

CLINICOPATHOLOGIC CORRELATION OF SURGICALLY REMOVED SUBMACULAR TISSUE

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SUMMARY

The histologic appearance of a consecutive series of 200 neovascular membranes was analyzed. Specific angiographic manifestations of exudative age-related macular degeneration such as classic or occult choroidal neovascularization, vascularized pigment epithelial detachment, tear of the retinal pigment epithelium, polypoidal choroidal vasculopathy and deep retinal vascular anomalous complex correspond with specific histoarchitectural patterns.

RÉSUMÉ

L'histopathologie de 200 membranes néovasculaires consécutives a été analysée. Les manifestations typiques de la dégénérescence maculaire liée à l'âge comme la néovascularisation classique ou occulte, le décollement vascularisé de l'épithélium pigmentaire, la déchirure de l'épithélium pigmentaire, la vasculopathie polypoidale et l'anomalie vasculaire rétinale profonde correspondent à une histo-architecture spécifique.

SAMENVATTING

De histopathologie van een consecutieve reeks van 200 chorioidale neovasculaire membranen werd geanalyseerd. Typische angiografische manifestaties van exsudatieve leeftijdsgebonden maculaire degeneratie zoals klassieke of occulte neovascularizatie,

gevasculariseerde pigment epitheeloslating, scheur van het retinaal pigment epitheel, polypoidale chorioidale vasculopathie of diep retinale vasculaire anomalie corresponderen met een specifieke histoarchitectuur.

KEY WORDS

Choroidal neovascularization, age-related macular degeneration, histopathology.

MOTS CLÉS

Néovascularization choroidienne, dégénérescence maculaire liée à l'âge, histopathologie.

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INTRODUCTION

Choroidal neovascularization is an important cause of visual loss not only in age-related macular degeneration but may also be observed in a variety of other fundus diseases. Whereas the pathology of choroidal neovascularization has been extensively described^{2-5,12}, there are only relatively few clinicopathologic correlations available⁵. This study was undertaken to investigate whether a specific histoarchitecture could explain the angiographic appearance of the lesion. Recently neovascular membrane surgical specimens have become available as a new interest has risen in the surgical removal of choroidal neovascularization in age-related macular degeneration.

The histologic appearance of a consecutive series of 200 neovascular membrane surgical specimens was analyzed, including age-related macular degeneration, pathologic myopia, punctate inner choroidopathy, idiopathic choroidal neovascularization and dominant drusen. A scheme of choroidal neovascularization in age-related macular degeneration is presented. Pathologic differences in choroidal neovascularization between young patients and elderly patients are discussed.

MATERIALS AND METHODS

Study population and ophthalmological examination.

200 patients undergoing surgical extraction of a submacular neovascular membrane had fundus photography and fluorescein angiography not more than 14 days before surgery. The large majority of age-related macular degeneration patients also had indocyanine green angiography not more than 14 days before surgery. The fluorescein angiogram was obtained after intravenous injection of 5 ml sodium fluorescein 10% with a Canon fundus camera linked to a Kodak high resolution camera. Pictures were taken up to 10 minutes after intravenous injection. The indocyanine-green angiogram was obtained after intravenous injection of 50 mg indocyanine green solved in 10 ml with the same camera system. Pictures were taken up to 30 minutes after intravenous injection.

Angiographic interpretation. Characterization of the choroidal neovascularization was performed following the guidelines of Bressler et al¹ and of the Macular Photocoagulation Study¹¹. *Three surgical techniques were applied.* Simple membrane extraction in younger patients and in some patients with age-related macular degeneration, simple membrane extraction with transplantation of iris pigment epithelial cells harvested from a 12 o'clock iridectomy in patients with age-related macular degeneration¹³ and foveal translocation or displacement of foveal neuroretina towards an area with healthier retinal pigment epithelium (RPE) after removal of the neovascular membrane.

Histological analysis.

1/ 180 specimens were fixed in 10% neutrally buffered formalin and embedded in paraffin for light microscopy. The membranes were serially sectioned and stained in a stepped fashion with haematoxylin-eosin, Masson trichrome (MTC) and periodic acid-Schiff (PAS). Multiple sections of each membrane were stained with phosphotungstic acid haematoxylin histochemical stain for fibrin (PTAH).

