Epiretinal pathology of vitreomacular traction syndrome

A Gandorfer, M Rohleder, A Kampik

Aims: To investigate the ultrastructure of the vitreoretinal interface in patients with vitreomacular traction syndrome.

Methods: 14 patients with vitreomacular traction syndrome underwent standard pars plana vitrectomy. After induction of posterior vitreous detachment, epiretinal tissue and the inner limiting membrane (ILM) of the retina were removed, and processed for transmission electron microscopy.

Results: Ultrastructural analysis revealed two basic patterns of vitreoretinal pathology in eyes with vitreomacular traction syndrome. Seven specimens showed mostly single cells or a cellular monolayer covering closely the vitreal side of the ILM, not resulting in a biomicroscopically detectable epiretinal fibrocellular proliferation. The other seven specimens revealed premacular fibrocellular tissue which was separated from the ILM by a layer of native collagen, resembling the clinical features of idiopathic epiretinal membranes. In both groups of eyes, the myofibroblast was the predominant cell type. Fibrous astrocytes and fibrocytes were less frequent. Retinal pigment epithelial cells and macrophages were absent. Deposits of newly formed collagen were present only adjacent to fibrocellular multilayers.

Conclusions: There are two distinct clinicopathological features of vitreomacular traction syndrome which suggest different forms of epiretinal fibrocellular proliferation: (1) epiretinal membranes interposed in native vitreous collagen and (2) single cells or a cellular monolayer proliferating directly on the ILM. The presence of remnants of the cortical vitreous which remain attached to the ILM following posterior vitreous separation may determine the clinicopathological feature of the disease. The predomination of myofibroblasts may help to explain the high prevalence of cystoid macular oedema and progressive vitreomacular traction characteristic for this disorder.

The hallmark of vitreomacular traction syndrome is a persistent attachment of the vitreous to the macula in eyes with an incomplete posterior vitreous detachment. The most common morphological configuration is a vitreous separation peripheral to a zone where the cortical vitreous remains attached to the retina at the macula and the optic nerve head. Traction on the macula causes decreased vision, metamorphopsia, photopsia, and micropsia. Pars plana vitrectomy has been shown to relieve macular traction and result in visual improvement in most cases.

There are remarkable variations concerning the vitreoretinal morphology in eyes with vitreomacular traction syndrome. This syndrome comprises a broad spectrum of frequently unrecognised clinical findings, ranging from peripheral vitreous separation with residual foveal attachment to multiple areas of traction retinal detachment caused by persistent, focal posterior and peripheral vitreous attachment. Clinically and histopathologically, the disorder shares similarities with idiopathic epiretinal membranes in eyes with complete posterior vitreous detachment, such as the presence of fibrocellular tissue at the macula as reported previously. However, there are also distinct differences, such as the clinical course of the disease and ultrastructural findings. Clinical and surgical experience has disclosed either a visible epiretinal membrane, or a layer of cortical vitreous, or both over the posterior pole. Ultrastructural evaluation of epiretinal tissue removed during vitrectomy for vitreomacular traction syndrome revealed fibrocellular membranes composed of fibrous astrocytes, fibrocytes, myofibroblasts, collagen, and fragments of the inner limiting membrane (ILM). However, material chosen for analysis has been epiretinal tissue rather than detached posterior hyaloid, and the pathology of the vitreous, the fibrocellular tissue, and the ILM of the retina, leading to persistent vitreomacular traction and fibrocellular proliferation has not yet been clarified. Whether anteroposterior traction alone causes macular pathology or whether tangential traction induced by fibrocellular proliferation is relevant to the pathogenesis of vitreomacular traction syndrome, is still a matter of debate. Moreover, the clinicopathological correlation in eyes with different clinical features of vitreomacular traction syndrome has not been addressed and determined as yet. Therefore, we describe the ultrastructure of the vitreoretinal interface in 14 eyes with vitreomacular traction syndrome with special regard to the clinical variation of the disease. We are aware that our approach is limited to the epiretinal pathology of the syndrome, and conclusions regarding anteroposterior traction can not be drawn from this study.

