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Subretinal choroidal neovascularization associated with choroidal nevus

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PURPOSE. *Evaluation of a large series of choroidal nevi inducing the formation of a neovascular membrane in order to more clearly define the clinical presentation and to evaluate the efficacy of various treatment options.*
METHOD. *Retrospective study of 22 clinical cases.*
RESULTS. *All nevi were situated in the posterior choroid. They had a mean diameter of 3.8 mm and a mean thickness of 1.4 mm. Neovascular membranes were classic in all cases, extrafoveal in 13 cases (59%), and subfoveal in 9 cases (41%). A serous retinal detachment was present in every case, hemorrhages were present in 13 cases (59%), and lipid deposits were present in 16 cases (73%). All extrafoveal neovascular membranes were successfully treated by thermal laser photocoagulation. Initial visual acuity was 0.1 in three cases, 0.2-0.4 in five cases, 0.5-0.8 in four cases, and 1.0 or more in two cases. Final visual acuity was 0.1 in one case, 0.2-0.4 in one case, 0.5-0.8 in four cases, and 1.0 or more in seven cases. Five subfoveal neovascular membranes were treated either by thermal laser, photodynamic therapy, or irradiation. No treatment was applied in four cases and in one of these cases, spontaneous resolution of the neovascular membrane was observed. No growth of the pigmented tumor was observed with a mean follow-up of 4.8 years.*
CONCLUSIONS. *Proliferation of a neovascular membrane on the surface of a pigmented choroidal tumor is a rare complication and is considered to be a relative indicator of a benign nature of the lesion. In the authors' experience, neovascular membranes are extrafoveal in more than half of cases and are accessible to laser photocoagulation. In contrast, the various modalities used to treat subfoveal neovascular membrane were ineffective and functional prognosis was unfavorable in these cases. (Eur J Ophthalmol 2004; 14: 123-31)*

KEY WORDS. *Choroidal nevi, Choroidal neovascularization, Laser photocoagulation, Photodynamic therapy*

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INTRODUCTION

Choroidal nevi are benign pigmented tumors that can occasionally cause severe loss of visual acuity or central scotoma (1). These lesions frequently induce secondary changes of the pigment epithelium and lead to the formation of drusen and, more rarely, serous retinal detachment and proliferation of choroidal neovascularization (2).

The clinical and histologic features of choroidal neovascularizations arising on the surface of nevi were described by Gass in 1967 (3). These neovascular membranes are generally responsible for hemorrhagic and exudative complications and, without treatment, a fi-

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TABLE I - SYMPTOMS REPORTED BY 20 PATIENTS AND THEIR DURATION (asymptomatic lesion discovered incidentally in two cases)

Symptoms	No. (%) of cases
Duration of symptoms, mo	
≤1	6 (30)
2–3	6 (30)
4–6	4 (20)
≥7	4 (20)
Symptoms	
Loss of visual acuity	11 (55)
Veil or blurred vision	5 (25)
Central or paracentral scotoma	3 (15)
Metamorphopsias	6 (30)
Micropsias	4 (20)
Loss of near visual acuity	2 (10)
Decreased luminosity	1 (5)
Impression of light haloes	1 (5)

brotic scar may develop (4, 5). The spectrum of the clinical presentation has been described in a limited number of published series or isolated cases (1, 5-13).

This retrospective study of a large series of cases was conducted in order to better define the clinical presentation of nevi complicated by subretinal choroidal neovascularization, as well as the natural history of these neovascular membranes, and to discuss the efficacy of various treatment options.

