Neovascularisation associated with posterior uveitis

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SUMMARY Twenty-six patients (39 eyes) with retinal neovascularisation associated with ocular inflammation were identified from the retinal vasculitis clinic at St Thomas’s Hospital. Eight patients had sarcoidosis, seven patients Behçet’s disease, and 11 had idiopathic retinal vasculitis. Twenty-three patients had required systemic therapy to control the inflammation and 11 patients received laser photocoagulation. Fluorescein angiography showed significant capillary closure in 15 eyes and diffuse microvascular leakage in the remaining 24 eyes. All patients had posterior vitreous detachment. The visual prognosis was good despite vitreous haemorrhage being the presenting feature in 22 eyes, and the new vessels resolved in 70% of cases. However, laser treatment was followed by a significant increase in cystoid macular oedema (p<0.01). This retrospective study suggests that medical therapy is the first line of treatment in this group of patients. Photocoagulation should be performed when the eye is quiet and should be reserved for patients with recurrent vitreous haemorrhages and significant capillary closure.

Neovascularisation affecting the retina and optic disc is an unusual but a well recognised complication of posterior uveitis.1 2 Such vessels may give rise to vitreous haemorrhage, which contributes significantly to the visual morbidity in this disease. The neovascularisation is associated in some cases with capillary closure on fluorescein angiography, and an angiogenic factor produced by ischaemic retina has been implicated in the pathogenesis.3- 6 However, new vessels may also appear in the eye unassociated with capillary closure, and fluorescein angiography shows diffuse microvascular leakage. In these cases it has been postulated that the neovascularisation is a direct result of the inflammatory process, a causal relationship being inferred from the fact that the vessels tend to regress with adequate control of the inflammation.7 The natural history of this complication has not been adequately studied, and at present therapy is directed towards control of the inflammation with systemic immunosuppressants, with laser photocoagulation being reserved for direct treatment of neovascular fronds, or the ablation of ischaemic areas. We have examined the clinical course of neovascularisation in a retrospective study and the effects of medical and laser treatments.

Patients and methods

The records of 200 patients with posterior uveitis of non-infectious aetiology who attended the Ophthalmology Department at St Thomas’s Hospital over the last 12 years were examined. All patients with diabetes mellitus, systemic vascular disease, or haematological disorders were excluded from the study. Twenty-six patients were identified with retinal neovascularisation due to inflammatory eye disease rather than primary retinal ischaemia. Fifteen patients were male and eleven female. Eleven patients had a diagnosis of idiopathic retinal vasculitis, eight had histologically confirmed sarcoidosis, and seven had Behçet’s disease. The age of the patients ranged from 6 to 45 years (mean 27 years). Patients had been followed up for a period of six months to 12 years (mean 4 years).

At each hospital visit a full ophthalmological assessment had been carried out, with particular note being made of inflammatory activity within the eye, the size and location of sites of neovascularisation and any associated retinal features—for example, periphlebitis, venous occlusion. Fluorescein angiography had been performed in all cases when new vessels were first noted, and follow-up angiograms were performed whenever clinically indicated. Initially patients had been treated with a combination of topical and systemic steroids (daily dose of 60–80
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mg prednisolone daily, tapering as the ocular inflammation was controlled. In some cases other immunosuppressants (azathioprine, chlorambucil, colchicine, and cyclosporin A) had been added to this regimen, either to increase the anti-inflammatory effect or as steroid sparing agents. The indications for laser photocoagulation of peripheral retina in this series were recurrent vitreous haemorrhage, significant capillary closure on fluorescein angiography (at least one quadrant), or neovascularisation which was unaffected by full immunosuppressive treatment. The visual acuity was recorded at the end of follow-up and the reasons for a poor corrected visual acuity (worse than 6/9 Snellen) were documented. Some illustrative case histories are presented below.

Case reports

Case 1

A 16-year-old schoolgirl presented with a two-year history of intermittent poor vision in her right eye. Her general health was good and general examination was unremarkable. Visual acuity was 6/9 in the right eye and 6/5 in the left, and she had moderate posterior uveitis with ++ vitreous cells and some snowballs in both eyes. Two months later her right vision suddenly dropped to counting fingers due to a vitreous haemorrhage which, cleared to reveal new vessels on the right disc (Fig. 1A). Fluorescein angiography showed peripheral microvascular leakage but no capillary closure (Fig. 1B). She was treated with systemic steroids, and despite a further vitreous haemorrhage the new vessels disappeared three years after presentation (Fig. 1C) and her vision returned to 6/5 in each eye.

