Graefe's Arch Clin Exp Ophthalmol
(2003) 241:269–276

CLINICAL INVESTIGATION

DOI 10.1007/s00417-003-0634-8

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Clinicopathological correlation of choroidal neovascularization after external beam radiotherapy in age-related macular degeneration

Received: 7 August 2002
Revised: 10 December 2002
Accepted: 8 January 2003
Published online: 22 March 2003

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Abstract *Purpose:* To analyze the histopathology of choroidal neovascularization after external beam radiotherapy in age-related macular degeneration. *Methods:* A retrospective non-case-matched comparative histopathologic study. The histoarchitecture of nine surgically removed subretinal specimens from nine patients that had undergone external beam radiotherapy for exudative age-related macular degeneration was studied. Seven patients had received 20 Gy in 10 fractions and two 15 Gy in 5 fractions with an average time interval between radiotherapy and surgical extraction of 14 months (range 3–28). A consecutive series of classic, mixed and occult choroidal neovascular membranes served as controls. *Results:* Clinical findings. Radiation-associated choroidal neovasculopathy was angiographically suspected in four patients: a coarse net of vessels on fluorescein angiography developing at the border of previously irradiated choroidal neovascularization was observed in three patients ; blebs at the margin of a plaque on indocyanine green angiography were observed in two patients. Pathological findings. Diffuse drusen as well as intra-Bruch's fibrovascular tissue was found in all irradiated specimens. In four specimens an edematous vascularized layer was seen between diffuse drusen and normal-appearing intra-Bruch's fibrovascular tissue. This lesion was not found in the control specimens. A particular correlation for the bleb lesion was not recognized. *Conclusion:* The appearance of an edematous subretinal pigment epithelial vascularized layer between diffuse drusen and normal-appearing fibrovascular tissue in four of nine irradiated membranes may be secondary to previous irradiation. It may correlate with the unusual exudative manifestations observed after external beam radiotherapy.

Introduction

External beam radiation has been suggested as an alternative means of treating exudative age-related macular degeneration. Earlier studies suggested that patients treated with radiation for choroidal neovascularization in age-related macular degeneration might experience less visual acuity loss than untreated patients [2, 3, 5, 8, 10, 11, 14, 15, 20, 21, 23, 30]. Some more recent reports, however, have questioned the efficacy of this approach [26, 38, 40]. Two prospective, double-blind trials failed to show any benefit from 16 Gy applied in 8 fractions [35] and from 14 Gy in 7 fractions [32] for subfoveal choroidal neovascularization. Three other prospective, randomized trials indicated a beneficial effect from 24 Gy in 6 fractions [4], 20 Gy in 10 fractions [25] and a single fraction of 7.5 Gy [9]. These latter three studies were unfortunately not double blind [31]. The most recent reports add to the confusion. Hart et al. [22] did not find a statistically significant difference in best-corrected visual acuity 24 months after delivery of 12 Gy in 6 fractions of external beam radiation to the macula of affected eyes versus observation only in a

prospective, single-masked study; however, they observed a trend towards better vision in the treated eyes. Valmeggia et al. [43] reported a statistically significant beneficial effect on best-corrected visual acuity 12 and 18 months after either 8 Gy or 16 Gy in 4 fractions versus 1 Gy in 4 fractions in a prospective, double-masked study.

Stalmans et al. [39] described a dismal outcome in 10% of their uncontrolled series after irradiation with 20 Gy in 2 Gy fractions associated with accelerated growth of the neovascular membrane and pronounced exudative reaction. Spaide, Leys et al. [41] recognized an unusual pattern of new vessel growth, namely round or oval blebs along the outer border of the original neovascular lesion, in patients treated with external beam radiation. These lesions profusely leak fluorescein dye and are best visualized by indocyanine green angiography. Such lesions have been recognized in 7–12% of patients treated with 10–20 Gy after a follow-up of at least 1 year [41]. The visual prognosis of eyes with this particular manifestation, termed "radiation-associated choroidal neovasculopathy", is very poor in comparison to irradiated eyes without this complication [41]. A marked increase in exudation and subretinal bleeding is associated with the development of these so-called blebs [41]. Other authors [19, 33, 34] have reported similar findings, whereas such complications were not reported in several controlled studies [22, 24, 25, 32, 35, 43].

