Endogenous candida endophthalmitis

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Until the early 1970s surgery of the retina consisted almost entirely of the treatment and prevention of rhegmatogenous retinal detachment, ie that of a condition that was unrelated to any other disease in the body. The advent, development and progressive sophistication of pars plana vitrectomy allowed the vitreoretinal surgeon to remove opacities in the vitreous (eg vitreous haemorrhage) and to work on the retinal surface. This enlargement of the surgical repertoire has enabled treatment not only of retinal detachment itself but also of other conditions that were previously inoperable. These conditions are often linked to disease elsewhere in the body bringing the retinal surgeon into contact with other medical disciplines. A good example is provided by the metastatic spread of the fungus *Candida albicans* to the eye and the object of this paper is to report the findings of endogenous ocular infection with this organism in a group of 14 patients encountered at St Thomas' Hospital, London over a 10-year period.

Candida endophthalmitis, an unusual condition, was first recognized in a pathological specimen in 1943[1] and since that time it has been described in a variety of clinical situations[2-7]. However, we have so far encountered candida endophthalmitis in only two main groups of patients, (i) Intravenous drug abusers and (ii) as a consequence to the use of intravenous lines.

In the drug abuser group (four cases) the organisms are introduced as a result of contamination at the time of injection[8]. In one outbreak in Glasgow infected lemon juice used to dissolve heroin by addicts was identified as the culprit[9]. Sporadic outbreaks of these cases were reported through the 1980s but are now much less commonly seen, possibly in response to better habits of drug users, subsequent to the publicity surrounding HIV and hepatitis infections.

Intravenous lines of various types (10 of our cases) and used for long periods of time for parenteral feeding and drug administration (often subsequent to bowel surgery) may result in cutaneous candidal infection around the site of entry of the catheter. The growth of candida is promoted by the administration of massive doses of broad spectrum antibiotics which serve to suppress the normal bacterial flora. Once infection has become established it may spread via the line to the blood stream. All our cases have involved adults, although we have recently seen a case in a premature baby.

We have not yet seen candida endophthalmitis occurring in immunosuppressed groups of patients and even in those cases of candidiasis that have been reported in these patients, ocular involvement is rather unusual[10].

When candidaemia occurs, it might be assumed that many different organs of the body would be affected. However, in only one of our patients who developed cutaneous candia folliculitis of the scalp was any tissue other than the eye involved as a consequence of spread via the blood stream. It is not understood why the eye itself should be singled out, but the recognition of ocular infection due to *Candida albicans* is important as this disease may result in blindness of an affected eye.

The organism typically causes inflammation in the choroid and retina, the vitreous and sometimes the anterior uvea. The ophthalmoscopic appearance is of one or more creamy white usually round and sometimes elevated retinal lesions sited mainly in the posterior pole of the eye and varying in size from small pin point lesions up to two disc diameters in width (see Figure 1). If the vitreous is involved multiple clumps may be formed within it, these clumps (puff balls) are often connected by thread like strands, so that a so-called 'string of pearls' appearance is produced.

Symptoms are produced by inflammation of the various structures involved. A retinal lesion if centred at the macula may result in reduced vision and inflammation of the vitreous and anterior uvea causes blurred vision and sometimes pain.

The diagnosis of ocular candidiasis is mainly dependent on the typical ocular clinical appearances. Serum antibody testing to candida is not diagnostic of ocular infection but the organism may be cultured from the vitreous samples taken at the time of pars plana vitrectomy.

The posterior segment lesions are mainly caused by invasion via the choriocapillaris, crossing the pigment epithelium to affect the retina, although invasion of the eye may also be gained via the retinal vessels. The organism may then pass into the vitreous cavity from the retina. The inflammation that is seen varies not only in its intensity, but also on the distribution within the eye. Thus, in some cases the disease is more or less entirely confined to the retinal structures,

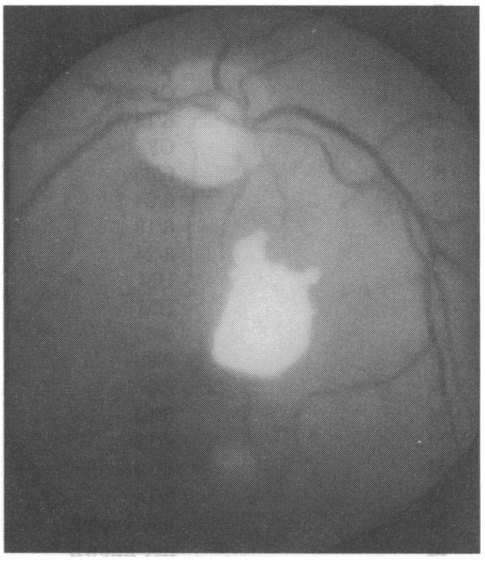

Figure 1. A typical candida lesion of the retina

whereas in others the vitreal element predominates. In others still, a very mixed picture of vitreoretinal disease may be found.