Comment. This case demonstrates that neovascularisation may regress with control of intraocular inflammation alone.

Fig. 1A Patient 1. Photograph of the right fundus showing extensive new vessels on the optic disc.

Fig. 1B Arteriovenous phase of fluorescein angiogram of the right eye. Diffuse capillary leakage of dye is present, but there is no capillary closure.

Fig. 1C Photograph of the right fundus three years after presentation confirms that the disc new vessels have resolved.
CASE 2
A 34-year-old bricklayer had been diagnosed as a case of Eales' disease 11 years previously. On presentation to St Thomas's in 1976 the visual acuity was counting fingers in the right eye and 6/9 in the left. He had bilateral vitreous haemorrhages. The right fundus could not be seen, but the left showed extensive peripheral retinal new vessels, and capillary closure was demonstrated on fluorescein angiography. He was initially treated with laser photocoagulation to the left eye, but despite this he developed new vessels at the optic disc (Fig. 2A). He was treated with systemic steroids and a further course of laser treatment, and both the disc and peripheral new vessels regressed. However, his visual acuity remained poor at counting fingers in both eyes due to chronic macular oedema (Fig. 2B).

Comment. This case illustrates that combined medical and laser treatment may be required to control neovascularisation but that cystoid macular oedema may develop despite such treatment.

CASE 3
A 28-year-old housewife had suffered from Behçet's disease for 10 years. On admission to St Thomas's Hospital the visual acuity was counting fingers in the right eye and 6/5 in the left. She had had recurrent vitreous haemorrhages in the right eye in which a traction retinal detachment involving the macula was present. An upper nasal branch vein occlusion was present in the left eye (Fig. 3A). New vessels were present on both the optic discs (Fig. 3B, C). She was treated with a reducing dose of systemic steroids, beginning with 60 mg daily, and the new vessels on the left optic disc resolved. However, she recently suffered a left inferotemporal branch vein occlusion involving the macula and has consequently developed more disc new vessels in the left eye (Fig. 3D).

Comment. This case illustrates that new vessels may settle spontaneously on medical treatment despite the presence of capillary closure.

CASE 4
A 34-year-old soldier with histologically confirmed sarcoidosis initially presented with blurred vision in the right eye due to posterior uveitis. The inflammation resolved following a course of systemic steroids, but six weeks later vision in the right eye was reduced owing to a vitreous haemorrhage. Fundus examination showed optic disc and peripheral neovascularisation associated with capillary closure (Fig. 4A). Right panretinal photocoagulation was carried out, and the abnormal vessels regressed (Fig. 4B). Six years later he presented with a further vitreous haemorrhage in the right eye, and more peripheral new vessels had developed. Further laser treatment was unsuccessful, and the right vision remained at hand movements due to persistent vitreous haemorrhage.

Comment. This case illustrates the initial beneficial effect of laser photocoagulation in the presence of capillary closure, though further treatment failed to produce regression of the new vessels.
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**Results**

In this study of 26 patients with retinal neovascularisation due to posterior uveitis, 39 eyes showed evidence of new vessels. Vitreous haemorrhage was a presenting feature in 22 eyes (56%), and in 12 of these (31%) it was a cause of significant visual loss (reduction of more than 3 lines on the Snellen chart). New vessels were found at the optic disc in 28 eyes (72%) and elsewhere in the retina in 11 (28%). Active inflammation in the posterior segment (2+ cells or more), and a posterior vitreous detachment was present in all affected eyes.

The fluorescein angiographic features are pre-

**Fig. 3A** Patient 3. Fluorescein angiogram of the right eye demonstrates capillary closure with collateral vessels in the upper nasal quadrant.

**Fig. 3B** Late phase fluorescein angiogram of the right eye. There is leakage of dye from the optic disc and the neovascular frond extending from the disc to the macula.

**Fig. 3C** The fluorescein angiogram of the left eye demonstrates new vessels in the superior margin of the optic disc.

**Fig. 3D** Fifteen months later the fluorescein angiogram of the left eye reveals that the new vessels on the superior margin of the disc have regressed but new ones have developed in the medial and lateral portions of the disc.

