20/40. Five months after the

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lens extraction, the visual acuity was 20/20, and the patient was given her permanent correction. The visual acuity remained excellent until 8 months after the operation, when there was a sudden onset of iritis in the aphakic left eye. Visual acuity dropped to 20/60 and there was a pronounced flare with cells in the anterior chamber. The iris appeared to be adherent to the vitreous face inferiorly and the fundus could not be seen satisfactorily. Treatment with 2 per cent. atropine, Meticorten (5 mg. five times daily), and topical cortisone was begun immediately. After 3 weeks some improvement was noted and there were fewer cells in the anterior chamber. The congestion had largely cleared and the same medications were continued. Towards the end of the 4th week of uveitis, the flare had almost cleared but inflammatory deposits were still present in the vitreous. Medications were not changed. However, one month after its onset, the uveitis became more intense and hypopyon was observed. The patient was hospitalized for ACTH therapy.

A week of hospitalization, continued therapy with ACTH (20 units daily for 5 days) and a short course of chloramphenicol produced no improvement. By this time a pupillary membrane had formed and filled the pupillary space. It appeared to involve the anterior layers of the vitreous but there was no evidence of iris *bombé*. A large whitish mass could be seen through the rather translucent membrane lying behind the lower iris leaf. No other details of the vitreous were discernible through the membrane. Light projection was excellent and the globe seemed to have normal tension on palpation.

It was at this time that the patient was first seen in consultation by one of us (B.S.F.). In view of the clinico-pathological picture which was considered so typical of post-operative mycotic endophthalmitis, a diagnosis of fungus infection was made. Mycostatin was started by mouth (one million units three times daily), and injected through clear cornea, through the tenacious, rubbery pupillary membrane, and into the whitish mass behind the lower iris leaf.* There was moderately severe pain during the night, but this slowly subsided and the eye became moderately injected (Fig. 1).

FIG. 1.—12 hours after the initial introduction of Mycostatin into the retro-iridic mass, the eye appears essentially the same as before, except for the perilimbal hyperaemia. The localized inflammatory mass, observed here through a translucent pupillary membrane, fills the lower half of the posterior chamber.

A second injection was given into the same site 36 hours after the first, but this time the pupillary membrane seemed dry and brittle and it collapsed when it was perforated by the needle. Rupture of the pupillary membrane permitted the white mass to rise into

*Experiments carried out in our laboratories have indicated that a suspension of Mycostatin (Squibb brand of Nystatin) in a dose of 200u in 0.1 ml. physiological saline is tolerated by the normal albino rabbit eye when given as a single injection by the direct intravitreal route. A second injection 36 hrs later results in the formation of vitreous strands, minute haemorrhages about the optic disc, glial proliferation, exudation of eosinophils and mononuclear cells about the nerve head, the retina, and into the anterior vitreous layers, and some posterior subcapsular degeneration of the lens.

the pupil and a small amount of exudate spread into the anterior chamber. Light projection was still good. The patient again experienced moderately severe pain during the night. By morning the anterior chamber had reformed. A small blood clot present on the iris at 12 o'clock extended to the white purulent exudate which filled the lower half of the pupil. A small amount of this white material lay on the iris leaf temporally, extending to the site of paracentesis (Fig. 2).

FIG. 2.—24 hours after the second intra-ocular instillation of Mycostatin and 60 hours after the initial injection, the exudate extends from the posterior chamber through the pupil and onto the anterior surface of the iris, along a curvilinear path (arrow), to the site of paracentesis.

Light projection was poor in the lower sectors but was still good in the upper. 48 hours later the eye was markedly inflamed, with early superficial corneal vascularization at the limbus and moderate corneal oedema. The pupil was almost filled with a yellowish-white mass. Tension was normal on palpation. Therapy with oral Mycostatin and potassium iodide was continued for almost 2 weeks but, because of chronic pain, progressive endophthalmitis, and some loss of appetite and weight, the eye was enucleated. This was done 2 months after the onset of uveitis and 10 months after the cataract extraction. Unfortunately the eye was fixed in formalin and cultures were not obtained.

Since enucleation the patient has been in good health and there has been no other evidence of mycotic infection.

Laboratory Examination

Examination of the eye in the laboratory revealed it to be normotensive and of normal size. The globe did not transilluminate. The anterior chamber appeared shallow, the peripheral iris grey, and the pupil filled with purulent exudate which protruded into the anterior chamber. The eye was opened in the vertical plane.

The anterior chamber was almost filled by yellowish-white exudate with a mass occupying the lens fossa and the anterior vitreous. The remainder of the vitreous was clouded and gelatinous in consistency anteriorly. The retina was separated from the choroid by a cloudy gelatinous exudate. The choroid was in normal position posteriorly but widely separated from the sclera peripherally. A whitish semi-gelatinous exudate was present in the suprachoroidea from the equator to the scleral spur (Fig. 3, overleaf).

