Graefe's Arch Clin Exp Ophthalmol (1982) 218:237–243

Graefe's Archive
for Clinical and Experimental
Ophthalmology

Three Basic Types of Foveal Involvement in Choroidal Melanomas*

J. Reimer Wolter
The Departments of Ophthalmology and Pathology of the University of Michigan Medical Center, Ann Arbor, Michigan, USA

Abstract. Three cases are used to demonstrate the main types of cystoid macular edema, which have been seen to occur in association with choroidal melanomas: 1) direct involvement in cases, where the neoplasm is located under the foveal retina, 2) indirect involvement due to a subfoveal exudate in choroidal melanomas distant to the fovea and 3) indirect foveolar involvement without associated subfoveal tumor or exudate. A recording of the pathology of these three basic reaction patterns of the central retina in choroidal melanomas is considered important. It is emphasized, that combinations of the reactions are common and may result in more complex situations.

Zusammenfassung. Drei Fälle werden benutzt, um die Haupttypen von zystoidem Maculaödem zu demonstrieren, die zusammen mit malignen Aderhautmelanomen gesehen werden: 1) direkte Foveabeteiligung in Fällen, in denen der Aderhauttumor im Foveabereich liegt, 2) indirekte Foveabeteiligung in Fällen mit subfovealem Exudat und extrafovealen Melanom und 3) indirekte Foveabeteiligung in Fällen, in denen im Foveabereich weder ein Melanom noch retroretinales Exudat gefunden werden. Ein Verständnis dieser drei fundamental verschiedenen Reaktionstypen der zentralen Netzhaut bei Aderhautmelanomen ist wichtig. Es wird darauf hingewiesen, daß Kombinationen dieser drei Hauptreaktionstypen häufig sind und zu komplizierteren Situationen führen können.

Choroidal melanomas cause central vision loss early in the clinical course, when they are located near the fovea and when the neoplasm directly interferes with the nutrition of the outer layers of the central retina. Exudative retinal detachment over and next to the choroidal melanomas add to the vision loss, of course. Such an exudate can be massive, but it is most commonly limited to an area over and around the choroidal neoplasm. Exudative detachment has a tendency to involve the foveal region, even when the tumor is located in the nasal periphery, for example, and when there is no visible connection to retroretinal exudation in the region of the tumor. This may be a result of the fact, that the retinal adhesion to the pigment epithelium in the region of the fovea is less than that of all other parts of the retina [1]. Melanomas distant to the fovea, finally, can also cause central cystoid retinal changes without clinically or pathologically detectable exudative detachment under the fovea.

Foveal involvement in choroidal melanomas occurs in almost as many variations as there are cases. In the present paper, an attempt will be made to give examples and to create a foundation for a better understanding of the basic types of the foveal reactions, that commonly occur in eyes with choroidal melanomas.

Case Reports

Case 1. This 80 year old male had a one-year history of central vision loss in his right eye. With a known cancer of the colon metastatic to the liver, the patient had remained in surprisingly good general health. In December 1980 vision was counts fingers in 1 foot in his right eye. A pigmented tumor was found in the foveal choroid of the right eye and this clinically exhibited overlying orange pigment clumps. The eye was enucleated on 12-1-80 and was fixed in buffered formalin immediately. Gross examination revealed a darkbrown tumor measuring $8 \times 7 \times 2$ mm in the choroid of the foveal zone. The vitreous was detached and partly retracted. The foveal retina on top of the tumor showed star-shaped folding of a somewhat irregular type. Sections revealed occasional lymphocytes in iris and ciliary body. Retinal folding of the inner layers consistent with the grossly observed star-shaped change was seen (Fig. 1). The nerve fiber and ganglion cell layers were well preserved. Henle's fiber layer was greatly thickened and exhibited multiple cystoid spaces of relatively small size (Figs. 1 and 2). The cystoid change also involved areas of the inner plexiforme and inner nuclear layers in the parafoveolar zone. Most of the cysts contained some loose fibrinous exudate (Fig. 2) and the cystic change was associated with loss of normal retinal tissue elements. The foveola was elevated due to a mild and somewhat irregular fold running vertically through the foveolar region. The central cones showed much degeneration and atrophy (Fig. 2). Serous exudate containing pigment-filled macrophages separated the retina from the pigment epithelium. The pigment epithelium also had much degeneration as well as loss of cells and separation from Bruch's membrane in its central part on top of the tumor (Fig. 2). Pigment epithelial cells in all stages of destruction were seen (Fig. 2). Bruch's membrane was intact. The vascular network of the choriocapillaris was compressed, but its remnants were still present in their normal attachment to Bruch's membrane (Fig. 2). The remainder of the central choroid was replaced by the neoplasm composed of densely arranged spindle-shaped cells. Some of these cells had nucleolated nuclei. The remainder of the retina,

* Supported by the Research To Prevent Blindness, Inc., New York, N.Y.

