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Nocardial endophthalmitis: report of two cases studied histopathologically

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SUMMARY We report two cases of nocardial endophthalmitis. Case 1 is a 66-year-old man whose left eye was enucleated about one month after onset of decreased vision. Ophthalmoscopic examination disclosed multiple choroidal masses. Six weeks before the onset of ocular manifestations he had undergone a prolonged carotid endarterectomy with intraoperative complications. The source of the ocular infection was probably exogenous. Case 2 is a 49-year-old woman who had systemic sclerosis (scleroderma) with severe pulmonary insufficiency. She had received moderate doses of corticosteroids. Seventeen months after initiation of therapy she developed ocular manifestations leading to enucleation of the eye one month later. Histopathologically, the enucleated eyes in both cases showed numerous branching, Gram-positive, filamentous organisms involving mainly the plane of Bruch's membrane and the subretinal space. The nosological and microbiological aspects of nocardiosis are reviewed.

Although nocardiosis was first described in Europe, all reported cases of nocardial endophthalmitis have appeared in the American literature except for a recently published one from Thailand.[1]

In this paper we describe our experience with two cases of nocardial endophthalmitis.

Case reports

CASE 1

A 66-year-old white man, a resident of Texas, consulted an ophthalmologist on 12 November 1979 because of decreasing vision in his left eye for the preceding two weeks. Corrected visual acuity in the left eye was 20/200.A mild anterior uveitis was present in that eye. On ophthalmoscopic examination 'multiple metastatic tumours of the choroid' were described. A comprehensive examination was undertaken in a search for a primary tumour elsewhere in the body, but the results of these studies were unremarkable except for detection of a 'testicular mass'. The patient was referred to a urologist but meanwhile had developed secondary glaucoma with forward displacement of the lens-iris diaphragm, and the eye was enucleated in December 1979.

On *gross examination* the chamber angle was occluded by peripheral anterior synechias and the lens-iris diaphragm was displaced anteriorly. The lens was cataractous. The vitreous body was yellow and was markedly condensed anteriorly by a funnel-shaped haemorrhagic retinal detachment. The vitreous body was generally cloudy and contained clumps of cellular material. Underlying the detached retina, both nasally and temporally, were several discrete white masses (Fig. 1) some of which arose from the inner aspect of the choroid and elevated the retinal pigment epithelium. The subretinal space contained an extensive exudate that was organised in some areas.

On *microscopic examination* the iris showed neovascularisation, and the chamber angle was occluded on one side by peripheral anterior synechia formation. There was a scattering of neutrophils in the posterior chamber and along the surface of the ciliary processes. The vitreous body contained fibrin and a moderate number of neutrophils. The retina was totally detached; the subretinal space contained a

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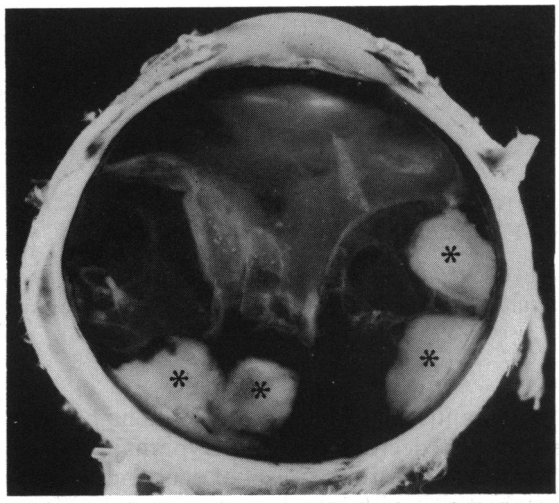

Fig. 1 *Case 1. Gross appearance of one calotte, depicting a bullous retinal detachment. Multiple detachments of the retinal pigment epithelium with greyish white mounds of coagulated proteinaceous exudate (asterisks) are noted.*

purulent exudate and proteinaceous material. There were multiple detachments of the retinal pigment epithelium. In those areas the retinal pigment epithelium was necrotic and was abruptly elevated by large collections of neutrophils and proteinaceous exudate (Fig. 2). The choroid was thickened and oedematous. An extensive infiltrate of neutrophils was located throughout its inner layers. Multiple microabscesses were present along the inner portion of the choroid. The inflammatory infiltrate extended throughout the sclera in some places. The episclera was thickened with areas of granulation tissue, capillary proliferation, and foci of inflammatory cells. Gram stains revealed numerous branching, Gram-positive, filamentous organisms that were located chiefly along the plane of Bruch's membrane and extended into both the subretinal space and the inner portion of the choroid (Fig. 3). The organisms were acid-fast and were morphologically highly characteristic of *Nocardia asteroides*.

