Postoperative abnormalities of the choriocapillaris in exudative age-related macular degeneration

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Abstract

Aims—To study the incidence and possible cause of abnormalities of the subfoveal choriocapillaris after surgical excision of subfoveal choroidal neovascularisation in age-related macular degeneration (ARMD).

Methods—The postoperative fluorescein angiograms and colour photographs of 29 eyes of 29 patients were reviewed after surgical excision of subfoveal choroidal neovascularisation in exudative ARMD. Preoperative and postoperative fluorescein angiograms were examined for perfusion of the subfoveal choriocapillaris. The excised subfoveal choroidal neovascular membranes from eight eyes that demonstrated postoperative abnormalities of the choriocapillaris were embedded in paraffin, serially sectioned and examined for the presence of the choriocapillaris.

Results—Postoperative fluorescein angiograms revealed abnormal perfusion of the subfoveal choriocapillaris in 26 of the 29 eyes (90%) and in all eight eyes that had histopathological examination of the surgical specimens. Examination of serial sections demonstrated that none of the excised neovascular membranes contained choriocapillaris.

Conclusions—Abnormal perfusion of the subfoveal choriocapillaris was frequently present following removal of the subfoveal neovascular membrane in ARMD. The histopathological study demonstrated that abnormalities of the choriocapillaris were not due to removal of the choriocapillaris at the time of surgery.

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The introduction of subfoveal surgery for the treatment of exudative age-related macular degeneration (ARMD) and the presumed ocular histoplasmosis syndrome (POHS) has established the technical feasibility of removing subfoveal neovascular membranes.^{1–4} However, the excision of subfoveal membranes in ARMD has not been associated with the return of foveal vision except in occasional patients.^{2–4} This is in contrast with the more favourable prognosis following similar surgery in patients with POHS.^{1–3} While the technique used to remove these membranes has been refined, these changes have not been accompanied by a significant improvement in visual outcome in exudative ARMD.

There are several possible explanations for the limited visual prognosis in ARMD patients

following submacular surgery including: (1) pre-existing or iatrogenic damage to the photoreceptors; (2) pre-existing or iatrogenic disruption of Bruch's membrane; (3) disruption of the retinal pigment epithelium (RPE) by the disease process or during surgery, with inability of the adjacent RPE to repopulate the denuded area; and (4) the absence of normal choriocapillaris beneath the fovea.

In this study, we reviewed the postoperative fluorescein angiograms of 29 eyes of 29 patients who had previously undergone surgery for subfoveal choroidal neovascularisation in exudative ARMD to determine the incidence of postoperative abnormalities of the subfoveal choriocapillaris. We identified surgically excised tissue from a subset of eight of the eyes which demonstrated abnormalities of the subfoveal choriocapillaris after surgery. We studied this subset of eight eyes with histopathology, to determine whether postoperative abnormalities of the subfoveal choriocapillaris were the result of removal of the choriocapillaris with the neovascular membrane.

Material and methods

We reviewed the records of 29 eyes of 29 patients who underwent surgical excision of subfoveal choroidal neovascularisation for exudative ARMD at the Washington University School of Medicine during 1991 and 1992, and had gradable postoperative fluorescein angiograms and colour photographs. Preoperative photographs and fluorescein angiograms were obtained up to 96 hours before surgery on all patients. Postoperatively, these tests were performed between 3 and 18 months after surgery. Only the most recent postoperative fluorescein angiograms and colour photographs were studied in patients who had more than one photographic study after surgery.

Patients were classified as demonstrating abnormal perfusion of the subfoveal choriocapillaris postoperatively if there was absence of a subfoveal ground glass appearance characteristic of choriocapillaris filling in the choroidal flush of the fluorescein angiogram. Fluorescein angiograms and colour and red-free photographs were examined to ensure that there was no blockage of subfoveal choroidal fluorescence.