Reprint requests to: J. Reimer Wolter, M.D., University of Michigan Medical Center, Ann Arbor, Michigan 48109, USA

0721-832X/82/0218/0237/$01.40

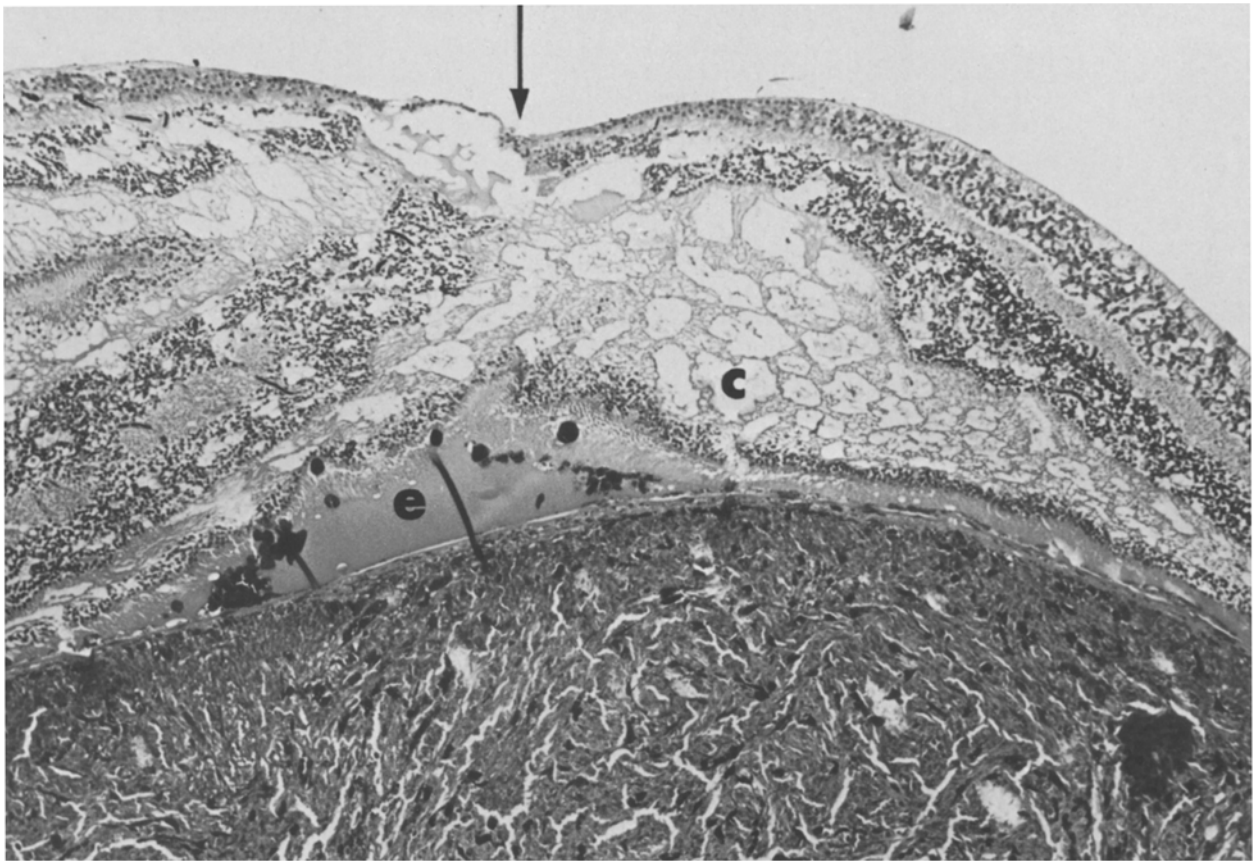


Fig. 1. Case 1, foveal retina with shallow foveola (*arrow*), a well preserved ganglion cell layer, advanced cystoid change (*c*) mainly in Henle's fiber layer and a vertical retinal fold through the foveola filled with serous exudate (*e*), macrophages and detached pigment epithelium. The mass of the choroidal melanoma is seen in the lower part of the figure. – Paraffin section, H and E stain, photomicrograph $\times 150$

the optic nerve and the sclera were about normal. A diagnosis of cystoid macular edema (CME) over a spindle-B cell melanoma of the central choroid was made.

Case 2. This 74 year-old female was first seen on 5–21–81 with vision of counts fingers in 2 feet in the left eye. A highly elevated and bilobed choroidal tumor was found in the nasal fundus of the right eye. Slight retinal detachment was seen over and next to the tumor. However, the central retina was in place and considered "unremarkable" by the examining ophthalmologist. A clinical diagnosis of choroidal melanoma was made. The eye was enucleated on 6–3–81 and immediately fixed in buffered formalin solution. The eye was opened in a horizontal plane and the large tumor involving the nasal choroid was found to measure $16 \times 13 \times 8$ mm. The tumor extended almost all the way between nasal ciliary body and the nasal aspect of the optic disk. It was surrounded by a thin layer of amber-colored retroretinal exudate. Some additional exudate was found in the subretinal space inferiorly at about 6 o'clock. The retina of the temporal half of the eye was in place, but a thin layer of localized exudate was grossly seen under the foveal retina. This was totally separate from the exudate next to the choroidal tumor on the nasal aspect of the fundus as well as the additional inferior subretinal exudate.