Patients and Methods

Fourteen patients with symptomatic vitreomacular traction syndrome underwent pars plana vitrectomy. Diagnosis was made clinically by slit lamp biomicroscopic examination with a 90 dioptre lens. All eyes had partial posterior vitreous detachment with persistent attachment of the vitreous to the macula. Retinal breaks were not present in any eye. The patients' histories were unremarkable with one exception: one patient had undergone uncomplicated cataract surgery previously. Patient data recorded before surgery included sex, age, complete medical history, previous ocular trauma or surgery, presenting symptoms, and duration of symptoms. Findings recorded at preoperative examination included Snellen visual acuity, presence and degree of posterior vitreous detachment, and status and characteristics of the vitreoretinal interface such as retinal surface wrinkling, presence of premacular fibrous tissue characterising an epiretinal membrane, macular distortion, or cystoid macular oedema. In selected cases, optical coherence tomography and fluorescein angiography were performed. Intraoperative observations included presence and extent of partial posterior vitreous detachment, and presence of an epiretinal membrane or a layer of cortical vitreous over the posterior pole.
The surgical procedure performed was a standard three port pars plana vitrectomy. In eight eyes, uncomplicated cataract surgery was combined with vitrectomy. Separation of the posterior hyaloid was initiated by suction with the vitrectomy probe over the optic nerve head and then continued peripherally. Preretinal tissue and the ILM were peeled “en bloc” from the macula, using indocyanine green as a vital dye in five eyes. Fluorescein angiography performed in five patients revealed cystoid macular oedema in all eyes.

The initial findings from slit lamp biomicroscopic assessment of the vitreomacular anatomy were confirmed during surgery. An abnormally adherent posterior vitreous was peeled from the macula in all eyes. Epiretinal membranes were present in seven eyes. In all eyes, the ILM was removed from the macula, using indocyanine green as a vital dye in five eyes. No intraoperative or postoperative complications occurred. Comparison of preoperative and postoperative visual acuity revealed an improvement of two or more Snellen lines in eight eyes. Visual acuity remained stable in five eyes and deteriorated by two Snellen lines in one eye. In five out of these six eyes without postoperative visual improvement, indocyanine green was used to stain the ILM.

Transmission electron microscopy disclosed three morphologically distinguishable cell types as determined by previously reported criteria (Table 2). Fibrous astrocytes were present in all specimens. They were characterised by masses of intracytoplasmic intermediate-type 10 nm filaments, junctional complexes of the adherence type, and polarisation with basement membrane production. Fibrous astrocytes were the predominant cell type in two specimen. Myofibroblasts were the predominant cell type in 12 out of 14 cases, and were characterised by rough endoplasmic reticulum, a fusiform

### Table 1 Clinical characteristics of patients with vitreomacular traction syndrome

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of symptoms in months</th>
<th>Presence of epiretinal membrane</th>
<th>Cystoid macular oedema</th>
<th>Preoperative visual acuity</th>
<th>Postoperative visual acuity</th>
<th>Follow up in months</th>
<th>Intraoperative use of ICG</th>
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Patient data are shown in Table 1. Six patients were women and eight were men. The average age at time of presentation was 70 years (range 48–79 years). Preoperative visual acuity ranged from 20/400 to 20/30. The known duration of visual decline and metamorphopsia ranged from 1 month to 3 years and could not be recalled in five patients. In all eyes, vitreoretinal anatomical findings in the fellow eye were normal. Before surgery, all eyes showed a partial posterior vitreous separation with residual vitreous attachment to the macula. The vitreomacular anatomy was of two basic patterns. In seven eyes, a non-vascularised epiretinal membrane was present at the macula. Seven eyes showed a smooth retinal surface without epiretinal tissue at the posterior pole. Fluorescein angiography performed in five patients revealed cystoid macular oedema in all eyes.

The surgical procedure performed was a standard three port pars plana vitrectomy. In eight eyes, uncomplicated cataract surgery was combined with vitrectomy. Separation of the posterior hyaloid was initiated by suction with the vitrectomy probe over the optic nerve head and then continued peripherally. Preretinal tissue and the ILM were peeled “en bloc” from the macula, using indocyanine green as a vital dye in five eyes. Fluorescein angiography performed in five patients revealed cystoid macular oedema in all eyes.