On establishment of the diagnosis of nocardial endophthalmitis the patient's past medical history was investigated further. Six weeks before the onset of ocular symptoms he had undergone carotid endarterectomy. The procedure was prolonged, requiring several hours for completion, because of rupture of the posterior wall of the artery. A search was made in an effort to find a primary focus of infection. A bone scan was normal, as were the results of chest roentgenography and intravenous nephrotomography. Urological examination revealed that the epididymis was thickened bilaterally, with globular enlargement of both tails. The masses were distinctly separate from the testes, which appeared normal. The clinical impression was of chronic epididymitis. The prostate gland was described as being slightly lumpy but otherwise unremarkable. A resection of the enlarged right epididymis was performed. Histopathological examination disclosed a chronic epididymitis of undetermined cause. Further follow-up studies four months after enucleation of the eye disclosed no evidence of localised or disseminated nocardiosis.

CASE 2

In February 1983 a 49-year-old white woman consulted a physician because of increasing dyspnoea on

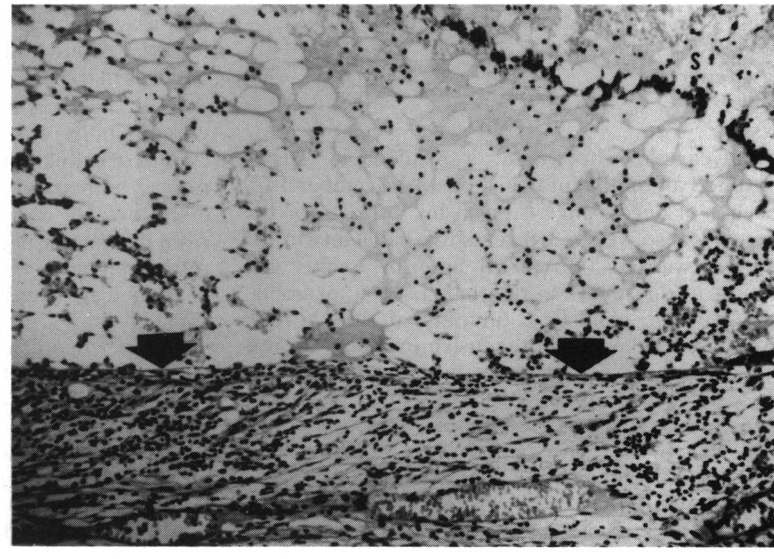

Fig. 2 *Case 1. Proteinaceous exudate containing numerous neutrophils is interposed between the elevated, detached retinal pigment epithelium (upper right corner of field) and the underlying intact Bruch's membrane (arrowheads). The choroid displays a diffuse lymphocytic infiltrate.* S: *Subretinal space. Haematoxylin and eosin.*