If the organism penetrates the internal limiting membrane of the retina and gains access to the vitreous cavity, it finds not only a good culture medium, but also one with little capacity to clear the organism and one into which drugs may penetrate poorly. The infective process however is insidious unlike for example the fulminating response to a metastatic pyogenic bacteria. The disease produced within the vitreous cavity and at the vitreoretinal interface, depends not only on the nature of the infective process but also on the relationship that the vitreous has to the retina. Thus, the state of the gel at the time of the invasion and of its subsequent response is important. In the elderly patient, the gel may be either already detached or may do so easily after the inflammatory provocation. In the degenerative eye (eg in age, myopia or even in chronic pathological states such as inflammatory eye disease) the hyaloid will separate from the retina. If vitreous detachment does become complete (an event that is by no means an invariable occurrence) the ensuing release of posterior vitreoretinal attachment means that the vitreous will play no further part in influencing disease on the retinal surface. If however, the posterior hyaloid is firmly attached and it is likely to be so in a young patient, then it becomes tethered to the retina by the invading candida mass which actually grows through the posterior hyaloid. The posterior hyaloid fixed in one or more places by inflammatory foci will incompletely detach and then contract, resulting in the severe sequel of traction retinal detachment and preretinal membrane formation (the latter may be vascularized and fused inseparably with the retina)[11].

The progression or lack of it of posterior vitreous detachment, an event that one may suspect clinically but one that is poorly seen, can be difficult to see in eyes with clear media. It is much more so if the vitreous is cloudy and the vitreoretinal relationships difficult to define. Treatment decisions cannot be based on sequential clinical observations of vitreous attachments, although ultrasound examination of the vitreous cavity may be helpful.

Pars plana vitrectomy by removing the vitreous scaffold will prevent the formation of traction retinal detachment[12]. The process of vitrectomy also debulks the vitreous cavity of infected material, confirms the diagnosis if the organism is cultured from the vitreous material, allows the intravitreal injection of antifungal agents, and also allows greater penetration of systemically administered drugs.

Table 1. Patient characteristics

Case	*Age*	*Eye*	*Sex*	*Anterior segment affected*	*Vitreous affected*	*Retina affected*
1	25	L	M	No	No	Yes
2	23	R	M	Yes	Yes	Yes
3	19	R	F	Yes	Yes	Yes
4	26	L	M	No	No	Yes
5	59	L	F	Yes	Yes	Yes
		R	F	No	No	Yes
6	52	R	M	Yes	Yes	Yes
		L	M	Yes	Yes	Yes
7	31	L	F	Yes	Yes	Yes
		R	F	Yes	Yes	Yes
8	42	R	F	Yes	Yes	Yes
9	20	L	M	Yes	Yes	Yes
10	66	L	M	Yes	Yes	Yes
		R	M	No	Yes	No
11	67	L	M	Yes	Yes	Yes
		R	M	Yes	Yes	Yes
12	81	L	F	Yes	Yes	No
		R	F	Yes	No	No
13	60	L	M	Yes	Yes	Yes
		R	M	Yes	Yes	Yes
14	41	R	M	No	No	Yes
		L	M	No	No	Yes

Table 2. Patient characteristics

Case	*Cause*	*Medical (M) or surgical (S) treatment*	*Initial VA*	*Final VA*	*Follow-up*
1	I/V addict	M	6/36	6/9	2/12
2	I/V addict	S	6/36	6/18	1/12
3	I/V addict	S	CF	6/60	1/12
4	I/V addict	M	C/F	C/F	1/12
5	I/V lines	M	CF	6/36	6/12
	I/V lines	M	6/18	6/6	6/12
6	I/V lines	S	CF	6/9	4 years
	I/V lines	S	6/36	6/9	4 years
7	I/V lines	S	6/24	6/6	10 years
	I/V lines	S	6/18	CF	10 years
8	I/V lines	S	6/24	6/6	6/12
9	I/V lines	S	HM	HM	2/12
10	I/V lines	S	HM	HM	6/12
	I/V lines	M	6/60	6/6	6/12
11	I/V lines	S	6/60	6/60	6/12
	I/V lines	S	6/9	HM	6/12
12	I/V lines	M	6/12	6/12	2/12
	I/V lines	M	6/12	6/12	2/12
13	I/V lines	M	6/12	6/18	1/12
	I/V lines	M	6/12	6/18	1/12
14	I/V lines	M	not known	not known	
	I/V lines	M	not known	not known	