It remains unsettled, however, whether external beam radiotherapy as a means of treating subfoveal exudative age-related macular degeneration should be further explored [1, 6, 7, 12, 13, 24, 43].

A single clinicopathologic correlation of choroidal neovascularization after external beam radiotherapy has been reported previously, but the authors did not recognize particular features that might be secondary to previous irradiation [29]. We have analyzed the histoarchitecture of nine surgically removed submacular tissue specimens at various time intervals after external beam radiotherapy. Four specimens had some indication of radiation-associated choroidal neovasculopathy. The histopathology of the study specimens is compared with the microscopic appearance of untreated choroidal neovascular membrane specimens.

Materials and methods

Study population

A consecutive series of nine surgical specimens from nine patients that had undergone previous external beam radiotherapy for mixed or occult subfoveal choroidal neovascularization in age-related macular degeneration was studied. The patients had experienced additional visual acuity loss within the last 3 months before macular translocation surgery. Their preoperative visual acuity ranged

Table 1 Summary of individual clinical data, angiographic findings and histopathologic features of study specimens. *1* Subretinal fibrovascular tissue (– absent, + present, ° subretinal fibrous tissue); *2* subretinal proteinaceous debris and outer segment remains (– absent, + present, ++ vessels with little surrounding stroma embedded within such material); *3* intra-Bruch's fibrovascular component; *4* a peculiar vascularized edematous layer in between diffuse drusen and normal appearing intra-Bruch's fibrovascular tissue. *Parentheses* element much smaller than other components of neovascular membrane. *CNV* Choroidal neovascularization; *Disci* disciform lesion, thick specimen predominantly consisting of densely collagenized stroma; *Rip* tear of RPE, area of rolled-up RPE and diffuse drusen

Case	Age (years)	Dose (Gy)	Interval (months)	Fundus findings (fluorescein angiography/ indocyanine green angiography)	1	2	3	4	Remarks
1	79	20	3	No lipoid exudation, subretinal hemorrhage (occult CNV / plaque)	–	+	+	–	
2	78	20	6	Moderate lipoid exudation (partial circinate) (coarse net [multiple trunks], occult CNV / plaque)	–	+	+	(+)	
3	78	20	8	Moderate lipoid exudation (partial circinate), macular hemorrhage occult CNV / plaque	–	++	+	(+)	
4	79	20	10	*Hemorrhagic maculopathy* (not available / not available)	+	–	+	–	Disci
5	64	20	11	Moderate lipoid exudation (partial circinate), serous detachment (mixed CNV / not available)	+	–	(+)	–	Disci
6	70	15	14	*Hemorrhagic maculopathy* (not available / not available)	(+)	+	+	–	Rip
7	76	20	23	Moderate lipoid exudation (partial circinate), serous detachment (coarse net [multiple trunks], occult CNV / not available)	(°)	++	(+)	–	
8	80	15	23	Prominent lipoid exudation (full circinate), serous detachment (occult CNV / plaque + marginal blebs)	–	+	+	+	
9	67	20	28	Moderate lipid exudation (partial circinate) (coarse net (multiple trunks), occult CNV / plaque + marginal blebs)	(+)	(++)	+	+	