PATIENTS AND METHOD

Review of the Jules Gonin Hospital Ocular Oncology Unit digital files identified 22 cases of choroidal nevus associated with choroidal neovascularization. An initial examination including measurement of best-corrected visual acuity on a Snellen chart, fluorescein angiography, and ultrasound measurement of tumor thickness was performed in all cases, and indocyanine green angiography was performed in 18 cases. The medical files were reviewed to record the patient's age and sex, the clinical symptoms and their duration, the referral diagnosis, the tumor diameter and thickness, the site of the choroidal neovascularization in relation to the fovea, and the presence or

TABLE II - CLINICAL CHARACTERISTICS OF THE NEVI, POSITION OF NEOVASCULAR MEMBRANES, ASSOCIATED SIGNS, VISUAL FUNCTION, AND APPEARANCE OF THE MACULA OF THE CONTRALATERAL EYE

Clinical characteristics of the nevi	Value
Diameter	
Range, mm	1.9 to 6
Mean, mm	3.8
≤2 mm, no. cases (%)	2 (9.1)
2.1 to 4 mm, no. cases (%)	11 (50)
4.1 to 6 mm, no. cases (%)	9 (40.9)
Thickness	
Range, mm	1.0 to 2.2
Mean, mm	1.4
≤1.1 mm, no. cases (%)	4 (18.2)
1.2 to 1.5 mm, no. cases (%)	11 (50)
1.6 to 2.2 mm, no. cases (%)	7 (31.8)
Distance from the fovea	
Range, mm	0 to 1.6
Contact or invaded, no. cases (%)	7 (31.8)
0.1 to 0.5 mm, no. cases (%)	8 (36.4)
≥0.6 mm, no. cases (%)	7 (31.8)
Distance from the optic disc	
Range, mm	0 to 4
Contact, no. cases (%)	11 (50)
0.1 to 1.0 mm, no. cases (%)	4 (18.2)
≥1.1 mm, no. cases (%)	7 (31.8)
Relations of the neovascular membrane with the fovea	
Subfoveal, no. cases (%)	9 (41.0)
Distance 0.1 to 0.5 mm, no. cases (%)	3 (13.6)
Distance ≥0.6 mm, no. cases (%)	10 (45.4)
Associated signs, no. cases (%)	
Serous retinal detachment	22 (100)
Hemorrhages	13 (59.1)
Lipid deposits	16 (72.7)
Pigment epitheliopathy	1 (4.5)
Drusen and/or retinal pigment epithelial changes	6 (27.3)
Visual acuity, no. cases (%)	
≤0.1	8 (36.4)
0.2 to 0.4	8 (36.4)
0.5 to 0.7	4 (18.2)
≥0.8	2 (9.0)
Status of the fellow eye, no. cases (%)	
Visual acuity	
0.7 to 0.8	4 (18.2)
0.9 to 1.0	14 (63.6)
≥1.25	4 (18.2)
Ophthalmoscopy	
No alterations	16 (72.7)
Sparse drusen	3 (13.6)
Confluent drusen	1 (4.5)
Retinal pigment epithelial changes	4 (18.2)
Neovascular membrane	0

absence of serous retinal detachment, hemorrhage, lipid deposits, pigment epitheliopathy, or orange pigment. The tumor diameter, its distance from the fovea and optic disc, and the distance of the choroidal neovascularization from the fovea were measured in papillary diameters on color photographs and angiography films. The measurements were converted into millimeters, considering the horizontal diameter of the optic disc to be equal to 1.5 mm.

Twenty of the 22 patients were regularly followed, while two patients failed to attend follow-up examinations. At each follow-up visit, the best-corrected visual acuity was recorded, and fluorescein angiography was performed, usually in conjunction with indocyanine green angiography. All ocular fundus photographic and angiographic documents were reviewed for the purposes of this study.

RESULTS

This patient series included 8 men and 14 women between the ages of 38 and 73 years (mean age 58.5 years). All but two of these patients were symptomatic. The symptoms reported and their duration are summarized in Table I. Referral diagnosis was suspected choroidal melanoma in 17 cases, age-related macular degeneration in 1 case, and nevus with secondary retinal detachment in 3 cases. Only one case was referred because of a nevus associated with choroidal neovascularization. The clinical characteristics of the nevi, the position of the choroidal neovascularization, visual function, associated signs, and the status of the fellow eye are summarized in Table II.