Patient data

There were 14 patients (8 male and 6 female). In eight of the patients there was bilateral involvement, ie a total of 22 eyes affected. In seven of the patients with bilateral disease the infection had resulted from intravenous lines, probably reflecting the more prolonged candidaemia associated with intravenous lines, as opposed to the relatively transient candidaemia in the drug abuser cases. Of the 22 eyes, in seven the disease was mainly confined to the retina and in a further four eyes retinal and vitreal involvement was very mild. In 11 there was severe infection of both vitreous and retina.

The main clinical features of these patients are summarized in Tables 1 and 2.

Medical treatment

The patients in this series were treated by a variety of systemic antifungal agents. The use of these drugs changed during the study reflecting our own experience and that of others. The drugs that were used were amphotericin B (this treatment was used in three patients in whom a positive blood culture for candida had been detected) and the other agents were flucytosine, ketoconazole and fluconazole.

Of the 11 eyes treated medically, resolution of the inflammation occurred in seven. In the remaining four eyes, two were clearly deteriorating (before the patient died) and in the remaining two eyes inflammation appeared unchanged (also before the patient died). Visual acuity in the 11 eyes was improved in three, unchanged in six, and there was no follow-up on a further two.

Surgical treatment

Eleven eyes were treated by pars plana vitrectomy using a standard 20 gauge triple port procedure. In these eyes visual acuity was improved in six and unchanged in four and worse in one. The main objective of pars plana vitrectomy (ie the clearing of infected vitreous and preventing retinal detachment) was achieved in seven eyes, but not achieved in four. In the latter cases the vitrectomy was performed too late in two of them (retinal detachment had already occurred) and in a further two cases there was recurrence of intraocular infection subsequent to surgery. In one of these cases this led to retinal detachment and in the other a further vitreous washout was performed to affect resolution.

Discussion

An uncontrolled case series such as this cannot prove the superiority of one therapy over another, although one or two lines of treatment do suggest themselves.

For the retinal phase of the disease where the lesions are accessible from the blood stream systemic antifungals are advised. The use of amphotericin B should be avoided due to its toxicity, especially as these patients may be sick. This substance has the additional disadvantage that it has to be administered by the intravenous route and has a poor intravitreal penetration. It is not indicated for purely ocular disease[13] and should only be considered if there is known or suggestive involvement of other organs.

Antifungals administered by the oral route were flucytosine, ketoconazole, and fluconazole. All of these drugs have the advantage that they penetrate the vitreous cavity[14-16], although they will not halt the vitreoretinal sequelae of the infection if heavy vitreous inflammation has become established. Candidal resistance may occur to flucytosine (particularly if used alone) and ketoconazole has the disadvantage of hepatotoxicity. We currently favour the administration of a combination of flucytosine (up to 10 g per day) and fluconazole (100-200 mg per day).

For mild vitreoretinal disease without much retinal involvement and not causing impairment of the retinal view then either no treatment at all, while the condition is watched or a systemic antifungal combination of fluconazole and flucytosine is advised.

In those patients with heavy infiltration of the vitreous, particularly if young or if retinal lesions can be seen to be extending progressively to involve the vitreous cavity, then pars plana vitrectomy is performed[17]. The simultaneous administration of a systemic antifungal is advised to help any retinal involvement. The use of intravitreal amphotericin B has been advocated to reduce risk of further infection after vitrectomy[18], even though its length of action in the vitrectomized eye is uncertain[19].

There are two main messages from our experience of these cases. We should be aware of those groups that are at risk. In the drug user group the patient will usually present with visual symptoms and the history of intravenous drug addiction and the characteristic ocular signs make the diagnosis obvious. Although drug addicts have enjoyed the benefits of some education of their habits it is likely that these cases will occur sporadically.

Personnel in contact with patients who have contracted the disease as a result of the use of intravenous lines (with the administration of massive doses of broad spectrum antibiotics), have to be aware of the possibility of candidiasis[20,21]. This applies to ophthalmologists who may be asked to see these patients either during or sometime after the illness, intensive care unit workers who should be encouraged to examine the eyes of these patients, and also microbiologists who will not only be involved in the antibiotic management of these patients, but will have the opportunity to suggest an ophthalmological examination, particularly if candida is grown from an indwelling line when it is removed, or if candida infections are identified at other sites.

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