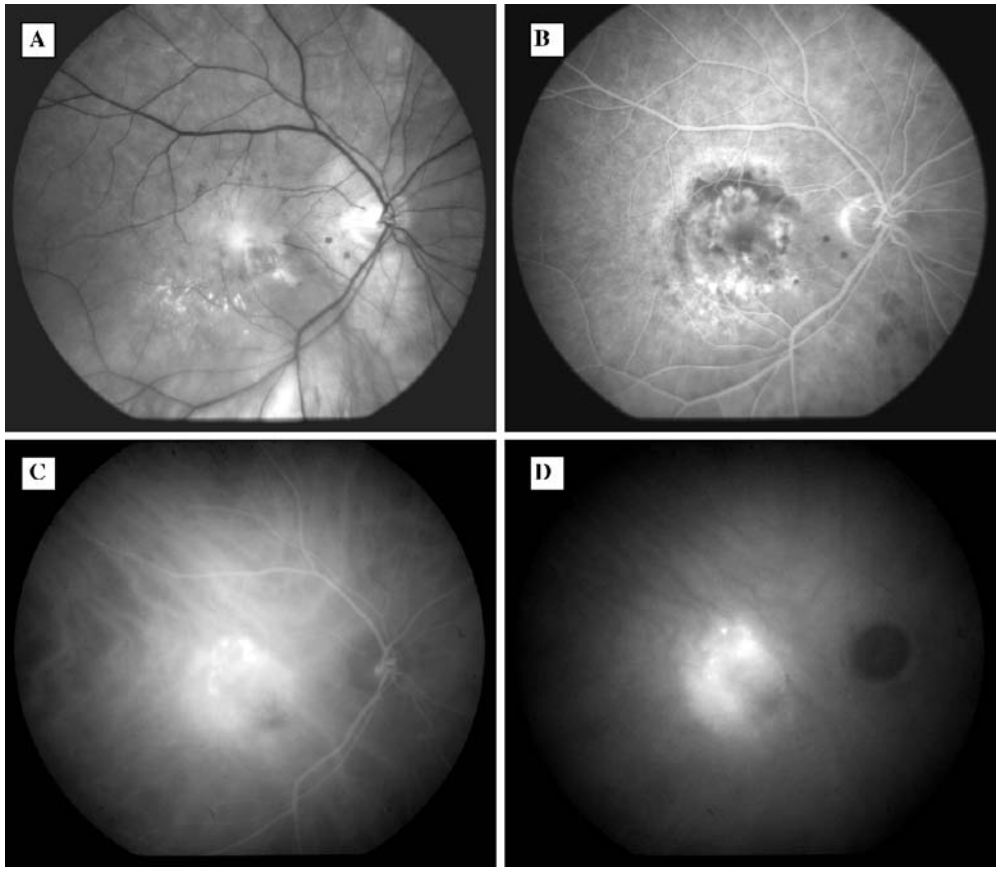

Fig. 1A–D Case 9. **A** Red-free fundus photograph shows scattered intraretinal lipoid exudates and hemorrhages. **B** Venous-phase fluorescein angiogram indicates choroidal neovascularization with dilated vessels at its superior margin. **C, D** Venous- and late-phase indocyanine green angiography shows blebs at the superior margin and overlying a plaque lesion

from 20/100 to 20/400, measured on an ETDRS chart, except for two patients with massive subretinal hemorrhage. None of these patients had diseases predisposing to choroidal neovascularization other than age-related macular degeneration, such as high myopia, multifocal choroiditis or angioid streaks. Three patients were male and six, female. The average age was 75 years (range 64–80). Seven patients had received 20 Gy in 10 fractions and two patients, 15 Gy in 5 fractions; the mean interval between radiotherapy and surgical extraction was 14 months (range 3–28). The individual data are summarized in Table 1. All nine study patients had a standard ophthalmological examination including fundus photography prior to surgery. Seven study patients had fluorescein angiography and five indocyanine green angiography not more than 14 days before surgery. Fundus angiography was not performed in two patients because of massive subretinal hemorrhage.

Control population

A consecutive series of 50 classic, 20 mixed and 20 occult choroidal neovascular membranes without associated serous pigment epithelial detachment surgically extracted from 90 patients with exudative age-related macular degeneration served as controls. These control patients had experienced visual acuity loss within the last 3 months before macular translocation surgery. The control patients were at least 60 years old and did not have any treatment for exudative AMD in the eye operated upon. None of these patients had diseases predisposing to choroidal neovascularization other than age-related macular degeneration, such as high myopia, multifocal choroiditis or angioid streaks. All 90 of the control patients had a standard ophthalmological examination including fundus photography and fluorescein angiography not more than 14 days prior to surgery. When angiographic interpretation was not straightforward because of associated subretinal hemorrhage, the specimen was excluded. None of the control eyes presented angiographic lesions with characteristics reminiscent of radiation-associated choroidal neovasculopathy. The histopathologic features of the comparison specimens have been reported previously [27, 36].