Microscopic study revealed diffuse mononuclear infiltration of iris and ciliary body as well as detachment of the pars plana of the ciliary body on the nasal side next to the tumor (Fig. 3). The retina was detached in its nasal aspect and a serous exudate separated it from the large underlying choroidal tumor. This tumor had caused extensive elevation of Bruch's membrane, but it had not broken through this layer. The pigment epithelium was quite degenerated on the surface of the choroidal tumor. The tumor was composed of spindle-shaped cells with nucleolated nuclei, predominantly, but occasional epithelioid tumor cellls were found. Necrosis had occurred in several areas within the tumor. Direct extraocular extension was not found. Ciliary arteries on the nasal aspect of the disk supplying the tumor were greatly enlarged. Early vitreous detachment was seen posteriorly, but this had not involved the region of the foveola (Figs. 3–5). A funnel-shaped attachment of vitreous to the foveolar region was preserved. In this zone the vitreous contained some loose fibrinous exudate (Figs. 4 and 5).

The retina temporal to the optic nerve exhibited artificial detachment due to shrinkage in the histological process of embedding. It appeared generally normal. However, an isolated retroretinal exudate of serous nature separated the foveal retina from the corresponding pigment epithelium (Fig. 3). This exudate was centered on the detached foveola and it contained a row of pigment-filled histiocytes next to the detached cones (Figs. 4 and 5). The foveola had lost its normal valley-like arrangement and it appeared in the horizontal sections as a mound – due to a shallow fold running in a vertical direction and additional swelling of Henle's fiber layer (Fig. 4). The foveolar retina also exhibited definite atrophy of the neurons in its outer layers, swelling and microcystic changes mainly in Henle's fiber layer as well as atrophy of central cones (Fig. 5). The inner retinal layers showed some wrinkling, but these layers were other-