Microscopically the limbus was congested and densely infiltrated with mononuclear inflammatory cells. There was vascularization of the peripheral corneal stroma, especially adjacent to the healing corneal scar superiorly. The central corneal stroma was infiltrated with polymorphonuclear leucocytes, most intensely in the posterior layers. Much of the anterior chamber was filled with pus, which extended through the pupil from several large abscesses in the anterior vitreous.

FIG. 3.—Enucleated eye opened in the vertical plane revealing a mass of dense white purulent exudate in the vitreous anteriorly and in the anterior chamber. Serous exudate fills the suprachoroida anteriorly where the ciliary body and peripheral choroid are detached; similar non-purulent exudate occupies the space beneath the detached retina.

The iris vessels were engorged, the stroma was filled with proteinaceous exudate, and the anterior layers, particularly of the upper iris leaf, were necrotic. The lens was absent.

Peripheral to the large central vitreous abscesses were smaller, discrete micro-abscesses overlying the peripheral retina and ciliary body (Fig. 4, opposite). Using the staining procedures recommended by Gridley (1953) and Grocott (1955), non-pigmented, septate, occasionally branching hyphae of a fungus averaging 2 microns in width were readily seen (Fig. 5, overleaf). No bacteria could be demonstrated with Gram stains. The posterior vitreous cavity, the peripheral subretinal space, and the peripheral choroid and ciliary body were all filled with proteinaceous exudate. The oedematous ciliary body was dislocated forward on the scleral spur.

Peripherally, pericipient cells and nerve fibres of the retina exhibited degenerative changes, but posteriorly about the nerve head the retina remained intact. There was perivascular cuffing of retinal vessels with lymphocytes and a number of polymorphonuclear leucocytes were present on the anterior retinal surface.

Comment

The foregoing clinical case was recognized as a probable post-operative intra-ocular fungus infection 9 months after cataract extraction and 38 days after the onset of uveitis. Treatment with antibiotics and steroids for 38 days had produced only transient and incomplete control of the uveitis. An attempt was then made to arrest the infection with oral administration and intravitreal injections of Mycostatin suspension, but the infection was far beyond control by the dosage used. This intravitreal dosage had proved successful in limiting early *Aspergillus* infections in experimental animals when the two important factors of size of inoculum and time of institution of specific therapy were under more rigid control.

FIG. 4.—There is intense infiltration of the detached ciliary body and iris by acute and chronic inflammatory cells. In addition to the diffuse polymorphonuclear leucocytic invasion of the anterior vitreous, there are several discrete micro-abscesses (arrows). The scar of the surgical incision may be noted at the upper limbus. Haematoxylin and eosin. $\times 3$.

However, this case does serve to illustrate the typical appearance of such an infection and to point out the characteristic clinical history that accompanies it. One must also consider in the differential diagnosis the possibility of lens-induced anterior segment inflammation. However, in cases of successful intracapsular lens extraction, phakogenic endophthalmitis would be most unlikely.

Delayed bacterial infections complicating filtering scars or glaucoma surgery are much more fulminating; they generally lead to rapid loss of vision and diffuse inflammation throughout the entire anterior chamber and vitreous.

We can only speculate as to the pathogenesis of these post-operative fungus infections, and this has already been done elsewhere (Fine and Zimmerman, 1959). Suffice it to say that we believe fungal elements are introduced into the eye at the time of intra-ocular surgery and that they may grow slowly or even remain dormant for long periods before provoking an inflammatory response. In this connexion we may observe that some of the medications employed during intra-ocular surgery, at the hospital where this patient's

FIG. 5.—Branching septate mycelial structures morphologically consistent with those of species of *Aspergillus*, *Cephalosporium*, and many other ubiquitous saprophytes. Gridley stain. $\times 1,200$.

cataract extraction was performed, were contained in conventional dropper bottles to which no preservatives (e.g. chlorbutanol or benzalkonium chloride) had been added. That hospital, like many others, has now abandoned use of the dropper bottles and has switched to disposable sterile containers for single patient use.

Summary

Exogenous intra-ocular fungus infections, which seemingly are on the increase, produce a rather distinctive clinico-pathological picture. We have reported here a typical case which appeared about 8 months after an uneventful intracapsular cataract extraction but which was not recognized for what it was until the uveitis had been treated with antibiotics and corticosteroids for over a month. An attempt to control the infection with the antifungal agent Mycostatin was without success. The infection was believed to have been too far advanced to have given the Mycostatin a fair trial. Prophylaxis is still all-important and deserves continued emphasis.

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