Surgical specimens suitable for histopathology were available from eight of these 29 eyes. Only a limited number of specimens were available because the choroidal neovascular membrane was removed with the vitrector in many patients. Surgically excised membranes

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Figure 1 Case 1. (A) Preoperative: fibrotic subfoveal choroidal neovascular membrane with an associated serous neurosensory detachment (arrows). (B) Choroidal membrane blocks fluorescence of the underlying choriocapillaris during the arterial phase of the fluorescein angiogram (area outlined by arrows). (C) Diffuse staining of the neovascular complex in the late arteriovenous phase. (D) Six months postoperative: there is absence of pigment in the area of the excised membrane. Large choroidal vessels are clearly seen (large arrows). (E) Six months after operation. There is filling of the large choroidal vessels (arrows) in the area of the excised neovascular membrane, but no normal filling of the choriocapillaris in this area. (F) Histopathology of the excised neovascular complex. Vascular channels are present in the membrane (large arrow). RPE lines one side of the excised specimen, and a thickened basement membrane is present under these cells (arrows). There is no choriocapillaris in this specimen (haematoxylin and eosin).

Fig 1A

Fig 1D

Fig 1B

Fig 1E

Fig 1C

Fig 1F

were preserved in 10% formalin for at least 24 hours and processed for light microscopy. The specimens were washed in cacodylate buffer and dehydrated in a series of alcohol baths before immersion in xylene. Specimens were then infiltrated with paraffin and embedded in paraffin blocks. All eight specimens were serially sectioned (5–6 μ m sections) and stained with haematoxylin and eosin. Serial sections were examined by light microscopy for the presence of choriocapillaris or capillary vessels in any of the excised membranes.

Results

Using the fluorescein angiographic criteria defined above, 26 of the 29 eyes (90%)

demonstrated abnormal perfusion of the subfoveal choriocapillaris postoperatively on fluorescein angiography.

Histopathological examination of serial sections of the surgical specimens did not demonstrate the presence of choriocapillaris in any of the eight specimens examined. Capillary vessels were only identified within the neovascular complex.⁵ The following examples illustrate the clinical and histopathological features exhibited by all eight of these cases.

CASE 1

A 73-year-old woman underwent surgical excision of a subfoveal neovascular membrane from ARMD in the right eye (Figs 1A–C).

Fig 2A

Fig 2C

Fig 2B

Fig 2D

Fig 2E

Figure 2 Case 2. (A) Preoperative. Choroidal neovascular membrane with an associated neurosensory detachment (arrows). (B) The edge of the membrane is barely beneath the centre of the fovea on fluorescein angiography in this hypertensive patient. (C) Postoperative appearance of the fundus at 1 month. An area of hypopigmentation is present. Persistent subretinal blood present nasal to the fovea is not uncommon 4 weeks after surgery. (D) Fluorescein angiography reveals filling of the large choroidal vessels (arrows) without normal filling of the associated choriocapillaris in the centre of the macula. (E) Histopathology of the excised neovascular membrane reveals an avascular fibrocellular stroma without evidence of excised choriocapillaris. Only a portion of the membrane is shown in the photograph, but the membrane appearance is uniform throughout the specimen (haematoxylin and eosin).

Perfusion of the underlying choriocapillaris could not be determined preoperatively because of blockage of fluorescence by the overlying membrane (Fig 1B). Six months postoperatively an area of hypopigmentation was present in the area of the excised neovascular complex (Fig 1D). Fluorescein angiography revealed filling of the large choroidal vessels without visible filling of the associated choriocapillaris (Fig 1E). Histopathology of the excised neovascular complex revealed small vascular channels only in the thickest

portion of the membrane (Fig 1F, large arrow). A row of RPE cells lined one side of the excised specimen. A thickened basement membrane which may contain some Bruch's membrane was present under these cells. There was no choriocapillaris in this specimen.

CASE 2

An 82-year-old woman underwent surgical excision of a subfoveal choroidal neovascular membrane from the right eye (Fig 2A). Perfusion of the choriocapillaris under the membrane could not be determined preoperatively because of blockage by the overlying neovascular complex (Fig 2B). One month postoperatively, an area of hypopigmentation was present under the centre of the excised choroidal neovascular membrane (Fig 2C). Fluorescein angiography revealed filling of the larger choroidal vessels in the early A-V phase, but there was no visible filling of the choriocapillaris under the centre of the fovea (Fig 2D). A line of pigmented RPE lined one side of the excised membrane, but there was no evidence of excised choriocapillaris (Fig 2E).