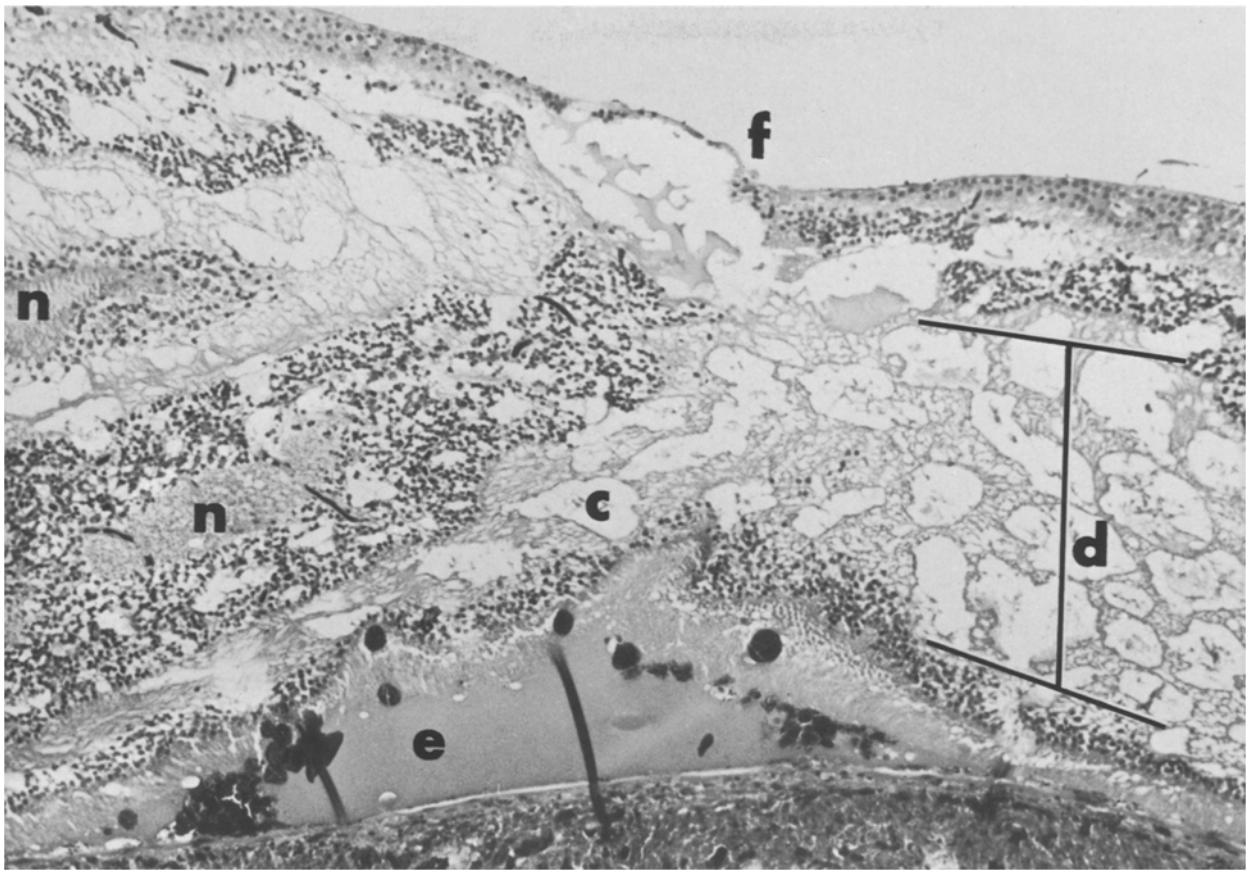
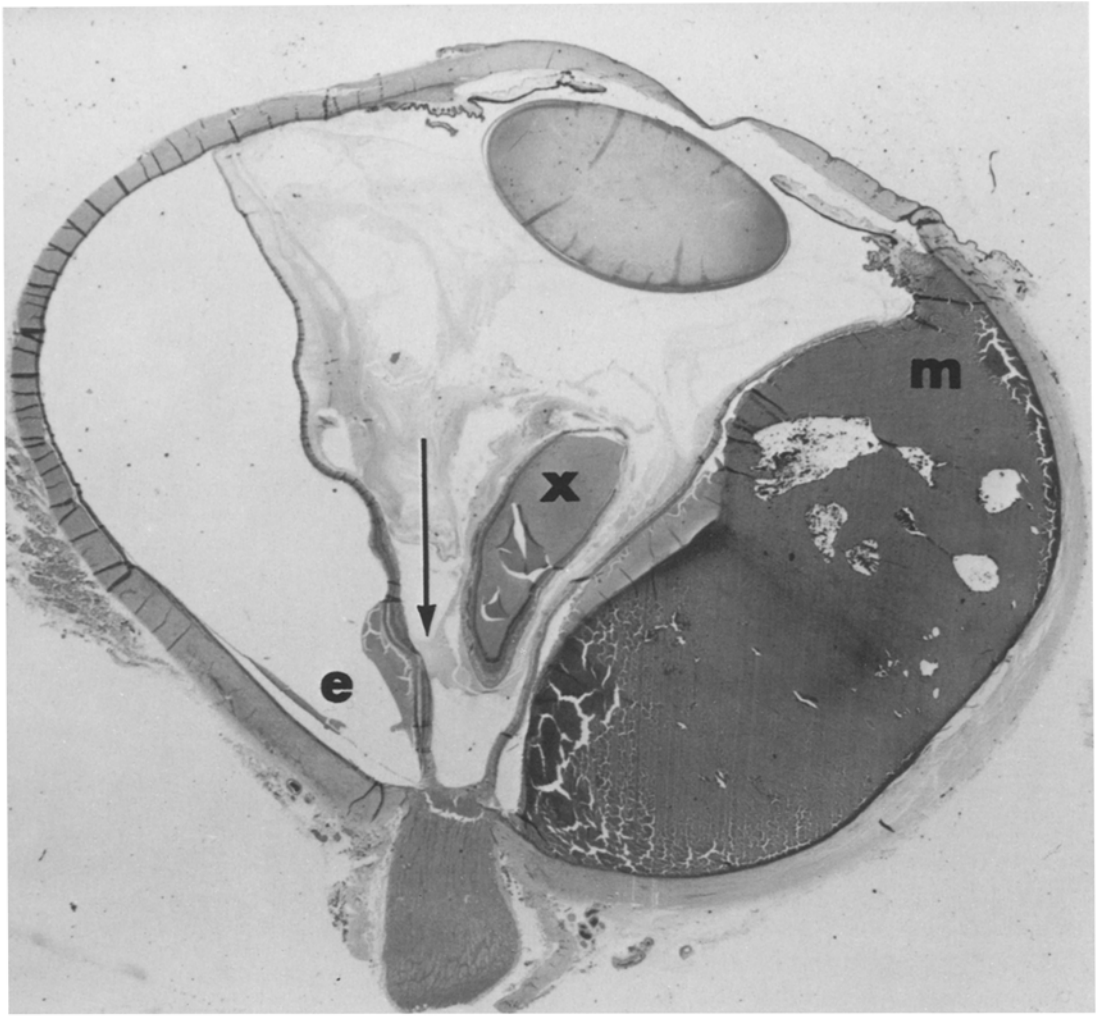


Fig. 2. Case 1, higher power view of Fig. 1 to show details of cystoid involvement of the foveola (*f*) with very thin surface layer. The double bars (*d*) indicate the cystoid (*c*) enlargement of Henle's fiber layer. Folding of the central retina results in reduplication of deep retinal layers (*n*) nasal to the foveola. The vertical fold through the foveola causes detachment of the cones with a serous exudate (*e*) containing pigment filled macrophages as well as separating and degenerating pigment epithelium. The tumor is seen below. – Paraffin section, H and E stain, photomicrograph 1300