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### Table 2 Ultrastructural features of vitreomacular traction syndrome

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Fibrous astrocyte</th>
<th>Myofibroblast</th>
<th>Fibroblast</th>
<th>RPE cell macrophage</th>
<th>Distribution of cells</th>
<th>Native collagen on ILM</th>
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– absent; + rare; ++ some; +++ many.
nucleus and cell body, the absence of intracytoplasmic intermediate-type 10 nm filaments or basement membrane, but aggregates of 5–7 nm subplasmalemmal cytoplasmic filaments with fusiform densities. Fibrocytes were present in five cases, and were characterised by abundant rough endoplasmic reticulum and a prominent Golgi complex, fusiform shape of the cell body and nucleus, and absence of intracytoplasmic filaments or basement membrane. Macrophages or retinal pigment epithelial cells were not noted in any specimen. All specimens revealed fragments of the ILM. Persistent vitreoretinal attachment is shown in Figure 1.

There were two different patterns of distribution of cells and extracellular matrix. In eyes which showed an epiretinal membrane preoperatively and intraoperatively, specimens revealed a fibrocellular multilayer of predominantly myofibroblasts which was separated from the ILM by a layer of native vitreous collagen, characterised by a diameter of collagen fibrils between 8–15 nm. Newly formed collagen with a diameter of collagen fibrils measuring more than 16 nm was only present adjacent to the fibrocellular layer, and was separated from the ILM by a continuous layer of native vitreous collagen (Fig 2).

Specimens of eyes without a detectable epiretinal membrane at the time of preoperative examination and surgery showed single cells or a cellular monolayer covering the vitreal side of the ILM. In these eyes, there was no collagen interposed between the cells and the ILM (Fig 3). One specimen revealed a three layered membrane consisting of a cellular monolayer in close contact with the ILM, a cellular multilayer, and newly formed collagen in between (Fig 4).

**DISCUSSION**

This study demonstrates two basic patterns of vitreomacular pathology in eyes with vitreomacular traction syndrome. One group of eyes showed mostly single cells or a cellular monolayer covering the vitreal side of the ILM, resulting neither in a biomicroscopically detectable epiretinal proliferation nor in wrinkling of the vitreomacular interface. The second group of eyes revealed premacular fibrocellular tissue which was separated from the ILM by a layer of native vitreous collagen, resembling the clinical features of idiopathic epiretinal membranes in eyes with complete posterior vitreous detachment.

In our series as described in previous reports, the vitreous was firmly adherent to the posterior pole. One may hypothesise whether the presence of an epiretinal membrane may have helped bind the cortical vitreous to the retinal surface, impeding complete vitreo retinal separation and promoting traction forces at the macula. Idiopathic epiretinal membranes are associated with complete posterior vitreous separation in 80% to 95% of eyes. However, a small percentage of eyes will have only partial posterior vitreous separation. Thus, from the clinical point of view, we could not exclude that idiopathic epiretinal membranes were associated with incomplete vitreo retinal separation in our series.

Ultrastructural analysis, however, disclosed different features of epiretinal membranes associated with vitreomacular...
traction syndrome compared to idiopathic epiretinal membranes.13 14 We observed a fibrocellular multilayer which was separated from the ILM of the retina by a layer of native vitreous collagen. In six out of seven fibrocellular membranes and in 12 out of 14 specimens overall, the predominant cell type was the myofibroblast. Myofibroblastic differentiation has been observed in epiretinal tissue of patients with idiopathic or secondary epiretinal membranes, in epiretinal membranes associated with idiopathic macular holes, in eyes with proliferative vitreoretinopathy, and in vitreomacular traction syndrome.11 13 14 17–20 It has been hypothesised that contraction of these cells may be responsible for tangential traction at the vitreoretinal interface resulting in retinal surface wrinkling, macular distortion, macular and retinal detachment, and formation and enlargement of macular holes.21 Myofibroblasts express transforming growth factor (TGF)-β1, its specific receptor TGF-βRII, α-smooth muscle (α-SM) actin, and fibronectin, all main inducers of myofibroblastic differentiation, as shown recently in epiretinal membranes.