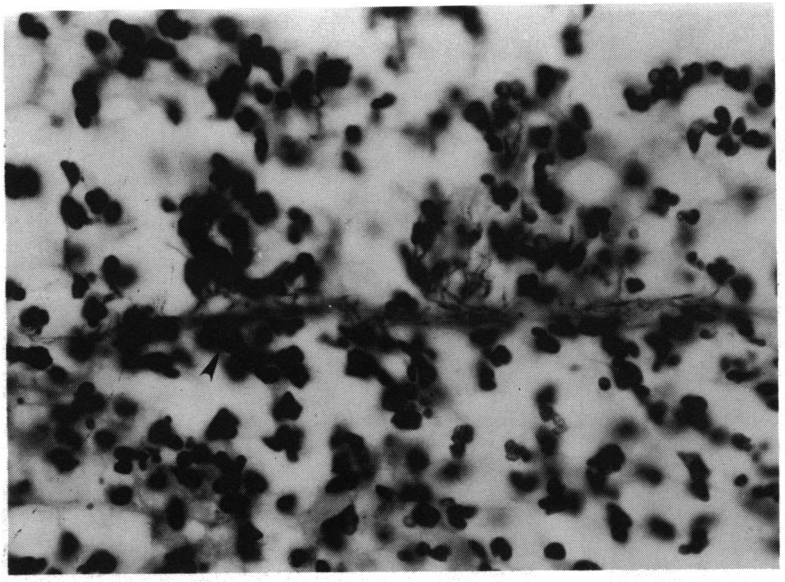

Fig. 3 *Case 1. Many branching, Gram-positive, filamentous organisms are observed on Bruch's membrane. Some of them extend superiorly into the subretinal space. Only a few organisms (arrowhead) are observed in the inner choroid. The latter contains a prominent neutrophilic infiltrate. Brown and Hopps stain.*

exertion and a non-productive cough of one year's duration. The patient, who lived in Virginia, had no previous history of pulmonary disease. Chest roentgenograms showed 'diffuse interstitial disease', and physiological testing disclosed considerable reduction of pulmonary function. A biopsy specimen of the lung was obtained at the time of bronchoscopy and demonstrated 'significant increase in fibrous tissue, with some lymphocytes and plasma cells present.' Treatment with prednisone (40 mg per day) was begun in April 1983. This afforded moderate symptomatic improvement over the next few months, but the results of pulmonary function testing did not show objective improvement. By the latter part of 1983 the prednisone had been reduced to 30 mg every other day.

In May 1984 the patient complained of increased dyspnoea on exertion and difficulty in swallowing solid food. Chest roentgenograms showed no change from those seen previously, but pulmonary function tests demonstrated a marked further decline in function. Investigation of her dysphagia included an upper gastrointestinal radiographic series, which showed abnormal oesophageal motility characteristic of that seen in systemic sclerosis (scleroderma). The patient also had tightening of her skin, which appeared glossy. A diagnosis of systemic sclerosis was made on the basis of the dermatological and gastrointestinal findings.

Her prednisone dose was increased to 60 mg per day because of her deteriorating pulmonary status. In September 1984 she was found to have a compression fracture of her seventh thoracic vertebra. At that time she also reported progressive decrease in visual acuity of her left eye, which she had first noted two months previously, and she was referred for ophthalmic examination. Associated symptoms and signs included redness, pain, and photophobia of the left eye. Visual acuity in her asymptomatic right eye was correctable to 20/25. The right eye was normal on detailed ophthalmic examination. With the left eye the patient was unable to perceive light. The left upper and lower eyelids were mildly swollen. The conjunctiva showed chemosis and prominent vascular injection. The left cornea was clear. The anterior chamber showed 3+ flare and cells. The pupil responded to light only consensually. Intraocular pressure was equivalent to 18 mmHg. The vitreous body contained a prominent exudate of cells and protein. Ophthalmoscopic examination disclosed extensive choroidal infiltration, with elevation of the optic nerve head. Multifocal, yellow-white, subretinal nodules were observed. There was an extensive retinal detachment.

Sinus roentgenograms, blood cultures, and a lumbar puncture were normal. B-mode ultrasonography demonstrated a 'total retinal detachment', with solid, homogeneous 'inflammation' of the choroid. Computerised tomography of the intracranial cavity gave a normal picture.

The eye was enucleated on 5 October 1984. We opened the unfixed eye to obtain material for microbiological examination. There was extensive detachment of the retina. The most striking abnormality was the presence of large, yellowish white nodular masses in the subretinal space (Fig. 4). There were scattered, small, retinal and subretinal haemorrhages. The vitreous body was only mildly opacified.