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**Fig. 313**

Laite psas elfs f Zress ceil 0I/I/I si' I/Icrig/u cv igogsos 0I/I/I s' I/Icig/u ci'v ti fC daf f r/ s ii (I /f I f s I I I/se I/st rc ii a'l /s thin II /us' tit ith 'tessitstv( on the superi sswargwi f) II/is icd h N c /Ist II Is' rfs g ' s II sN C UIIIi 1Is' fl fC daf

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sented in Table 1. These features fell into two main groups at presentation. New vessels were present in association with significant capillary closure (at least one quadrant) in 15 eyes (38%), and in half of these a branch vein occlusion was present. In the remaining 24 eyes significant capillary closure was not found, but diffuse microvascular leakage was present, and frank venous leakage associated with periphlebitis was seen in 12 eyes—some eyes having both. Cystoid macular oedema appeared in 16 eyes, eight with capillary closure and eight without such changes.

The treatment that the patients received is summarised in Table 2. Topical steroids were given to all patients except one who received no treatment of any sort. Twenty-three patients received courses of systemic steroids and six patients required additional immunosuppressives. Eleven patients received laser photocoagulation (eight panretinal, three localised to areas of capillary closure), and in one patient this was the only treatment given. Direct photocoagulation to neovascular fronds was not given, and surgical intervention as a primary procedure for vitreous haemorrhage was not performed in any patient. The change in visual acuity from initial presentation to most recent follow-up visit, with special reference to those eyes that had vitreous haemorrhages and laser photocoagulation, is shown in Figs. 5 and 6. The visual prognosis was generally good in the presence of vitreous haemorrhage, but some patients who received laser treatment showed subsequent deterioration mainly due to the development of cystoid macular oedema.

The complications which arose during treatment are documented in Table 3. Cystoid macular oedema developed significantly more often in eyes that received photocoagulation than in those that did not (p<0.01; χ² test; Table 4). Traction retinal detachment was rare, possibly because all eyes showed posterior vitreous detachments. Persistent visual loss due to vitreous haemorrhage occurred only in two eyes, and a posterior subcapsular cataract in one eye. The fate of the new vessels is shown in Table 5. The new vessels resolved in 70% of cases (27 eyes).

### Table 1 fluorescein angiographic features on presentation

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant capillary closure (at least 1 quadrant)</td>
<td>15</td>
</tr>
<tr>
<td>Diffuse microvascular leakage</td>
<td>24</td>
</tr>
<tr>
<td>Venous leakage</td>
<td>12</td>
</tr>
<tr>
<td>Cystoid macular oedema</td>
<td>8</td>
</tr>
<tr>
<td>Branch vein occlusion</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 2 Treatment given

<table>
<thead>
<tr>
<th>Treatment given</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroids</td>
<td>24</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>7</td>
</tr>
<tr>
<td>Systemic steroids and immunosuppressives</td>
<td>6</td>
</tr>
<tr>
<td>Systemic steroids and photocoagulation</td>
<td>10</td>
</tr>
<tr>
<td>Photocoagulation alone</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>2</td>
</tr>
</tbody>
</table>

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Fig. 5 Change in visual acuity during study period comparing patients with and without vitreous haemorrhage.

Following treatment (medical and/or surgical), but in nine eyes the neovascular process was unaffected by treatment, and in three eyes assessment was not possible due to poor visibility.

Discussion

Neovascularisation is a fundamental element of the postinflammatory healing process in all parts of the body, and continues for as long as the appropriate angiogenic stimulus is present. In the eye such stimuli have been suggested to arise from hypoxic retina,\(^8\) inflamed retina,\(^9\) or from inflammatory cells themselves.\(^1\) Previous series examining the natural history of new vessels in ocular inflammatory disease are few. The original paper by Eales\(^2\) described young men with repeated intraocular haemorrhage, distended tortuous retinal veins, and retinal haemorrhages. The natural history was not recorded in what was presumably a heterogeneous group of diseases. Felder and Brockhurst\(^1\) reported 15 patients with intermediate uveitis who developed new vessels at the disc (three patients), and Spalton and Sanders\(^4\) reported on eight patients with sarcoidosis and retinal neovascularisation—six at the optic disc and two in the periphery associated with branch vein occlusion. Two of these are included in the present series and were treated by panretinal photocoagulation. The new vessels regressed in one, but the other developed macular oedema following treatment.