Histological analysis

All specimens were fixed in 10% neutrally buffered formalin, dehydrated and embedded in paraffin for light microscopy. The membranes were serially sectioned and stained in a stepped fashion with Masson trichrome (MTC) and periodic acid–Schiff (PAS). Multiple sections of each membrane were stained with phosphotungstic acid hematoxylin histochemical stain for fibrin (PTAH). The histologic appearance of the study specimens is described in detail, while the findings of the control specimens are summarized in table 2. Diffuse drusen refers to the deposition of abnormal material, identified by light microscopy, at the basal or choroidal side of the retinal pigment epithelium (RPE) [16, 17, 37]. It represents deposition of a granular PAS-positive material that stains metachromatically on MTC stain. Diffuse drusen correspond to basal laminar deposits and basal linear deposits, both recognized on electron microscopy. Diffuse drusen can be clearly differentiated from Bruch's membrane itself, which on light microscopy appears as a "glass membrane" in those specimens where some choroidal tissue was traumatically removed. Diffuse drusen, a light-microscopic lesion, cannot be detected clinically and should not be confused with the funduscopic lesions termed "hard", "soft" or "large" drusen.

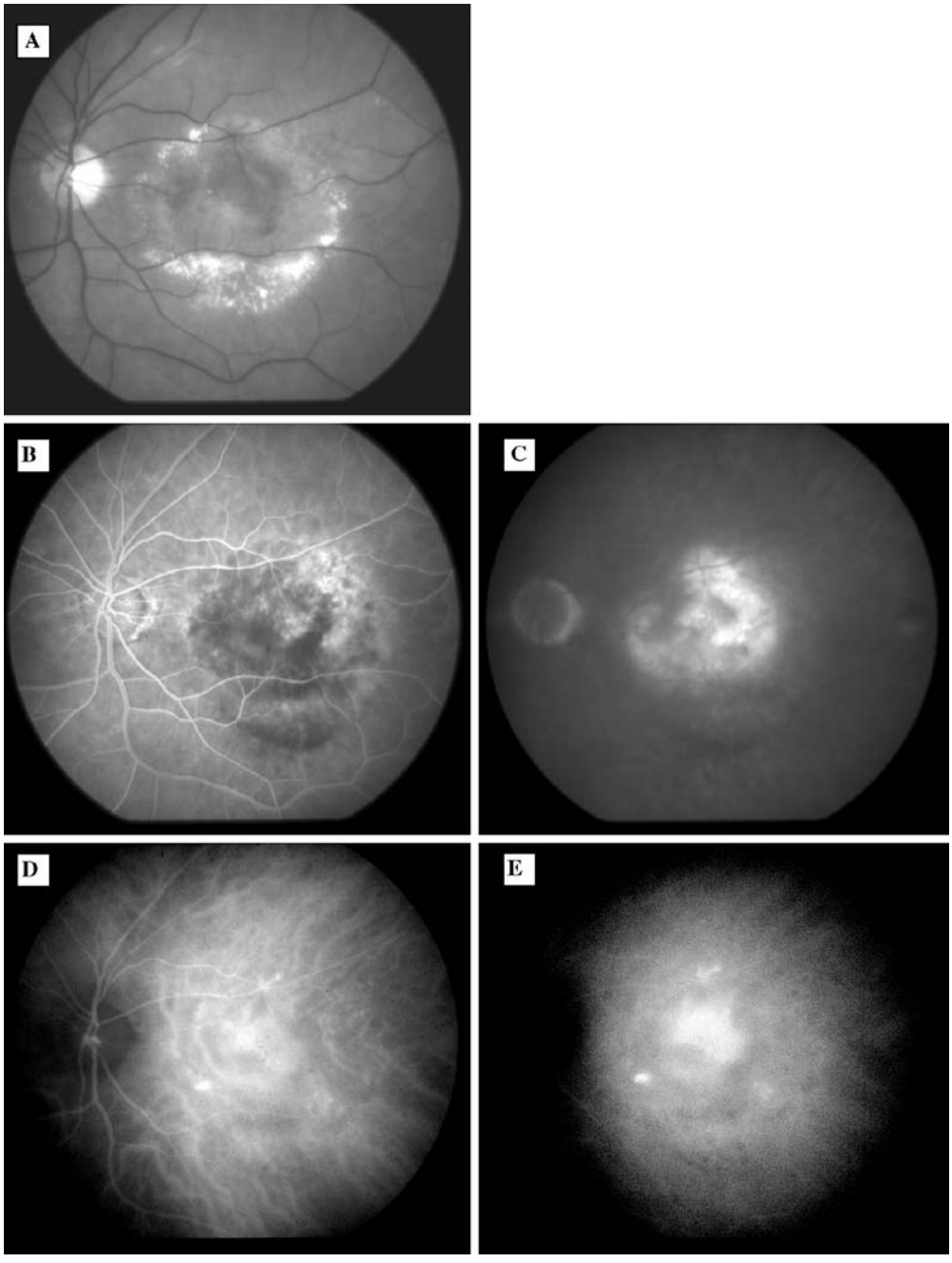