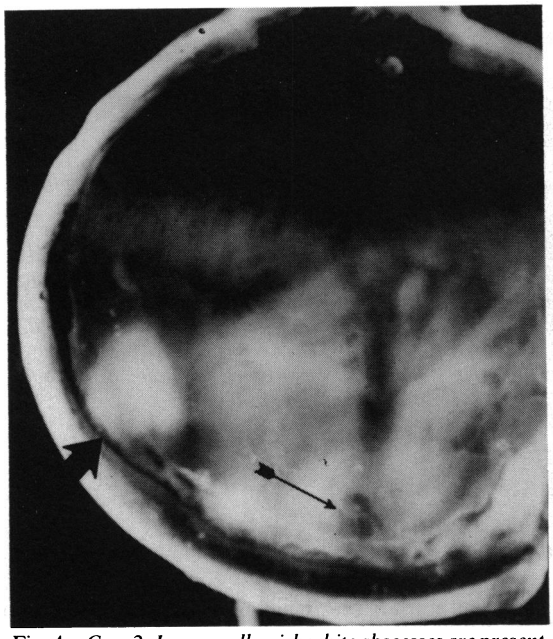

Fig. 4 *Case 2. Large, yellowish white abscesses are present in the subretinal space. The one on the left (heavy arrow) has a nodular configuration. Farther centrally in the field the subretinal abscess formation is more diffuse. There are scattered retinal haemorrhages, one of which is indicated with the fine arrow.*

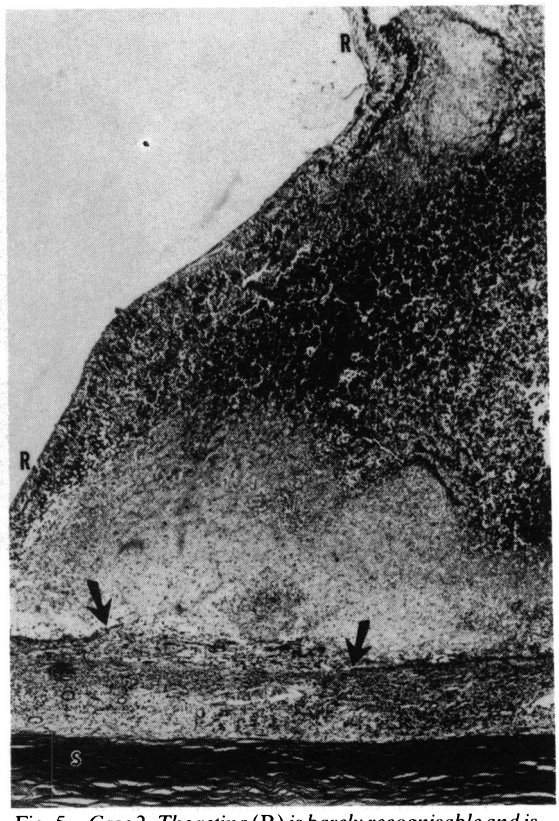

Fig. 5 *Case 2. The retina* (R) *is barely recognisable and is markedly elevated by a suppurative mass in the subretinal space. The choroid is thickened. The retinal pigment epithelium and Bruch's membrane are intact on the right and left sides of the field. But centrally (between the arrows) these structures have been destroyed, permitting confluence of the choroidal inflammatory process with the subretinal abscess.* S: *Sclera. Haematoxylin and eosin.*

On *microscopic examination* the anterior chamber contained a scanty fibrinous exudate, immersed in which were occasional inflammatory cells, chiefly neutrophils. Extensive, narrow, peripheral anterior synechias were present. There was a slight to moderate inflammatory cell infiltrate in the iris, but the ciliary body contained only a light sprinkling of inflammatory cells. The vitreous body contained a mild proteinaceous exudate and a mild to moderate scattered infiltrate of inflammatory cells, chiefly neutrophils. The most striking findings were in the posterior segment. The retina was extensively detached. Where it did remain in place it was sealed by dense scars to the underlying choroid. Throughout much of its extent posteriorly the retina was barely recognisable and was markedly elevated by a suppurative inflammatory mass (Fig. 5) in which neutrophils predominated.

The choroid was diffusely thickened. Particularly in the outer layers of the choroid the inflammatory cell infiltrate consisted chiefly of lymphocytes, plasma cells, and plasmacytoid cells. In the inner portion of the choroid neutrophils were considerably more numerous, and focal areas of the choriocapillaris exhibited abscess formation. In some planes of section the inflammatory features were granulomatous in nature, with many epithelioid cells and giant cells being present, particularly in the inner layers of the choroid (Fig. 6).