Choroidal neovascularization was extrafoveal in 13 cases and subfoveal in 9 cases. It was situated close to the geographic center of the pigmented nevus and was not larger than the nevus in 20 cases and was situated close to the limit of the nevus and extended onto the choroid toward the fovea in the other 2 cases. Choroidal neovascularization was in all cases classic without occult component.

Extrafoveal choroidal neovascularization was treated in all cases by laser photocoagulation. Permanent occlusion of the choroidal neovascularization, demonstrated by fluorescein angiography, was obtained in every case, and no recurrence was observed during follow-up since the last visit ranging from 1 to 10 years (mean 3.9 years). A single photocoagulation session was sufficient to eradicate the choroidal neovascularization in nine cases, but two sessions were necessary in three cases and three sessions were necessary in one case. The serous retinal detachment resolved after occlusion of the choroidal neovascularization (Fig. 1), and the lipid deposits and hemorrhages were resorbed in every case. The final visual acuity compared to the baseline visual acuity is summarized in Table III. An increase of the visual acuity was observed in nine cases and the visual acuity remained stable in four cases.

TABLE III - CROSS TABULATION OF VISUAL ACUITY BEFORE AND AFTER LASER PHOTOCOAGULATION OF 13 CASES OF EXTRAFOVEAL NEOVASCULAR MEMBRANE ASSOCIATED WITH CHOROIDAL NEVUS

Visual acuity after treatment	≥1.0	1	2	2	2
	0.5–0.8		3	1	
	0.2–0.4	1			
	0.1	1			
		0.1	0.2–0.4	0.5–0.8	≥1.0
	Visual acuity before treatment				

Various treatment modalities were used in the nine cases with subfoveal choroidal neovascularization. Two cases were treated by accelerated proton beam irradiation, two cases were treated by verteporfin photodynamic therapy, one case was treated by laser photoablation, and four cases did not receive any treatment, one of which resolved spontaneously.

The visual acuity of the three untreated cases was 0.1 or less. Two of these patients were lost to follow-up, and the third has been reviewed with a follow-up of 5 years; his visual acuity has remained unchanged throughout the observation period, and the choroidal neovascularization, which has not changed in size, has gradually been transformed into inactive fibroglial tissue.

The two cases treated by accelerated proton beam therapy presented a visual acuity of 0.2 and less than 0.1. Treatment was performed after delineation of the target volume by tantalum clips, with an irradiation dose of 40 Gy, delivered in four fractions, according to the same protocol as that used for the treatment