Fig. 2A–E Case 8. **A** Red-free fundus photograph indicates serous sensory macular detachment and almost a full circinate of retinal exudates. **B, C** Venous- and late-phase fluorescein angiography reveals the presence of occult choroidal neovascularization. **D, E** Venous- and late-phase indocyanine green angiography indicates blebs at the outer margin of a plaque lesion

Results

Funduscopic and angiographic findings in the study patients

Six patients had moderate retinal lipid exudates (circinate covering about one third of the macular area) and one had very pronounced retinal lipid exudation with a circinate over about two thirds of the macular area. Three patients had extensive subretinal hemorrhages: in one an occult choroidal neovascularization with an adjacent hemorrhagic pigment epithelial detachment was found on fluorescein angiography and in two others angiography was not performed because of massive subretinal hemorrhage. None of these patients was on peroral anticoagulation.

Seven patients had preoperative fluorescein angiography. An occult choroidal neovascular membrane was recognized in six and a mixed choroidal neovascular membrane in one. In three of six occult membranes a peculiar, coarse vascular net was seen in the outer perimeter of the lesion (Fig. 1). These lesions were not considered mixed choroidal neovascularization because of the

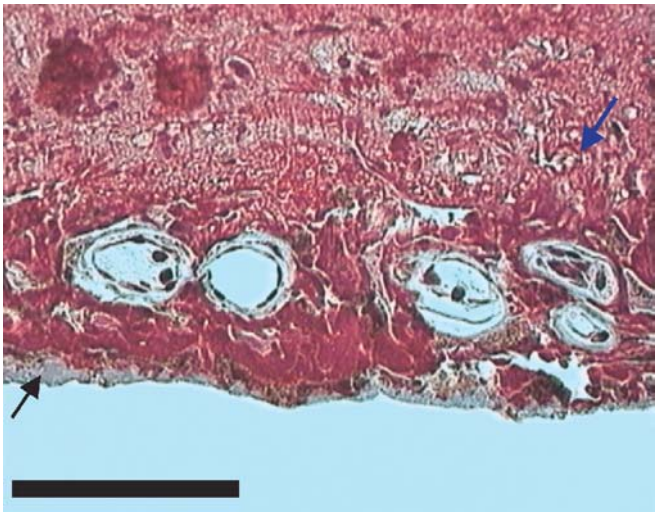

Fig. 3 Detail of specimen 7 demonstrating subretinal vessels with little surrounding stroma embedded in subretinal amorphous debris close to the RPE and the diffuse drusen. *Black arrow* RPE and diffuse drusen, *blue arrow* subretinal debris. MTC; *bar* 100 µm