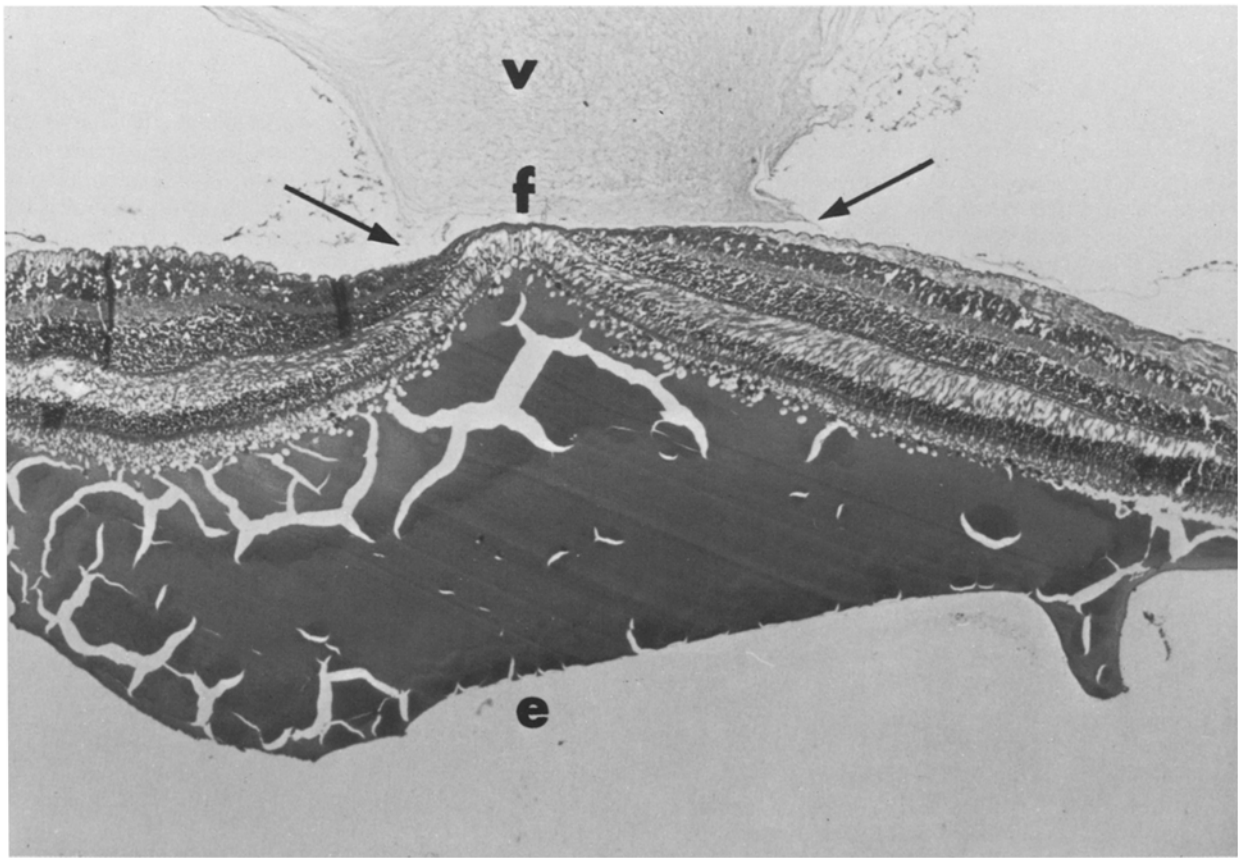
wise almost normal. The pigment epithelium in the foveal zone was normal except for some very small drusen. The retroretinal exudate also had firm adhesions to this layer and, thus, it was split artificially in the process of embedding (Fig. 3). The choroid was diffusely congested and exhibited some mononuclear infiltration. The optic nerve was about normal and the central retinal vessels were open. The histopathological diagnosis was: large choroidal melanoma of a mixed type with epithelioid cells exhibiting localized exudative detachment of the foveal retina with a mild vertical fold, swelling and cystoid changes in Henle's fiber layer, posterior vitreous detachment with preservation of the vitreous attachment in the foveolar zone and atrophy of the central cones and their cell bodies.

Case 3. This 71 year-old white male was first seen by an ophthalmologist on 2–2–81. The patient had observed a peripheral vision defect in his right eye for more than a month, but loss of central vision had occurred in this eye about one week before the examination. Vision on 2–2–81 was 20/200 in the right eye and ophthalmoscopy showed a large choroidal mass of round shape located in the midperiphery nasally and inferiorly to the disk. This protruded from the retina without associated retinal detachment. A melanoma was suspected and the eye was enucleated on 2–4–81. The eye was fixed in buffered formalin immediately. After opening the eye in a horizontal plane, an oval tumor of gray color measuring $10 \times 12 \times 9$ mm was found protruding from the nasal retina. A small zone of localized exudative retinal detachment peripheral to the tumor was recognized grossly. The remaining retina including the foveal zone was in place. However, the retina in the foveolar region appeared grossly irregular and thickened. The vitreous was detached and retracted.