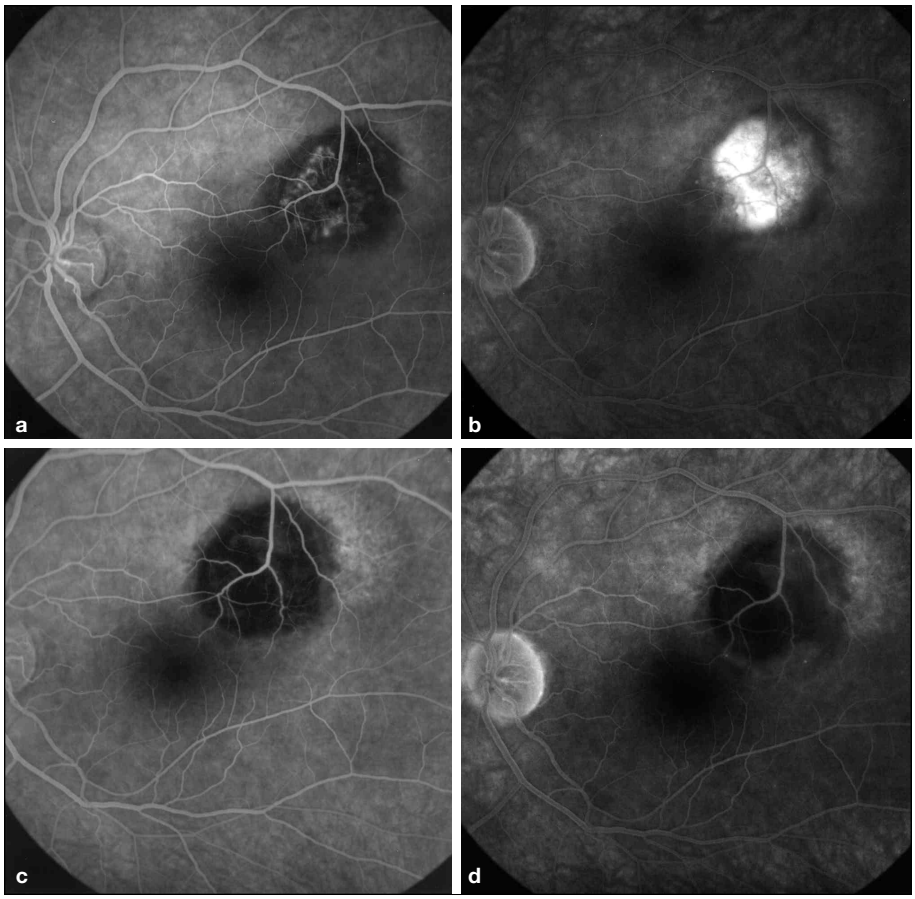

Fig. 1 - *Laser photocoagulation of a choroidal neovascularization on the surface of a paramacular nevus. Visual acuity reduced to 0.3.* **a, b)** *Fluorescein angiography, arteriovenous and late films. Presence of a subtle choroidal neovascularization on the surface of the tumor producing a serous exudation.* **c, d)** *Fluorescein angiography 6 months after treatment, arteriovenous and late films. No change in the limits of the pigmented tumor. Occlusion of the choroidal neovascularization and recovery of visual acuity to 0.8.*

of melanomas (14) and choroidal hemangiomas (15). Partial resolution of the choroidal neovascularization was obtained in both cases. One patient developed radiation maculopathy and his visual acuity decreased from 0.2 to 0.1 after a follow-up of 3 years. In contrast, the visual acuity of the other case improved from less than 0.1 to 0.1, 6 months after treatment, after which time he was lost to follow-up.

The visual acuity of the two cases treated by photodynamic therapy was 0.4 and 0.2, respectively. Treatment was performed according to identical parameters to those used for choroidal neovascularization secondary to age-related macular degeneration (16, 17) and, in both cases, was repeated 3 months after the first application. However, progression of exudative and hemorrhagic phenomena and extension of the choroidal neovascularization with marked reduction of visual function were observed in both cases. Therefore, we performed secondary laser photoablation (Fig. 2), which resulted in reapplication of the retina, resorption of lipid deposits, and eradication of the choroidal neovascularization. The visual acuity decreased from 0.4 to 0.1 after 3 years in the first patient, and from 0.2 to counting fingers after 1 year in the other case.

The visual acuity of the only case treated by first-line laser photoablation for subfoveal choroidal neovascularization was 0.1 and remained unchanged 18 months later.

One case in this series presented an unusual course with spontaneous resolution of the subfoveal choroidal neovascularization. This patient was 53 years old at the time of appearance of the choroidal neovascularization secondary to a nevus situated in contact with the optic disc. He was referred by his ophthalmologist, 7 years previously, to confirm the diagnosis of a large nevus partially surrounding the optic disc. Visual acuity at that time was 1.0 and fluorescein angiography demonstrated alterations of the pigment