Discussion

Advances in pars plana vitrectomy techniques have made it technically feasible to remove subfoveal choroidal neovascular membranes in patients with ARMD, POHS, and other miscellaneous disorders.¹⁻⁴ In POHS, up to 40% of

patients experience an improvement of two lines or more in visual acuity after surgery^{1-3a}; however, similar improvement in visual acuity is uncommon in patients with ARMD.²⁻⁴ Many factors may account for the limited visual prognosis in ARMD patients following submacular surgery, including pre-existing or postoperative damage to the outer retina, RPE, Bruch's membrane, or choriocapillaris.

In this study, 26 of 29 eyes (90%) demonstrated abnormalities of the subfoveal choriocapillaris on fluorescein angiography performed after surgery for subfoveal choroidal neovascularisation in ARMD. All patients had preoperative fluorescein angiography, but it was not possible to evaluate the subfoveal choriocapillaris preoperatively because the choroidal neovascular complex blocked fluorescence from the underlying choriocapillaris in these eyes. Postoperative fluorescein angiography revealed filling of the large choroidal vessels in the early phase without visible filling of the overlying choriocapillaris. This fluorescein angiographic finding is consistent with an abnormality of the choriocapillaris beneath the excised choroidal neovascular membrane. We cannot definitively conclude that the subfoveal choriocapillaris is absent on the basis of fluorescein angiography. We cannot exclude the possibility that the choriocapillaris is present but does not leak fluorescein, similar to its behaviour during indocyanine green angiography. However, it is clear that the behaviour of the choriocapillaris on fluorescein angiography is markedly abnormal after subfoveal surgery in these eyes.

Histopathological examination of serial sections of eight membranes demonstrated that the choriocapillaris was not present in any of the neovascular complexes examined histologically from patients with ARMD. The question arises as to whether or not it is possible to identify the choriocapillaris if it is removed with the subfoveal choroidal neovascular membrane. We have previously identified choriocapillaris in histological sections of a choroidal neovascular membrane in a patient with angioid streaks (unpublished observation). Thus, absence of the choriocapillaris on histopathology in this study suggests the choriocapillaris was not removed at the time of surgery. There are two possible explanations for these observations: (1) the choriocapillaris was not perfused preoperatively, implying that abnormal perfusion of this vascular structure was part of the primary disease process⁶⁻⁸; or (2) the choriocapillaris was normal preoperatively but became abnormal after surgery.⁹

Regardless of whether it occurred preoperatively or postoperatively, it is likely that changes in the choriocapillaris occurred secondary to dysfunction of the RPE. Henkind and Gartner have identified RPE loss to be a cause of choriocapillaris degeneration in retinitis pigmentosa,¹⁰ and Miller and colleagues noted similar findings in an experimental model of thioridazine retinopathy.¹¹ Korte *et al* used sodium iodate to selectively destroy the RPE in rabbits.¹² Degenerative changes in the RPE and choriocapillaris were observed 1 week after iodate injection. One month later patches of

Bruch's membrane became devoid of RPE and the choriocapillaris in these regions was found to be markedly atrophic. In contrast, the choriocapillaris had a normal appearance in areas where the RPE still appeared healthy.

We have previously developed a model to study the effects of RPE debridement on the morphology of the overlying retina and underlying choriocapillaris in the domestic pig and non-human primate.^{13 14} Previously debrided areas of Bruch's membrane were covered by a layer of hypopigmented RPE in most areas 1 month after RPE debridement, and the choriocapillaris, inner retina, and outer nuclear layer were ultimately intact in areas containing RPE.^{13 14} Some areas of Bruch's membrane remained devoid of RPE 4 weeks after surgery, and there was atrophy of the choriocapillaris, outer segments, and outer nuclear layer in these areas.¹³ These results suggest that absence of RPE leads to atrophy of the underlying choriocapillaris and overlying outer nuclear layer. The RPE may release a diffusible 'vascular modulating factor' which is necessary to preserve the morphology and function of the choriocapillaris.¹² Recently, Yang and colleagues¹⁵ isolated a soluble angiogenic factor from human RPE which may be the postulated 'vascular modulating factor'.