Sections revealed early rubeosis and diffuse mononuclear infiltration of iris and ciliary body. The tumor originated in the nasal choroid and it was composed of very atypical epithelioid cells mainly. The retina was absent in the region of the neoplasm. The inner surface of the tumor was formed by rather loosely arranged tumor cells and some of these cells were seen in the process of separation. Neoplastic cells in islands or in isolation were freely floating in the vitreous space. The same kind of cells had formed seedings on the retinal surface all over. Different stages of invasion of the retina next to retinal blood vessels could be observed histologically. A small zone of secondary detachment with a serous retroretinal exudate was seen next to the tumor in the nasal periphery. The foveal retina exhibited distinct swelling of Henle's fiber layer (Figs. 6 and 7). This was associated with a sharp fold of the outer retinal layers running through the foveolar zone in a vertical direction. The detachment of the retina seen in the sections clearly is an artifact. The cones in the fold showed signs of distortion and degeneration with cystoid spaces (Fig. 7). The outer nuclear layer exhibited a distinct decrease in the humber of nuclei. Henle's fiber layer also exhibited microcystoid changes (Fig. 7). The inner retinal layers



3



4

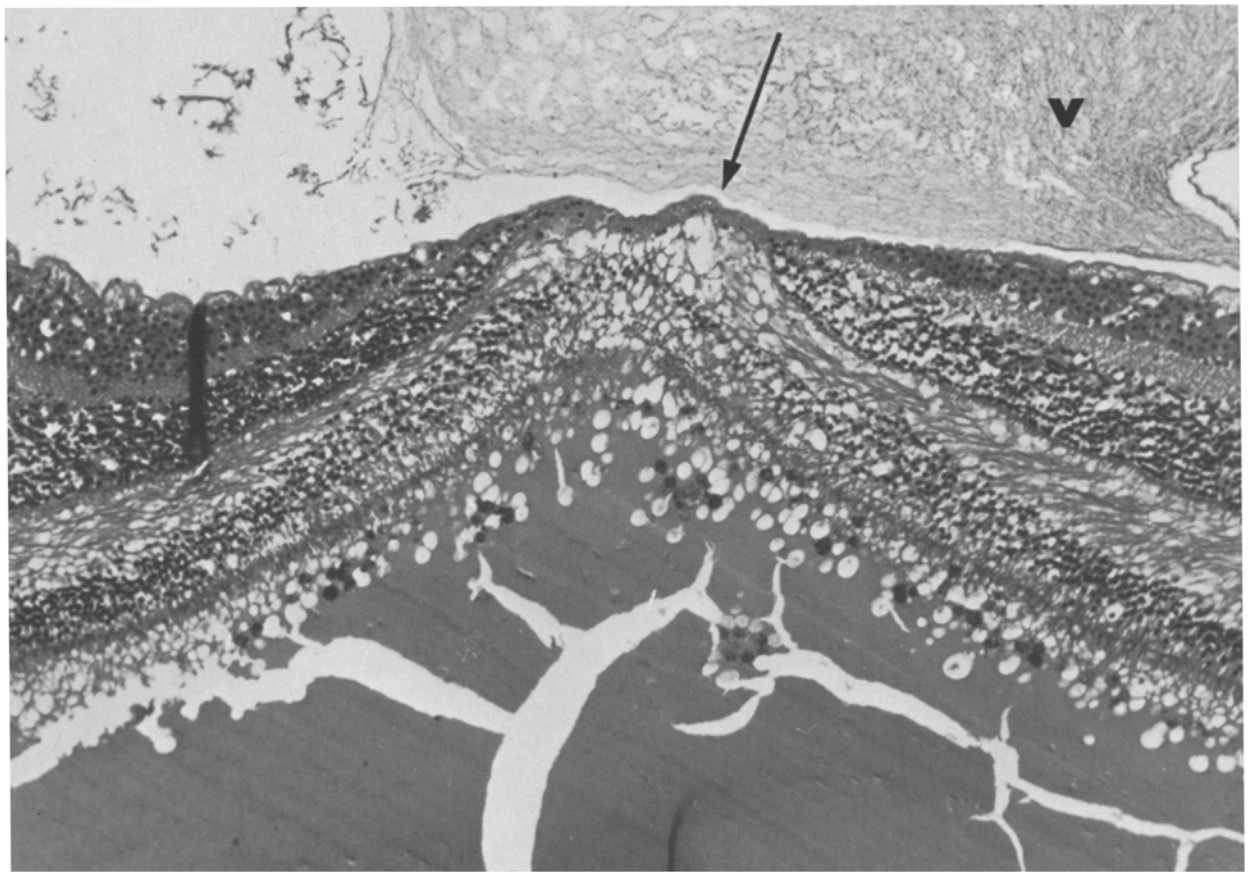


Fig. 5. Case 2, high power view to show cystoid and microcystoid changes in the foveola (*arrow*), central vitreous adhesions (*v*) and degeneration of foveal cones with accumulation of pigmentfilled macrophages in the serous subretinal exudate. – Paraffin section, H and E stain, photomicrograph ×300

were about normal and did not take part in the coarse folding, but these inner layers exhibited wavy vertical wrinkling of lower "frequency" (Fig. 7). The central pigment epithelium was normal. There was no exudate separating central retina and choroid (Fig. 6). The choroid exhibited diffuse vascular congestion. A histopathological diagnosis of a choroidal melanoma of an epithelioid type with extensive evidence of lytic destruction of overlying retina, seedings all over the retinal surface and a vertical folding of the retina through the foveolar zone with microcystoid changes in Henle's fiber layer was made.