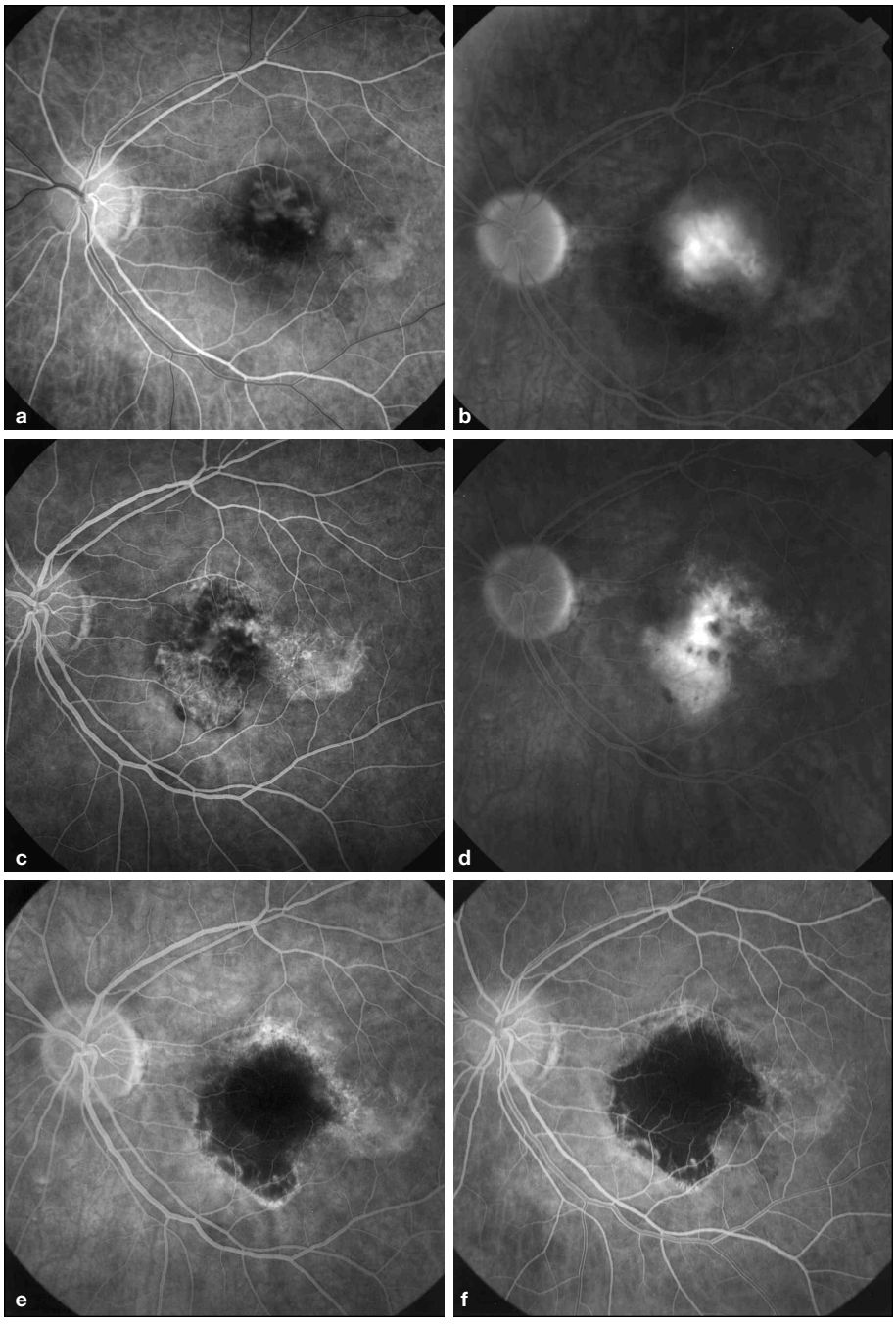

Fig. 2 - *Verteporfin photodynamic therapy of a subfoveal choroidal neovascularization on the surface of a posterior pole nevus.* **a, b)** *Initial examination. Fluorescein angiography, arteriovenous and late films. Small pigmented tumor of the macular region, covered by choroidal neovascularization with geographical contours giving rise to marked exudation on the late films. Visual acuity reduced to 0.2.* **c, d)** *Fluorescein angiography, arteriovenous and late films 6 months after the first treatment and 3 months after the second photodynamic therapy. Progression of the choroidal neovascularization beyond the limits of the pigmented tumor and increased serous exudation and lipid deposits. Loss of visual acuity to counting fingers.* **e, f)** *Fluorescein angiography, early and late arteriovenous films, 1 year after the initial examination and 6 months after laser photoablation of the choroidal neovascularization. No signs of recurrence. Stable central scotoma and unchanged visual acuity.*