2/ 14 specimens were fixed in glutaraldehyde and postfixed in osmiumtetroxide. These specimens were embedded in a resin for electron-microscopy. Semithin sections were made until the specimen was oriented and then a specific area of interest was selected for thin sectioning.

3/ 6 specimens were cryofixed and sectioned with a cryotome.

RESULTS

From October 1997 until May 2000, 200 consecutive choroidal neovascularization surgical resection specimens were collected from the University Eye Clinic in Cologne, Germany. The series consisted of 174 age-related macular degeneration specimens including 46 classic choroidal neovascular membranes, 38 occult choroidal neovascular membranes, 8 choroidal neovascular membranes after external beam radiotherapy, 8 deep retinal vascular anomalous complexes, 3 vascularized pigment epithelial detachments and 7 tears of the retinal pigment epithelium (table). The remaining 26 specimens were extracted from eyes with pathologic myopia (9x), idiopathic choroidal neovascu-

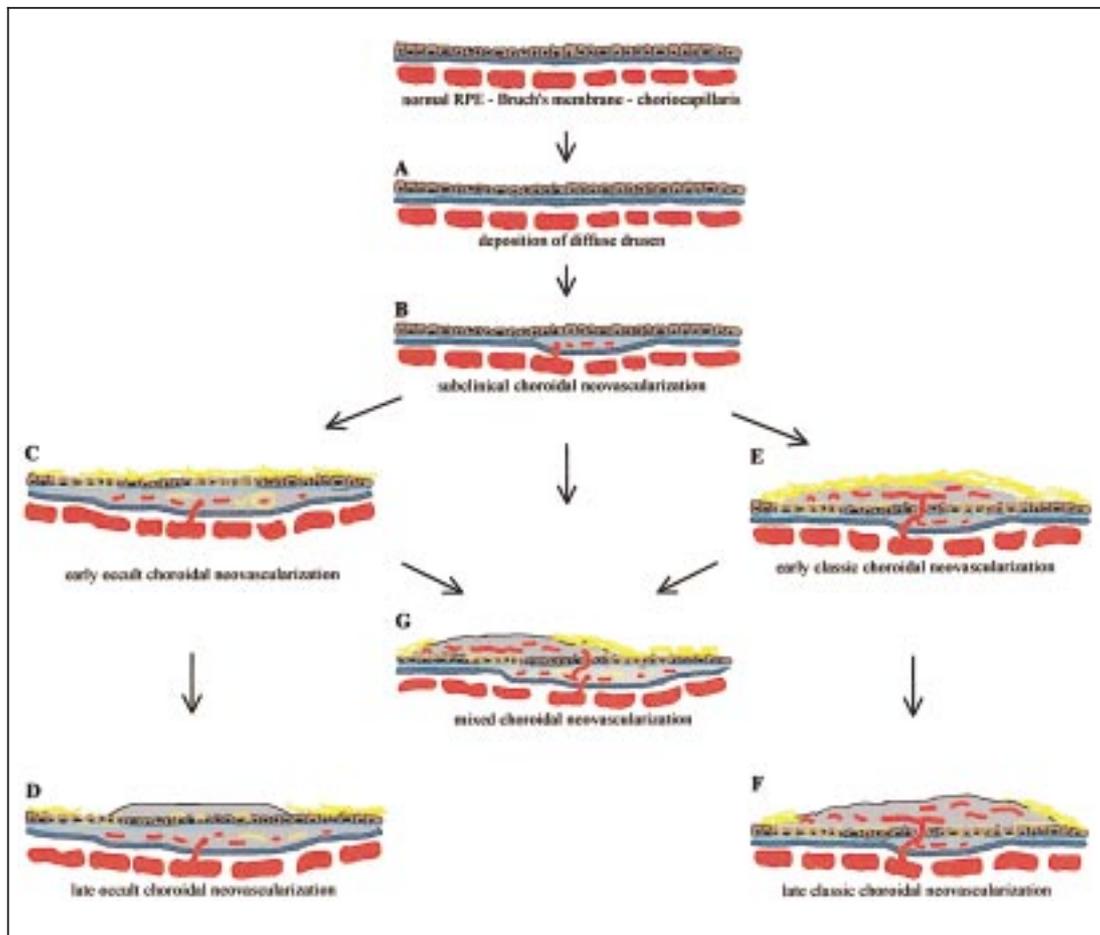


Figure: schematic representation of changes in age-related choroidal neovascularization.