Figure 2  Epiretinal membrane located on a layer of native vitreous collagen. (A) The fibrocellular multilayer is situated on the vitreal side of a collagenous layer, which covers the ILM throughout the specimen. (B) A myofibroblast located on the collagenous layer. Arrowheads indicate aggregates of 5–7 nm subplasmalemmal cytoplasmic filaments with fusiform densities. (C) The cellular layer is composed of fibrous astrocytes and myofibroblasts. Note the wrinkled and distorted aspect of the ILM. (D) High magnification of (C). The collagenous layer consists of native vitreous collagen covering the ILM (asterisk). (E and F) Newly formed collagen is interposed between epiretinal cells and the layer of native vitreous collagen. (A, C: 1800×; B: 4800×; D: 28 000×; F: 60 000×)
removed from eyes with proliferative vitreoretinopathy and proliferative diabetic retinopathy. Myofibroblasts were the main cellular components of these membranes, and α-SMactin was present in 100% of cells, emphasising the high contractile potential.

Features of myofibroblastic differentiation are well recognised in cells found in all forms of epiretinal membranes, and explain the contractile properties of epiretinal tissue as evidenced both histopathologically and clinically. In patients with idiopathic macular pucker, however, myofibroblasts are less frequent than all other cell types. This finding contrasts with the high rate of cells with myofibroblastic differentiation in the current series of vitreomacular traction syndrome. The high prevalence of myofibroblasts may reflect an increased tendency for this cell type to reproliferate. Myofibroblastic differentiation, however, may only be present for a short time during membrane formation, and differences in the predominant cell type may be attributed to the time course of cell differentiation, the time interval following partial posterior vitreous separation, and the time of surgery. Today, advanced surgical techniques and skills enable us to dissect epiretinal tissue at an earlier stage of membrane formation.

Figure 3  Single cells and a cellular monolayer in close contact with the ILM. (A, B, C) A myofibroblast with aggregates of 5–7 nm subplasmalemmal cytoplasmic filaments with fusiform densities (arrowheads) firmly attached to the ILM (asterisk). Ring in (C) highlights the cellular attachment to the ILM. (D, E, F) A cellular monolayer situated on the vitreal side of the ILM. (F) Aggregates of 5–7 nm subplasmalemmal cytoplasmic filaments with fusiform densities (arrowheads) characteristic for myofibroblasts. Note the absence of collagen between the cells and the ILM in both specimens. (A and E: 4800×; B: 28 000×; C and F: 60 000×; D: 1800×).
and peeling of the ILM offers complete removal of the vitreo-macular interface. This may account for the predominance of myofibroblasts in the present series compared to the predominance of fibrous astrocytes in previous studies. The striking predominance of myofibroblasts in eyes with vitreomacular traction syndrome reported here, however, may help explain the high prevalence of cystoid macular oedema and progressive vitreomacular traction resulting in detachment of the macula in selected cases as reported in the literature. Both the high prevalence of cystoid macular changes and the progressive course in some eyes with vitreomacular traction syndrome are infrequently found in eyes with idiopathic epiretinal membranes.

In the present study, notably absent were retinal pigment epithelial cells which predominate in cases of proliferative vitreoretinopathy and in cases of macular pucker. The specimens were also devoid of macrophages. This suggests different mechanisms of formation of epiretinal tissue in each entity, possibly involving a glial source for the epimacular proliferation in eyes with vitreomacular traction syndrome. Epiretinal membranes are likely to develop following transient vitreomacular traction during evolution of posterior vitreous

Figure 4  A cellular multilayer covering the vitreal side of the ILM (asterisk). Preoperative biomicroscopy revealed cystoid macular oedema, but no detectable epiretinal tissue. (A) Note the slightly wrinkled aspect of the ILM. (B) The epiretinal tissue shows a three layered structure. (C) A cellular monolayer is located directly on the ILM. (D) Newly formed collagen is interposed between the monolayer and a multilayer. (E) The multilayer is composed of myofibroblasts and fibrous astrocytes characterised by masses of intracytoplasmic intermediate-type 10 nm filaments (F). [A: 1800×; B: 4800×; C and E: 9500×; D and F: 28 000×].