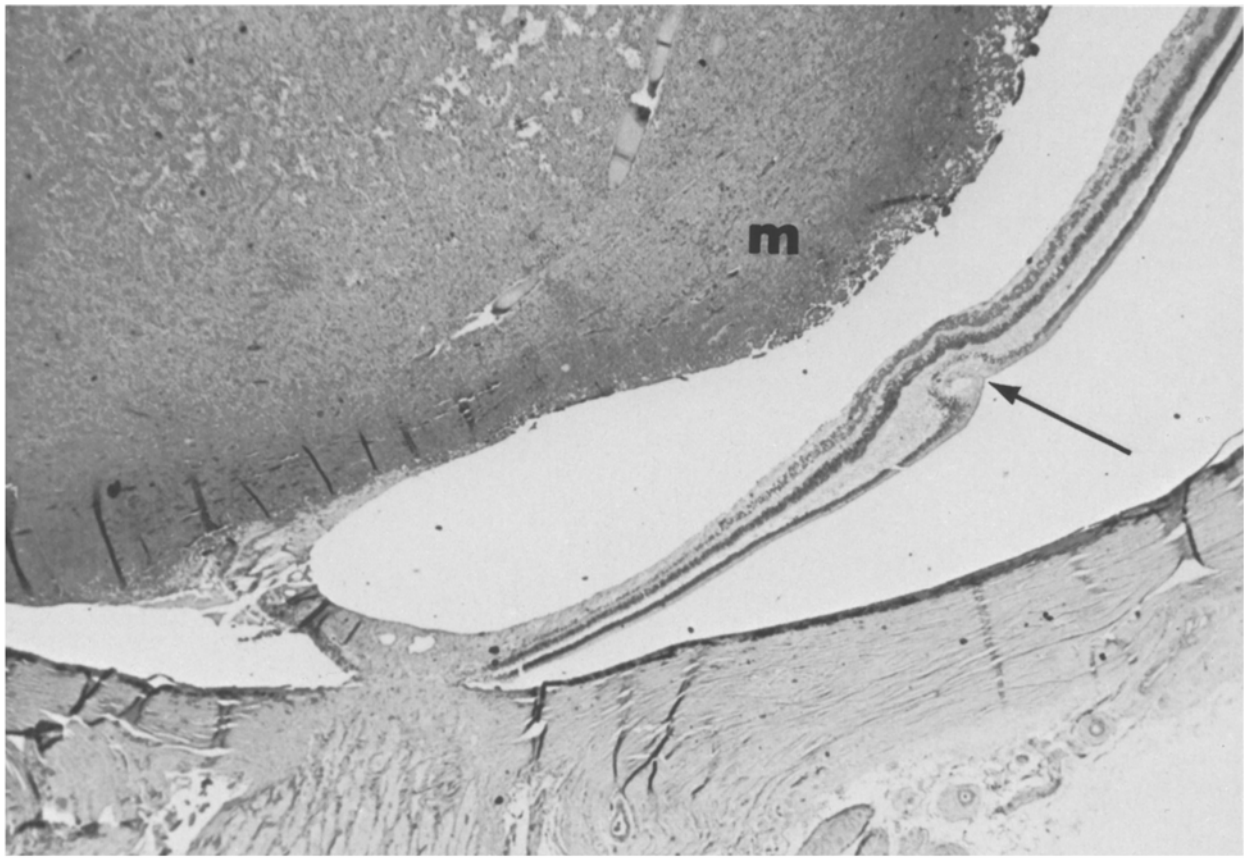
Discussion

Simplification can be helpful for better understanding, when a process presents in an overwhelming number of variations. Cystoid macular edema as a complication of choroidal melanomas, thus, occurs in three basic appearances: 1) as a direct reaction on top of the neoplasm, 2) as an indirect reaction to retinal detachment due to a secondary subretinal exudate extending into the foveal region and 3) as an indirect retinal reaction without exudate or detachment. The three cases of this paper represent these three possibilities. It has to be stated, immediately, that all kinds of combinations of these three presentations are seen – and that many unusual changes in the foveal retina complicate the picture in eyes with melanomas. These may be composed of features of simple retinal edema, retinal necrosis or hemorrhage, exudative detachment with signs of CME or direct tumor invasion into the retina, for example.