larization (11x), multifocal choroiditis or punctate inner choroidopathy (5x) and dominant drusen (1x).

The primary goal of the histologic analysis was to reconstruct the architecture of the membrane from a serially sectioned specimen, in other words to describe its various components as being either subretinal, sub-RPE or a combination of both. This proved to be feasible on paraffin embedded tissue using two clues for orientation: 1/ diffuse drusen, a linear streak of variably granular eosinophilic material, positive on PAS stain and metachromatic blue-purple on MTC stain, reveal the choroidal side of the RPE and 2/ amorphous tissue with striation perpendicular to the plane of the membrane,

representing degenerated outer segment material, indicates the neuroretinal side of the specimen. On paraffin embedded tissue the distribution of fibrin was studied with phosphotungstic acid haematoxylin stain. Fibrin consisted of fine, eosinophilic fibrillogranular material, staining red on MTC stain. Its presence was confirmed by the PTAH stain for fibrin. The components of the membrane could also be relatively easily disclosed on resin-embedded semithin sections stained with toluidine blue. However reconstruction of the entire specimen was not possible as specific areas of interest were selected for ultrastructural examination. Cryosectioned material was too distorted to allow reconstruction of the membrane's architecture.

Table:

| | <i>n</i> | <i>reference</i> |
|--|----------|------------------|
| <i>AGE-RELATED MACULAR DEGENERATION</i> | | |
| primary classic | 46 | 10 |
| primary occult | 38 | 10 |
| primary mixed | 15 | 10 |
| recurrent choroidal neovascularization | | |
| after laser photocoagulation | 2 | 8 |
| primary hemorrhagic / disciform lesion | 35 | --- |
| vascularized pigment epithelial detachment | 3 | 9 |
| tear of the RPE | 7 | 9 |
| polypoidal choroidal vasculopathy | 2 | 6 |
| deep retinal vascular anomalous complex | 8 | 7 |
| choroidal neovascularization / choroidal neovascularopathy | | |
| after external beam radiotherapy | 8 | --- |
| <i>VARIA</i> | 28 | --- |
| (myopia, punctate inner choroidopathy, idiopathic,...) | | |
| <i>LOST IN PROCESSING</i> | 8 | --- |

The deposition of diffuse drusen was specifically seen in age-related macular degeneration specimens but absent in choroidal neovascularization from other causes except for a few myopic membranes in elderly patients. In these cases reconstruction is more difficult as one of the two clues is not available.

DISCUSSION

A scheme for the growth of choroidal neovascularization in age-related macular degeneration is suggested based on the available histopathologic correlations⁶⁻¹⁰. The deposition of diffuse drusen is an early pathologic marker of the disease (fig A). Choroidal neovascularization in age-related macular degeneration corresponds to the growth of new vessels in the sub-RPE space (between the inner and outer Bruch's membrane) but also in the subretinal space (between the photoreceptors and the RPE). Sarks et al¹² have histologically identified subclinical choroidal neovascularization to be characteristically located in the sub-RPE space (fig B). When the membrane continues to grow in the sub-RPE space it will be recognized as occult choroidal neovascularization on fluorescein angiography: in an early stage it will be covered by proteinaceous, fibrinous debris