Although Bruch's membrane remained intact throughout most of the eye, there were focal areas in which this structure was destroyed, permitting confluence of the inflammatory masses in the choroid and subretinal space (Fig. 5). A Brown-Brenn stain demonstrated Gram-positive, delicate filaments, no more than 1 μm in diameter, which showed prominent branching at right angles.

The organisms were most abundant in the subretinal necrotic inflammatory exudate. None were present in the vitreous body or in the choroid, though organisms were identified within the retinal pigment epithelium, for which they appeared to have a certain avidity. The bacteria were not stained by haematoxylin and eosin, or by the periodic acid Schiff-

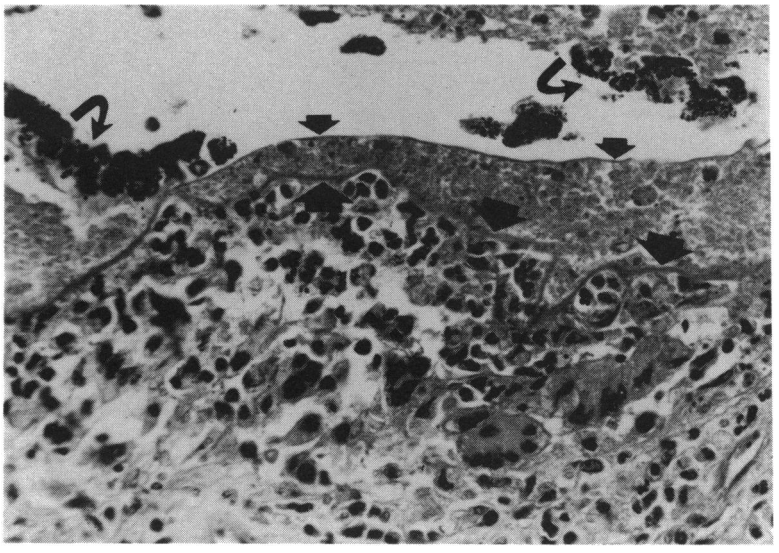

Fig. 6 *Case 2. Bruch's membrane (arrowheads) is split, the two layers being separated by purulent debris. Curved arrows indicate retinal pigment epithelium, which in the upper right part of the field is necrotic and adjoins the abscess in the subretinal space. The innermost layers of the choroid contain a prominent infiltrate of inflammatory cells, most conspicuous of which are several large giant cells on the right side of the field. Haematoxylin and eosin.*

haematoxylin (PAS-H) stain. The Gomori methenamine silver (GMS) stain demonstrated them readily (Fig. 7A), considerably better than did the Brown-Brenn stain. The organisms were also demonstrated extremely well with the van Orden stain (Fig. 7B), and stained weakly with the acid fast technique.

On the basis of these histopathological observations we made a diagnosis of nocardiosis. Several days later we received word from the microbiology laboratory that *Nocardia asteroides* was beginning to grow from material we had obtained from the inflammatory intraocular mass at the time of gross examination.

After we established the diagnosis of nocardiosis the patient's dose of prednisone was tapered to 10 mg every other day. A long-term course of treatment with oral sulphonamides was begun immediately. We borrowed the paraffin block containing lung tissue that had been obtained at the time of bronchoscopy in 1983. In the small tissue sample we found no evidence for systemic sclerosis. Special stains failed to demonstrate any organisms. Follow-up examination in April 1986 disclosed that the patient's health had improved markedly. She had gained 10 lb (4·5 kg) in weight and was feeling much stronger. Pulmonary function studies gave unchanged results, and her right eye showed no change.