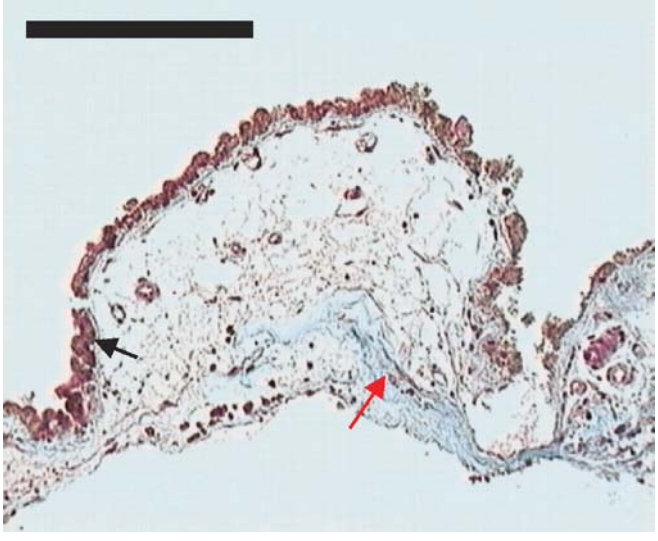

Fig. 4 Detail of intra-Bruch's fibrovascular tissue close to the margin of specimen 8. Some vessels and a few inflammatory cells are lying in an apparently "empty" matrix between the diffuse drusen and more collagenized intra-Bruch's fibrovascular tissue. *Black arrow* RPE and diffuse drusen, *red arrow* intra-Bruch's fibrovascular tissue. MTC; *bar* 200 µm

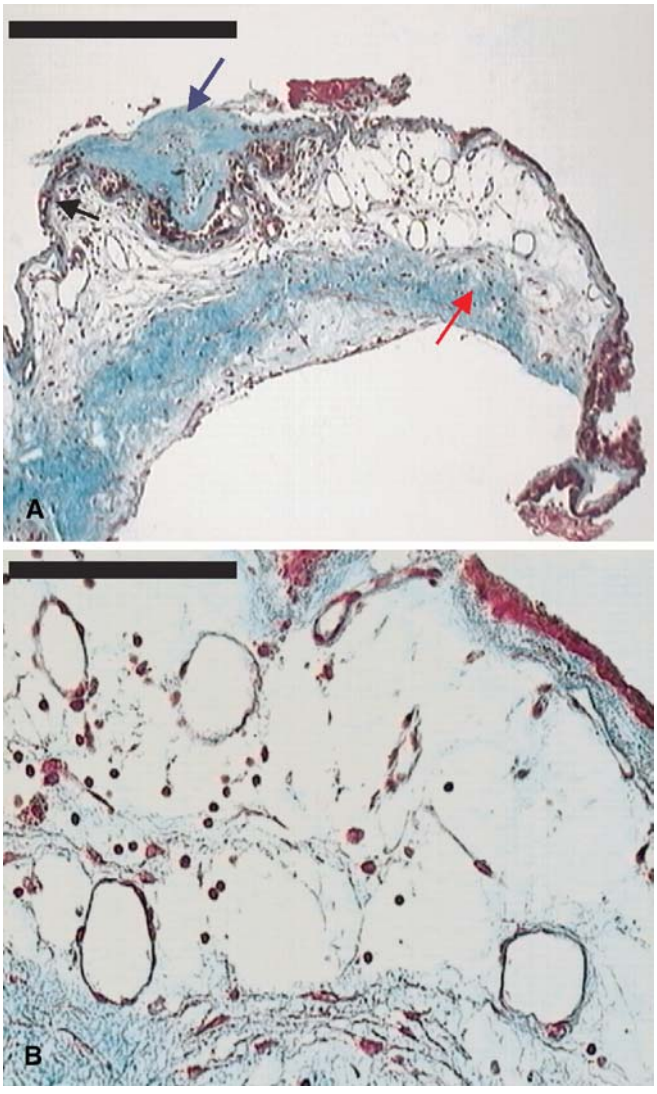

Fig. 5 **A** Overview and **B** detail of specimen 9. Subretinal and intra-Bruch's fibrovascular tissue is seen. An edematous vascularized layer with scattered inflammatory cells is found between the diffuse drusen and the more collagenized remainder of the intra-Bruch's fibrovascular tissue. *Black arrow* RPE and diffuse drusen, *blue arrow* subretinal fibrovascular tissue, *red arrow* intra-Bruch's fibrovascular tissue. MTC; *bar:* **A** 400 µm, **B** 100 µm

peculiar coarse vascular net. This kind of appearance likely represents the fluorescein angiographic appearance of radiation-associated choroidal neovasculopathy. In all seven choroidal neovascular membranes a very prominent progressive fluorescein leakage was observed.