Although initial attempts at RPE transplantation in ARMD have not been successful,^{16 17} the question remains open as to whether RPE transplantation will become an adjunct to submacular surgery in ARMD. If abnormalities develop in the choriocapillaris postoperatively, replacement of dysfunctional RPE with healthy RPE at the time of surgery might prevent postoperative changes in the subfoveal choriocapillaris. The pathological changes occurring in Bruch's membrane in ARMD¹⁸ will probably not be reversed by replacing dysfunctional, senescent RPE by healthy RPE, but reversal of Bruch's membrane changes may not be necessary for visual recovery.

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History of ophthalmology

Do you have a Roman connection?

The Romans occupied Britain from AD 43 to around AD 410. Ophthalmic care was available from itinerant oculists who usually prescribed eye salves (collyria) or drops which were made from a block that was diluted with a fluid such as egg. The solid blocks were often stamped with details of the medicament and the name of the oculist. Some 300 stamps have been found in the Roman empire with 30 of these in Britain (see table).¹ There are 20 modern day eye departments near to where finds have been made. Probably the most closely located is Moorfields Eye Hospital. A cup with an

oculist's inscription by Lucius Iulius Senex for a saffron eye salve was found at nearby Moorgate Street in 1929. Single finds have been made in Wales, Scotland, and southern Ireland. Four of the stamps have been unearthed over the past 25 years. Perhaps there is one lying undiscovered near your hospital.

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¹ Collingwood RG, Wright RP. *The Roman Inscriptions of Britain*. Volume II. Stroud: Alan Sutton Publishers, 1992: 43-62.

Roman oculists' stamps found in Great Britain

Location of find (Roman name)	Year of find	Named ingredients	Oculist's name
Bath (<i>Aquae Sulis</i>)	1731 1923	Vinegar, quince	T Iunianus Flavius Litugenus
Bedford (Biggleswade) (Harrold)	1873 1895	Vinegar, celandine, poppy Copper oxide, misy*	Gaius Valerius Amandus Gaius Iunius Tertullus Lucius Iulius Salutaris Marinus
Cambridge (<i>Durolopon</i>)	1984		Quintus Iulius Martinus
Chester (<i>Deva</i>)	1973	Saffron	
Cirencester (<i>Corinium</i>)	1808	Frankincense, quince	Minervialis
Colchester (<i>Camulodunum</i>)	1900	Frankincense, quince, poppy	Atticus
Dorchester (<i>Durnovaria</i>)	1719	Saffron, quince	Quintus Iulius Murranus
Edinburgh (Tranent)	1975	Saffron	Martialis
Gloucester (Lydney Park)	1937	Saffron	
Hereford (Kenchester)	1846	Saffron	Lucius Valerius Latinus
Ipswich (<i>Magnis</i>)	c 1830	Quince	Iulius Iucundus
Kendal (Watercrook)	1842	Nard, frankincense	Titus Vindacius Ariovistus
Lincoln (Littleborough)	1963	Copper oxide, gall	Aurelius Polychronius
London (<i>Londinium</i>)	1931		
Newport (<i>Caerleon; Isca</i>)	1974		Publius Clodius
Norwich (Caistor St Edmunds) (<i>Venta Icenorum</i>)	1927		
Oxford (Wilcote)	1965		Maurus
Shrewsbury (Wroxeter)	1808		Tiberius Claudius M
St Albans (<i>Virocontium</i>)	1981	Frankincense	
Waterford (<i>Verulamium</i>)	1739	Balsam, myrrh	Lucius Iulius Iuvenis Flavius Secundus Marcus Iuventus Tutianus
York (Clonmel)	1842	Misy	
	1930	Misy	Iulius Alexander

*Probably copper pyrites.