Discussion

Nocardiosis is typically caused by *Nocardia asteroides*.[2] The organism is named for the star-like appearance of the colonies on agar and for Edmond Nocard, a French bacteriologist and veterinary pathologist. He isolated a filamentous organism from bovine farcy and in 1889 the name *Nocardia farcinica* was given to it.[2] Bovine farcy is now known to be caused by an unusual strain of mycobacterium that resembles nocardia.[2] It is not known whether the organism originally isolated by Nocard was *Mycobacterium farcinogenes* or what is now classified as *Nocardia asteroides*. The latter was finally identified in 1896 by Blanchard from an organism that Eppinger had called *Cladothrix asteroides* after he isolated it in 1891 from the brain abscess of a patient with systemic nocardiosis.[2]

Nocardia asteroides was formerly thought to be a fungus but is now classified as a bacterium. The organisms are soil borne. They are natural soil saprophytes and are often found in decaying organic matter, such as wet hay or straw. Filamentous branching cells (Fig. 7A) occur during logarithmic phase growth, but these later fragment to small coccobacillary forms (Fig. 7B).[3] The delicate, filamentous organisms are rarely more than 1 μm in diameter and show prominent right-angle branching. The bacteria are diffusely distributed in the purulent exudate of the lesions, thus differing from the filaments of *Actinomyces israelii*, which form granules.[4] *Nocardia asteroides* is not stained by haematoxylin and eosin or by Schiff's periodic acid technique. The organisms are well demonstrated by Gram stains (they are Gram-positive) and by the Gomori methenamine silver stain, provided the time in the silver nitrate solution is increased by about 50%.[4] *Nocardia asteroides* is partially, and weakly, acid-fast by the Ziehl-Neelsen method. Acid-fast stains (particularly the Cross modification to prevent exces-

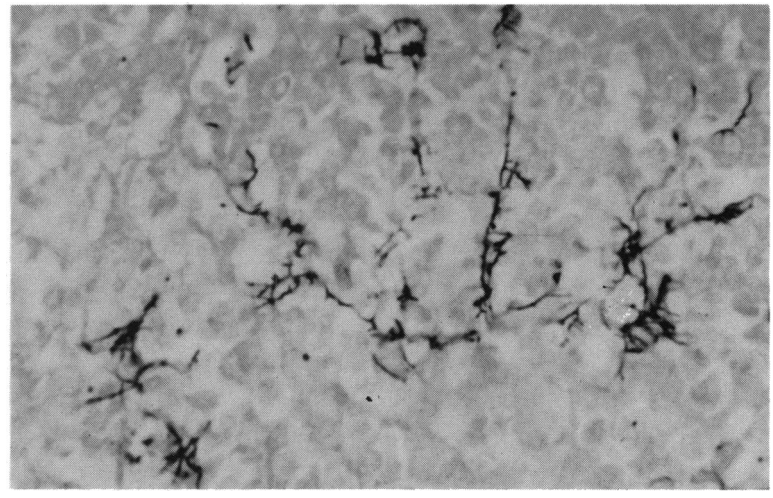

Fig. 7A *Case 2. Branching filamentous organisms in the subretinal abscess. Gomori methenamine silver.*

sive decolorisation) will clearly demonstrate the organism, but its tendency to fragment into coccobacillary forms may cause it to be confused with *Mycobacterium tuberculosis* or atypical mycobacteria.[3,4] The van Orden stain demonstrates the organisms extremely well (Fig. 7B).

The organisms are not fastidious in culture, but they tend to grow slowly. They will grow on virtually any bacterial, fungal, or mycobacterial medium that lacks antibiotics, and will grow within a wide temperature range. Growth of *Nocardia asteroides* is facilitated by 10% carbon dioxide. In pure culture the colonies often grow out after only 48 hours of incubation, but in mixed culture or in primary isolation from clinical material the colonies can take as long as two to four weeks to appear.[2] Unless the organism is suspected, its recognition poses a practical problem, because culture plates tend to be overgrown by microbial contaminants (especially in sputum) and are often discarded after 48 hours, whereas *Nocardia asteroides* may require considerably longer for growth. As a result, the organism is more likely to be identified on media used for mycobacteria or fungi, which are observed for longer periods.[3] In our second case we made the diagnosis of nocardiosis by examining tissue sections before the organism appeared on culture media in the microbiology laboratory.