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detachment when deficiencies in the ILM arise, which allow migration and proliferation of glial cells on the inner retinal surface. Recently, Shinoda and coworkers detected glial fibrillary acidic protein (GFAP) and vimentin in two out of five eyes with vitreomacular traction syndrome. GFAP is restricted to astrocytes of the retina and central nervous system. Vimentin is specific for immature glial cells, normal and reactive astrocytes, and mesenchymal cells. This may support the theory of glial cell migration from the retina into the vitreoretinal interface. However, the origin of the cells which proliferate on the vitreoretinal interface is controversial, and hyalocytes of vitreous or haematogenous origin have also been suggested to migrate into or within the vitreous and cause fibrovascular proliferation at the vitreoretinal interface.

In our series, myofibroblasts and fibrous astrocytes formed a cellular multilayer which was separated from the ILM of the retina by a layer of native vitreous collagen. Newly formed collagen was present only adjacent to the fibrocellular complex, separated from the ILM by a continuous layer of native vitreous collagen. The continuous collagenous layer which was interposed between the ILM and the fibrocellular tissue in all specimens with epiretinal membranes in the present series raises the question of whether retinal glial cells indeed migrate through native vitreous collagen and form epiretinal membranes on the inner aspect of the vitreous cortex, or whether these cells are of different origin—that is, resident vitreous cells. Ultrastructural analysis alone, however, can not clarify this question.

As reported previously, native collagen was a common finding whereas newly formed collagen was rare. Shinoda and coworkers frequently found new abnormal collagen, with type I collagen in all cases and fibrous long spacing collagen in two out of five patients with vitreomacular traction syndrome. However, they used immunohistochemical techniques, and the precise location of deposition of newly formed collagen remained unclear.

Previous theories of epiretinal membrane formation in vitreomacular traction syndrome were based on the presence of an incomplete vitreoretinal separation with persistent vitreous attachment to the posterior pole. Vitreoretinal separation may not occur cleanly between the vitreous cortex and the ILM, leaving a layer of cortical vitreous adherent to the vitreomacular interface. In an necropsy series of normal human eyes with spontaneous vitreous detachment, 26 of 59 (44%) eyes had cortical vitreous remnants at the fovea. In patients with proliferative diabetic retinopathy, partial persistence of the vitreomacular traction syndrome. However, they used immunohistochemical techniques, and the precise location of deposition of newly formed collagen remained unclear.

On the other hand, it remains unclear whether single cells or a cellular monolayer as observed in the remaining seven eyes of the present study may cause clinically significant macular changes, and whether removal of these cells together with the ILM, as proposed in macular hole surgery, does show any benefit for the patient suffering from this variant of vitreomacular traction syndrome.

Epiretinal membrane formation is a continuous sequence of cellular migration, proliferation, and modulation of extracellular matrix leading from single cells to a fibrocellular multilayer. Single cells, which are closely adherent to the ILM, however, cannot form fibrocellular multilayers, which are separated from the ILM by a layer of native vitreous collagen. Therefore, we assume that the two different clinicopathological features of vitreomacular traction syndrome described here may be determined by the presence of either a bare ILM or a layer of cortical vitreous remaining attached to the macula following posterior vitreous detachment.

Recently, optical coherence tomography demonstrated two distinct patterns of vitreoretinal adhesions in eyes with vitreomacular traction syndrome—focal and multifocal. Gallear and coworkers show examples of focal vitreofoveal adhesions and of multifocal adhesions of the vitreous to an epiretinal membrane. This is in accordance with our clinicopathological findings.

Authors’ affiliations
A Gandorfer, M Rohleder, A Kampik, Department of Ophthalmology, Ludwig-Maximilians-University, Mathildenstrasse 8, D - 80336, München, Germany

REFERENCES
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