Five patients underwent indocyanine green angiography preoperatively. In all five patients a plaque lesion was seen. In two patients the plaque was associated with marginal hotspots, so-called blebs, which represent the indocyanine green finding characteristic of radiation-associated choroidal neovasculopathy (Figs. 1, 2). In one case, the blebs corresponded with the fluorescein angiographically recognized coarse vessels.

Histopathologic findings in the study specimens

Diffuse drusen were recognized in the nine specimens. Seven specimens had a prominent subretinal accumulation of proteinaceous debris including fibrin (PTAH posi-

Table 2 Summary of the histopathologic findings in study specimens and control specimens (*CNV* choroidal neovascularization)

	CNV after irradiation	Controls (nonirradiated CNV)		
		Classic	Mixed	Occult
Basal laminar deposits	9/9	44/50	20/20	20/20
Orientation failed	0/9	1/50[a]	0/20	0/20
Fibrovascular tissue	9/9	50/50	19/20[b]	19/20[b]
Subretinal component	6/9	49/49[a]	16/20	5/20
Fibrovascular tissue	4/9	46/49[a]	12/20	1/20
Fibrous tissue	1/9	0/49[a]	3/20	4/20
Only vessels embedded in debris	3/9	4/49[a]	2/20	0/20
Intra-Bruch's component				
Fibrovascular tissue	9/9	24/49[a]	19/20	19/20
Edematous vascularized layer	4/9	0/49[a]	0/20	0/20

[a] One specimen consisted only of fibrovascular tissue that could not be oriented as remains of outer segments and diffuse drusen were not recognized
[b] One specimen consisted of subretinal amorphous debris, RPE and diffuse drusen

tive), remains of outer segments and scattered red blood cells. This subretinal material probably corresponds to clinically visible serous sensory retinal detachment. In three specimens vessels with little surrounding stroma were embedded within this subretinal debris material (Fig. 3). Four specimens contained subretinal fibrovascular tissue, in two of which the subretinal fibrovascular component was much smaller than the intra-Bruch's fibrovascular component. In one specimen a small area of subretinal fibrous tissue was seen. Intra-Bruch's membrane fibrovascular tissue was found in all specimens. In four specimens a peculiar edematous layer, consisting of vessels and a few inflammatory cells surrounded by an almost "empty"-appearing stroma, was seen between diffuse drusen and the remainder of more normal-appearing intra-Bruch's fibrovascular tissue (Figs. 4, 5). In two specimens, 6 and 8 months after radiation therapy, this edematous layer was discontinuous and covered about one third of the surface of the intra-Bruch's fibrovascular tissue, whereas in two other specimens, 23 and 28 months after radiation therapy, this layer covered almost entirely the underlying normal-appearing fibrovascular tissue.

Two specimens were rather thick and consisted predominantly of fibrous tissue rather than fibrovascular tissue. One specimen from a patient with hemorrhagic maculopathy contained torn and rolled-up RPE and diffuse drusen, indicating a tear of the RPE. A conspicuous infiltration of inflammatory cells (lymphocytes) adjacent to the rolled-up RPE and diffuse drusen was found in the latter case.

The histopathologic findings in study and control specimens are summarized in Table 2.