Nocardiosis is presumed to result from inhalation of airborne bacteria. There is no evidence for spread from infected persons or animals. Although the disease can occur in apparently normal people, it is

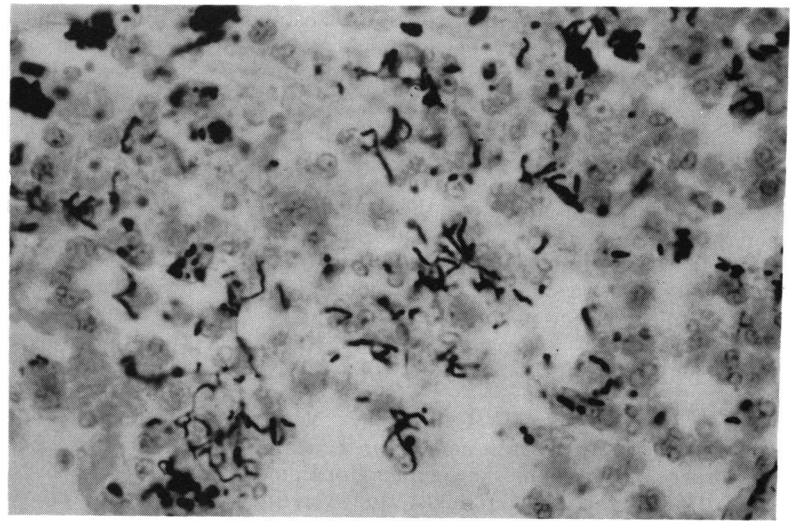

Fig. 7B *Case 2. In another area of the eye the bacteria have forsaken their filamentous growth pattern and have fragmented into small coccobacillary forms. van Orden stain.*

encountered much more commonly in immunosuppressed patients.[2] Nocardiosis appears as a pneumonic process in about 75% of cases. In 25 to 40% of patients there is dissemination to the central nervous system. Other common sites of dissemination include the skin and subcutaneous tissues, pleura and chest wall, kidney, liver, and lymph nodes.[3]

A total of 11 cases[2 5–12] of *endogenous* nocardial endophthalmitis has been reported in the literature. Each of these reports concerns a single patient except the articles by Bullock[2] and by Meyer and coworkers,[6] in both of which two cases of endogenous nocardial endophthalmitis were described. Pathological examination of the eye was carried out in all 11 of these patients except for one of the two patients reported on by Bullock. An unpublished case of endogenous nocardial endophthalmitis (from Chicago) was presented by Robert Levine at the 1979 meeting of the Armed Forces Institute of Pathology Ophthalmic Alumni.[13] All these reports of endogenous nocardial endophthalmitis appeared in the American ophthalmic literature and we are unaware of any such cases that may have been presented at ophthalmic pathology society meetings outside the United States.

Five reports[1 6 14–16] (each involving a single case) of *exogenous* nocardial endophthalmitis following either accidental or surgical penetrating wounds of the eye have been published.

Common features in the other cases of nocardial endophthalmitis that have been examined pathologically are the suppurative and necrotising nature of the inflammatory response in the inner layers of the choroid and in the retina, and the presence of subretinal abscesses. In only one of the reported cases has the inflammatory response assumed a granulomatous quality in some areas.[10] As in our second case, the epithelioid cells and giant cells were most prominent in the inner layers of the choroid and immediately adjacent thereto, in the region of the retinal pigment epithelium and Bruch's membrane.[10] In both of the cases we are reporting the organisms showed a remarkable tendency to grow along Bruch's membrane and seemed to have a peculiar affinity for the retinal pigment epithelium. On reviewing the previously published cases in this regard we find some of them too sparing in detail to permit evaluation of this point. But in at least five of the previously described cases[6 9–12] the authors mentioned the prominent growth of the organisms along Bruch's membrane, often associated with detachments of the retinal pigment epithelium.

Nocardiosis is a systemic disease for which sulphonamides are the treatment of choice. The duration of therapy is poorly standardised, but should be prolonged because relapse is common. In patients with intact host defences treatment should be continued for at least six weeks following clinical recovery. In immunosuppressed patients therapy should be given for at least one year.[3] Reducing the dose, as the clinical situation permits, of any immunosuppressive drugs the patient may be taking is a keystone of management.

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