epithelium with limited diffusion of fluorescein and several leakage points close to the posterior margin of the tumor, around the superior temporal margin of the optic disc (Fig. 3, a and b). Periodic observation was recommended and the patient was subsequently referred for investigation of decreased visual acuity accompanied by metamorphopsias due to serous and hemorrhagic macular detachment. Corrected visual acuity had decreased to 0.5, but the size of the nevus had not changed since the previous photograph. Fluorescein angiography demonstrated the presence of a choroidal neovascularization between the edge

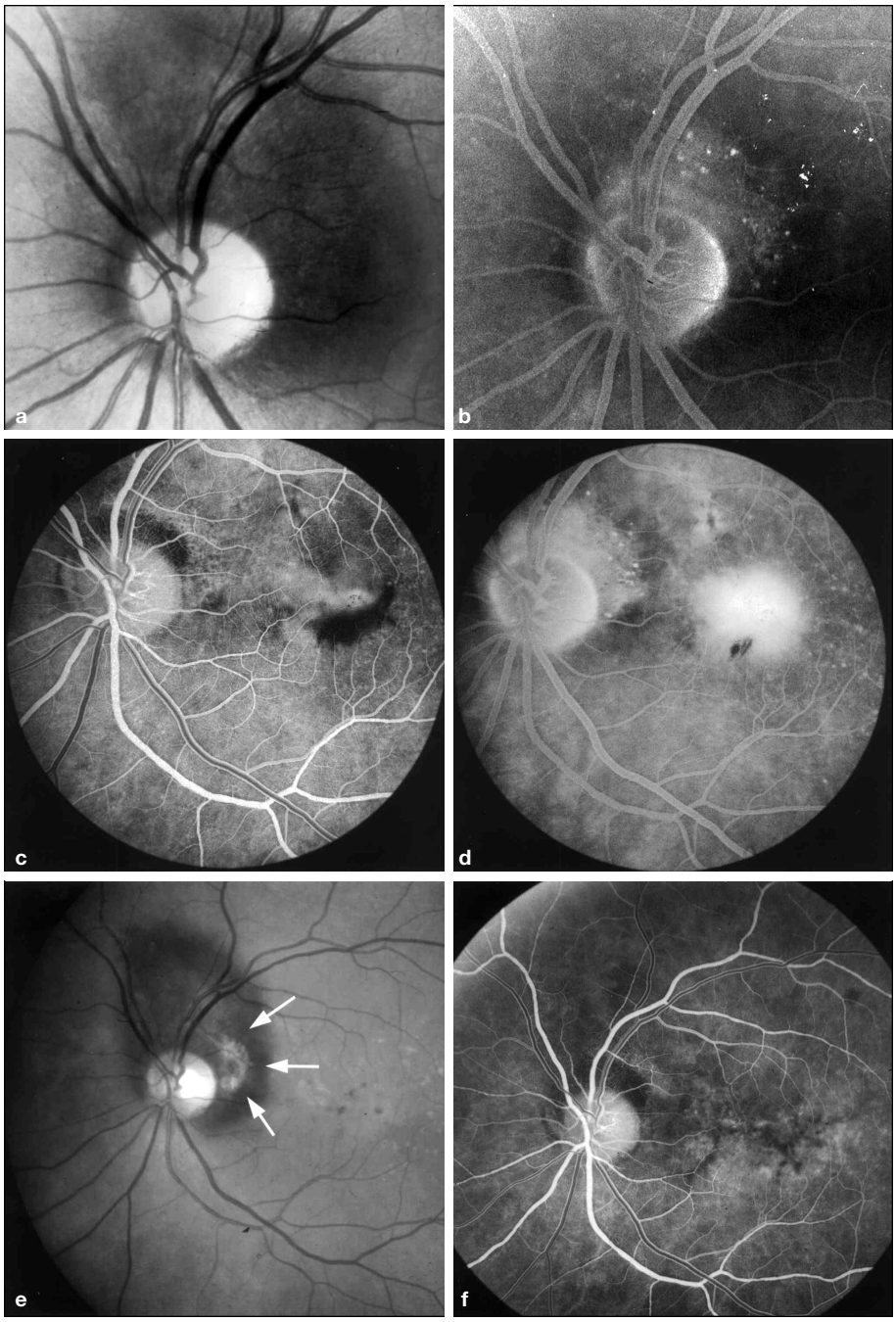

Fig. 3 - *Spontaneous regression of a subfoveal choroidal neovascularization on a peripapillary nevus.* **a, b)** *Ophthalmoscopy and fluorescein angiography of a choroidal nevus partially surrounding the optic disc, performed 7 years before formation of the choroidal neovascularization. Pigment epithelium changes on the surface of the tumor, close to the superior temporal margin of the optic disc. Presence of numerous leakage points on the late arteriovenous film. Visual acuity: 1.0.* **c, d)** *Fluorescein angiography performed after appearance of macular changes. Formation of a serous retinal detachment between the fovea and the inferior temporal margin of the pigmented tumor, containing a choroidal neovascularization lined by subretinal hemorrhage. Marked exudation on the late films and reduction of visual acuity to 0.5. Note the presence of nonconfluent drusen.*
e, f) *Ophthalmoscopy and fluorescein angiography performed 11 years after appearance of the choroidal neovascularization and 9 years after its spontaneous resolution that led to recovery of visual function. No change in the size of the pigmented tumor. Pigment epithelium changes at the site and along the path of the choroidal neovascularization. Presence of a spot of subretinal fibrosis close to the inferior temporal margin of the tumor, at the site of the presumed origin of the choroidal neovascularization (arrows). Visual acuity: 0.8.*

of the pigmented tumor and the fovea and revealed the formation of numerous macular drusen that were absent on the angiography performed 7 years previously (Fig. 3, c and d). No treatment was performed at that time because of the subfoveal site of the choroidal neovascularization, and the patient was simply observed periodically. Two years later, spontaneous resolution of the serous retinal detachment was observed with improvement of visual acuity. At the last follow-up examination, 11 years after appearance of the choroidal neovascularization, visual acuity was 0.8, the retina was flat, the dimensions of the nevus remained un-