The present study has shown the clinical and angiographic features found in 39 eyes of 26 patients with neovascularisation due to posterior uveitis, and has attempted to assess their progress in response to medical and laser treatment. It is evident that such neovascularisation occurs in younger patients, and that the visual prognosis, even in the presence of significant vitreous haemorrhage, is good. In the majority of patients intraocular inflammation subsided on medical treatment, and in half of these

Table 3 Complications arising during treatment

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystoid macular oedema</td>
<td>7</td>
</tr>
<tr>
<td>Persistent vitreous haemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>Traction retinal detachment</td>
<td>2</td>
</tr>
<tr>
<td>Cataract</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4 Incidence of cystoid macular oedema (CMO)

<table>
<thead>
<tr>
<th></th>
<th>CMO</th>
<th>No CMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not associated with photocoagulation</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Associated with photocoagulation</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

\(\chi^2=p<0.01\).

Table 5 Fate of new vessels

<table>
<thead>
<tr>
<th>Fate of new vessels</th>
<th>No. of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>New vessels regressed on no treatment</td>
<td>1</td>
</tr>
<tr>
<td>New vessels regressed on medical treatment only</td>
<td>16</td>
</tr>
<tr>
<td>New vessels regressed on laser treatment only</td>
<td>1</td>
</tr>
<tr>
<td>New vessels regressed on combined medical and laser treatment</td>
<td>9</td>
</tr>
<tr>
<td>New vessels unaffected by all treatments</td>
<td>9</td>
</tr>
<tr>
<td>State of vessels unassessed (vitreous haem/cataract)</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
</tr>
</tbody>
</table>
patients this was sufficient to cause regression of the fronds, regardless of the aetiology of their uveitis. It is also noteworthy that one patient who never received systemic treatment also showed regression of new vessels with a reduction in intraocular inflammation.

The role of laser photocoagulation is less clear. In this series direct ablation of neovascular fronds was not attempted, though this regimen has been reported with good results. The only patient who received laser photocoagulation alone responded well, but the new vessels were peripheral in a small patch of minimal capillary closure and may have settled despite treatment. Laser treatment frequently caused regression of new vessels, but the high incidence of subsequent cystoid macular oedema, especially in those patients with significant capillary closure, was unexpected. Major series discussing the role of photocoagulation in the presence of non-inflammatory ischaemic conditions, such as diabetes, have shown the benefit of this treatment and the low incidence of subsequent macular oedema, though this complication is becoming more recognised. The visual prognosis was generally good in these patients, in contrast to patients with ischaemic proliferative retinopathy. Notably, traction retinal detachment, a common complication of proliferative diabetic retinopathy (51% of untreated cases), was rare in this series. This may be because of the transient nature of the vessels and that in all eyes examined a posterior vitreous detachment was present, thus excluding a scaffold on which new vessels could grow.

The pathogenesis of neovascularisation in the eye is unknown. However, there is increasing evidence that factors present in retinal tissue may stimulate angiogenesis, while others in the vitreous will inhibit it. In posterior uveitis there are three sources of possible angiogenic factors. Capillary closure, and thus hypoxic retina, occurs in this disease. This is often associated with branch vein occlusion, which has been shown in a number of conditions to be postively correlated with the development of new vessels. Retinal capillaries which have damaged endothelium leak and may be stimulus for neovascularisation. The disruption of the retinal vascular network is exemplified by the fluorescein angiograms of many patients who show diffuse microvascular leakage. However, this hypothesis has been challenged on the grounds that neovascularisation is not a feature of many retinal vascular diseases where there is persistent intraretinal oedema, for example. Coats’ disease or diabetic maculopathy. Lastly, it has been proposed that the inflammatory cells themselves, either a subpopulation of stimulated T-lymphocytes or macrophages, produce soluble factors (for example, lymphokines) which are angiogenic. The latter hypothesis is particularly attractive in the case of posterior uveitis, where new vessels may appear regardless of the state of the underlying retinal vasculature and regress with adequate control of the inflammation.

This study indicates that retinal neovascularisation associated with ocular inflammation behaves in a different manner from retinal neovascularisation not associated with ocular inflammation. The visual prognosis is better in the presence of intraocular inflammation, and this is also true for vitreous haemorrhage. We would recommend that full and adequate medical treatment should be used to suppress the intraocular inflammation, with laser photocoagulation being reserved for further treatment once the eye is quiet and if recurrent vitreous haemorrhages occur.

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References
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