Discussion

A single clinicopathologic correlation of choroidal neovascularization after external beam radiotherapy [29] and none of radiation-associated choroidal neovasculopathy have been reported. We collected surgically extracted choroidal neovascularization specimens in nine patients after previous radiotherapy with an interval ranging from 3 to 28 months. Some of these patients were suspected to have radiation-associated choroidal neovasculopathy. The goal of the study was to identify features of irradiated membranes that may differentiate them from untreated choroidal neovascularization. Three consecutive series of untreated choroidal neovascular membrane specimens served as controls.

Light microscopy allows the recognition of the major components of choroidal neovascularization, such as RPE, vascular endothelium, fibrocytes, macrophages, outer segments, collagen, diffuse drusen and fibrin [18]. Recognition of diffuse drusen is instrumental in the orientation of the specimen [27]. Prominent diffuse drusen and intra-Bruch's fibrovascular tissue were found in the nine irradiated specimens, confirming the diagnosis of age-related macular degeneration [16, 17, 37].

A marked accumulation of proteinaceous debris and remains of outer segments was observed in seven specimens. In three of these specimens, vessels lied scattered in this subretinal debris with little surrounding stroma at all. These vessels tended to be located eccentrically within the specimen. In two of the three specimens (cases 7 and 9) coarse vessels were clearly seen on fluorescein angiography, whereas in the third specimen (case 3) such coarse vessels could be recognized neither on fluorescein angiography nor on indocyanine green angiography. Therefore it does not seem likely that this lesion is characteristic for radiation-associated choroidal neovasculopathy. Such vessels are not specific for choroidal neovascular membranes after irradiation, as similar lesions have also been recognized in untreated choroidal neovascular membranes, albeit less frequently (about 10% of classic and mixed choroidal neovascular membranes).

In four specimens subretinal fibrovascular tissue was found that appeared light microscopically similar to fibrovascular tissue observed in untreated classic and mixed choroidal neovascularization. Two of these specimens (cases 4 and 5) had histopathologic characteristics of a disciform scar. One specimen extracted from an eye

with hemorrhagic maculopathy (case 6) showed rolled-up RPE corresponding with a recent tear of the RPE, and diffuse drusen were found without a dense collagenous capsule [28, 42]. The last specimen (case 9) was suspected to have radiation choroidal neovasculopathy because coarse vessels were identified in the outer perimeter of the lesion on fluorescein angiography. In this case the subretinal fibrovascular component was much smaller than the underlying intra-Bruch's fibrovascular component and appeared to be situated rather centrally within the specimen.

In all specimens intra-Bruch's fibrovascular tissue was found. In two specimens the intra-Bruch's fibrovascular component was smaller than the associated subretinal fibrovascular component. An unusual feature, namely an edematous layer containing thin-walled vessels and some inflammatory cells, almost without surrounding collagenous stroma or fibroblasts, was found between diffuse drusen and normal appearing fibrovascular tissue in four specimens, three of which had angiographic signs of radiation-associated choroidal neovasculopathy. The edematous layer was more extensive, stretching over almost the entire area of intra-Bruch's fibrovascular tissue, in the two cases with a long interval (23 and 28 months) between membrane removal and external beam irradiation than in the two cases with a short interval (6 and 8 months), where it covered only about one third of the surface of intra-Bruch's fibrovascular tissue. Such an edematous layer within intra-Bruch's fibrovascular tissue was not seen in the control specimens. However, this finding has not been reported after radiation therapy for other intraocular diseases, e.g. tumors, metastasis and thyroid eye disease. Although this edematous subretinal epithelial vascularized layer was observed only in some of the specimens, it might therefore represent a peculiar feature after radiation therapy of choroidal neovascular membranes due to age-related macular degeneration, where neovascularization is present at the time of external beam irradiation. Whether it does relate to the previously applied radiotherapy and does correspond to the peculiar angiographic lesion of radiation-associated choroidal neovasculopathy remains unclear, as this edematous layer is observed in the outer perimeter as well as centrally within the neovascular membrane complex and it was found in only three of four specimens with suspicion of radiation-associated choroidal neovasculopathy.

In conclusion, we present uncommon histological observations in choroidal neovascularization specimens of patients with a history of radiotherapy for exudative AMD. Larger histology series of radiation-treated choroidal neovascularization are needed to confirm these findings.

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