changed, and an area of subretinal fibrosis situated at the presumed site of origin of the choroidal neovascularization was observed at the inferior edge of the nevus (Fig. 3E, arrows). Fluorescein angiography (Fig. 3F) and indocyanine green angiography confirmed the absence of any exudative activity and demonstrated pigment epithelium changes throughout the zone of the serous retinal detachment. No obvious changes were observed in the number and appearance of the posterior pole drusen.

The mean follow-up at the time of the last visit for this series was 4.8 years (range 6 months to 11 years). None of the nevi presented any signs of growth during this follow-up period, which could suggest a diagnosis of small choroidal melanoma.

DISCUSSION

Choroidal nevi can be responsible for loss of visual acuity by inducing serous retinal detachment and degeneration of photoreceptors, combined with modifications of pigment epithelium cells, or by inducing a choroidal neovascularization (1, 5, 10, 18-20).

Proliferation of a choroidal neovascularization on the surface of a nevus is a rare event, and only about 50 well-documented cases, describing the various clinical features of this complication, have been published (1, 3-11, 13, 18, 21).

It has been reported that the presence of choroidal neovascularization on the surface of a pigmented tumor tends to suggest that the tumor has been present for several years and consequently presents a low growth potential (5). This is confirmed by our clinical cases: with a mean follow-up of 4.8 years, none of the 22 tumors in this series presented any signs of progression. In the literature, choroidal neovascularizations proliferating on the surface of the tumor have been reported in a context of uveal melanoma in one case (22), malignant transformation of a nevus in two cases (10, 23), and nevus presenting signs of progression in one case (9). However, although the presence of a choroidal neovascularization constitutes an important argument in favor of a benign tumor (24), this sign is not one of the criteria used in the various published studies to statistically estimate the risk of progression of small, intermediate pigmented tumors (25-30). The presence of a choroidal neovascularization on the surface of a pigmented tumor must therefore be considered as a clinical indicator, but not as a statistically significant element in favor of a tumor with a low potential for progression.