(fig C) which will be replaced by an avascular fibrous layer in a later stage (fig D). The choroidal neovascular membrane may grow in the subretinal space after breaking through the RPE and the diffuse drusen. Such a membrane will likely be recognized as classic choroidal neovascularization on fluorescein angiography. Initially the membrane will be covered by proteinaceous debris (fig E) but later on this material will only be seen at its lateral edges (fig F). A combination of both sub-RPE and subretinal growing fibrovascular tissue may give rise to mixed choroidal neovascularization (fig G). Choroidal neovascularization, whether classic or occult, will ultimately lead to a disciform scar, being a thick fibrovascular scar on both sides of the RPE. Other specific angiographic manifestations of exudative age-related macular degeneration such as vascularized pigment epithelial detachment⁹, tear of the RPE⁹, polypoidal choroidal vasculopathy⁶ and deep retinal vascular anomalous complex⁷ also appear to correspond with specific histoarchitectural patterns. The adherence of the RPE to the Bruch's membrane has weakened because of the deposition of diffuse drusen. This explains why a large defect in the RPE is invariably seen after membrane extraction in age-related macular degeneration.

REFERENCES

- 1) BRESSLER N.M., BRESSLER S.B., GRAGOU DAS E.S. - *Clinical characteristics of choroidal neovascular membranes*. Arch Ophthalmol 1987; 105: 209-213.
 - 2) GREEN W.R., ENGER C. - *Age-related macular degeneration histopathologic studies*. The 1992 Lorenz E. Zimmerman lecture. Ophthalmology 1993; 100: 1519-1535.
 - 3) GREEN W.R., MCDONNELL P.J., YEO J.H. - *Pathologic features of senile macular degeneration*. Ophthalmology 1985; 92: 615-627.
 - 4) GROSSNIKLAUS H.E., GREEN G. - *The Submacular Surgery Trials Research Group. Histopathologic and ultrastructural findings of surgically excised choroidal neovascularization*. Arch Ophthalmol 1998; 116: 745-749.
 - 5) GROSSNIKLAUS H.E., HUTCHINSON A.K., CAPONE A., WOOLFSON J. - *Clinicopathologic features of surgically excised choroidal neovascular membranes*. Ophthalmology 1994; 101: 1099-1111.
 - 6) LAFAUT B.A., AISENBREY S., VANDEN BROUCKE C., BARTZ-SCHMIDT K.U. - *Polyoidal choroidal vasculopathy: a clinicopathologic correlation*. Retina, in press.
 - 7) LAFAUT B.A., AISENBREY S., VANDEN BROUCKE C., BARTZ-SCHMIDT K.U. - *Clinicopathologic correlation of deep retinal vascular anomalous complexes in age-related macular degeneration*. Br J Ophthalmol, in press.
 - 8) LAFAUT B.A., AISENBREY S., VANDEN BROUCKE C., DI TIZIO F., BARTZ-SCHMIDT K.U. - *Clinicopathologic correlation in exudative age-related macular degeneration: recurrent choroidal neovascularization*. Graefes Arch Clin Exp Ophthalmol, in press.
 - 9) LAFAUT B.A., AISENBREY S., VANDEN BROUCKE C., KROTT R., JONESCU-CUYPERS C., REYNDERS S., BARTZ-SCHMIDT K.U. - *Clinicopathologic correlation of retinal pigment epithelial tears in exudative age-related macular degeneration: pretear, tear and scarred tear*. Br J Ophthalmol, submitted.
 - 10) LAFAUT B.A., BARTZ-SCHMIDT K.U., VANDEN BROECKE C., AISENBREY S., DE LAEY J.J., HEIMANN K. - *Clinicopathological correlation in exudative age-related macular degeneration: histological differences between classic and occult choroidal neovascularization*. Br J Ophthalmol, 2000; 84: 239-243.
 - 11) Macular Photocoagulation Study Group. - *Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the Macular Photocoagulation Study*. Arch Ophthalmol 1991; 109: 1242-1257.
 - 12) SARCS S.H. - *New vessel formation beneath the retinal pigment epithelium in senile eyes*. Brit J Ophthalmol 1973; 57: 951-965.
 - 13) THUMANN G., AISENBREY S., SCHRAERMEYER U., LAFAUT B., ESSER P., WALTER P., BARTZ-SCHMIDT K.U. - *Transplantation of autologous iris pigment epithelium after removal of choroidal neovascular membranes*. Arch Ophthalmol, 2000; 118: 1350-1355.
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