Age-related degenerative lesions – isolated or confluent drusen and pigment epithelium changes – in the affected eye or contralateral eye were present in 27.3% of cases in our series. Callanan et al (9), in a series of 22 cases with a much higher mean age than in our series (66 years vs 58.5 years), reported a higher proportion of cases (10/22) with age-related macular degeneration. These findings suggest that age-related macular degeneration may sometimes constitute a risk factor for the formation of choroidal neovascularization on the surface of a choroidal nevus. However, in 90.9% of cases of our series, regardless of the site of the nevus, the choroidal neovascularization was situated in the central, most prominent part of the tumor, supporting the hypothesis that alterations of Bruch's membrane, allowing proliferation of the choroidal neovascularization, are essentially due to mechanical compression and/or degenerative phenomena induced by contact of nevus cells with the overlying tissues. Furthermore, none of the cases in our series presented signs of neovascular age-related macular degeneration in the contralateral eye, which constitutes an additional argument in favor of a direct relationship between choroidal nevi and choroidal neovascularizations.

Laser photocoagulation was used to treat all extrafoveal choroidal neovascularizations (13 cases, 59%). This treatment was effective, inducing permanent occlusion of the choroidal neovascularization, and stabilization (4 cases) or improvement (9 cases) of visual function. The final visual acuity was ≥1.0 in seven cases. Positive results after laser photocoagulation of extrafoveal choroidal neovascularization have also been published by Waltman et al (13) (3 cases), Minès et al (11) (2 cases), Folk et al (10) (2 cases), and Callanan et al (9) (6 cases). This therapeutic approach can therefore be highly recommended for this type of choroidal neovascularization.

On the other hand, we have not found a satisfactory therapeutic solution for subfoveal choroidal neovascularizations. When left untreated, this type of choroidal neovascularization generally progresses in a slow and limited way, undergoing fibrous changes and inducing loss of central vision, as observed in our cases (9). All treatment modalities applied to these cases,

with some rare exceptions (31), gave disappointing results. In our experience, accelerated proton beam irradiation used in two cases and photodynamic therapy used in two other cases failed to produce a local control of the subretinal neovascularization.

Finally, we used laser photoablation as first-line treatment in one case with a subfoveal choroidal neovascularization. However, only extrafoveal vision can be preserved by this treatment modality, which controls progression of the choroidal neovascularization and also limits the extent of the scotoma (10). This type of treatment would therefore be exclusively recommended in cases of documented progression of the choroidal neovascularization with continuous loss of visual function, as choroidal neovascularizations on the surface of nevi have sometimes been reported to stabilize spontaneously (9) or regress (4).

CONCLUSION

In view of the limited number of cases (about 50 well-documented cases) published to date and our experience (22 cases), proliferation of a choroidal neovascularization on the surface of a nevus is a rare complication reflecting a chronic tumor and representing a sign in favor of a benign lesion.

In our experience, more than half of choroidal neovascularizations are extrafoveal and responded well to laser photocoagulation therapy. The short-term and medium-term functional prognosis of extrafoveal choroidal neovascularizations is excellent. However, in subfoveal choroidal neovascularizations, no treatment has been shown to be effective to preserve or restore central visual function. Apart from a few exceptional cases of spontaneous regression or stabilization of the choroidal neovascularization, the functional prognosis of subfoveal choroidal neovascularizations is generally poor.

Fluorescein angiography is recommended in every case of a small pigmented choroidal tumor accompanied by serous retinal detachment, in order to determine the presence of a choroidal neovascularization that might profit from laser photocoagulation. As the presence of a choroidal neovascularization does not formally exclude progression of the tumor, regular long-term follow-up is also recommended.

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