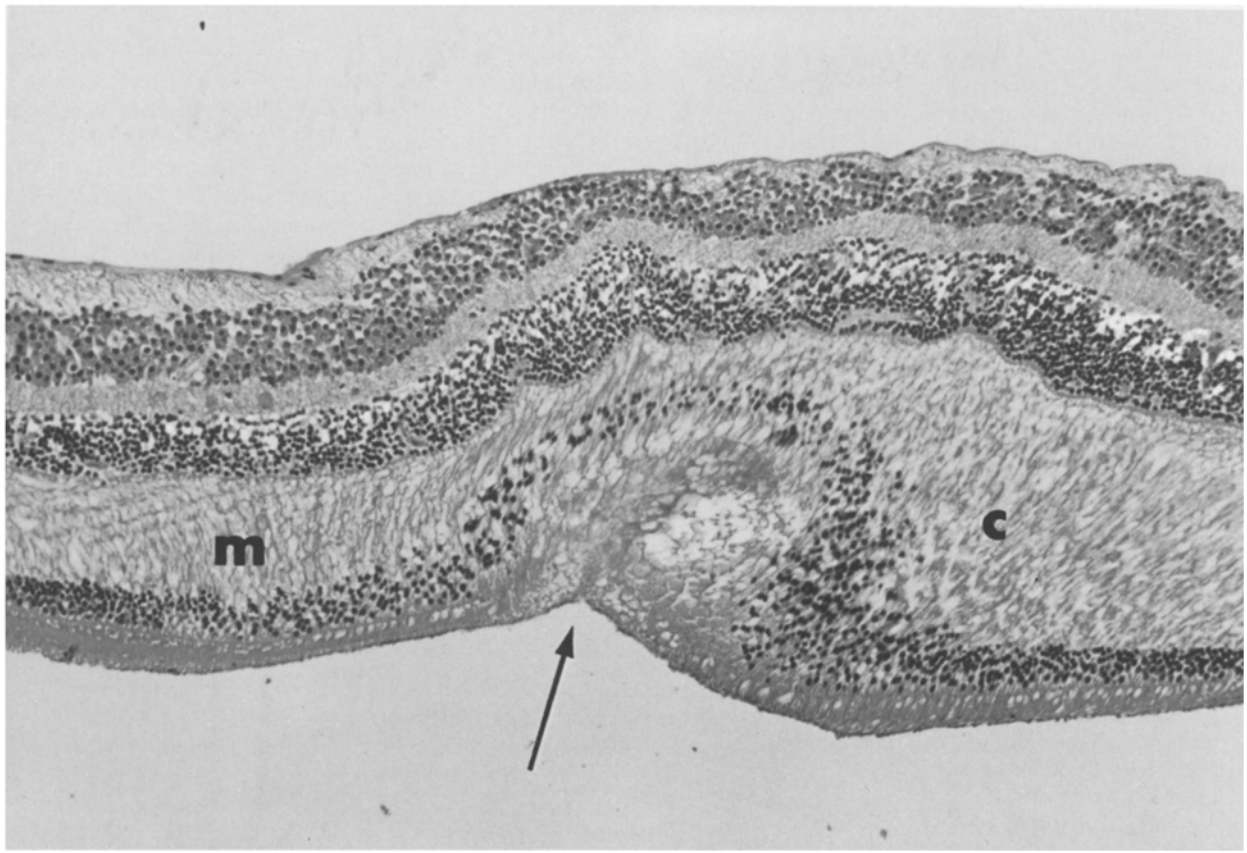
The typical histological picture of CME on top of a melanoma has been known for a long time. It is shown, for example, in Duke-Elder's System of Ophthalmology [2]. Domarus and Hinzpeter [3, 4] have made a positive correlation of histological findings similar to those of the present first case with the clinical picture of typical CME in one instance. Thus, the present first case can serve to expand and reinforce the observations of these authors. The second case shows, that choroidal melanomas have a tendency to cause an accumulation of retroretinal serous exudate in the foveal region. Most interestingly, this is associated

Fig. 3. Case 2, horizontal cross section of the eye showing the large choroidal melanoma (*m*) with six larger areas of necrotic infarction. A high inferior retinal fold with subretinal exudate appears like an island in the center of the section (*x*), More exudate is seen on top of the tumor. The arrow points to the foveola, which exhibits a localized subretinal exudate (*e*), part of which sticks to the pigment epithelium. The detachment of the retina on the left is artificial. – Paraffin section, H and E stain, photomicrograph ×6

Fig. 4. Case 2, the foveal retina with the central foveola (*f*) presenting as a mound. Vitreous (*v*) containing a loose exudate is attached to the foveolar zone (between arrows). The localized subfoveal serous exudate (*e*) is artificially cracked in the embedding process. – Paraffin section, H and E stain, photomicrograph ×100



6



7

Fig. 6. Case 3, view of the large melanoma (*m*) originating in the nasal choroid above. The optic nerve head and the sclera are seen below. The retina temporal to the disk is artificially separated and exhibits a distinct vertical fold (arrow) through the parafoveolar zone. – Paraffin section, H and E stain, photomicrograph ×12

Fig. 7. Case 3, high power view of the vertical retinal fold in a horizontal section slightly below the foveola showing regular vertical wrinkling of ganglion cell, inner plexiform and inner nuclear layers. Henle's fiber layer is involved with swelling and microcystoid change (*c*). So-called concentric microwaves of Henle's fibers (m) are seen in Henle's fiber layer between disk and fovea (to the left in the photograph). Sharp infolding of the outer nuclear layer and the cones (*arrow*) is seen in the center. This is associated with distortion and degeneration of foveolar cones as well as formation of cystoid spaces in the fold. There also is loss of cellular nuclei in the outer nuclear layer overlying the fold. – Paraffin section, H and E stain, photomicrograph ×300

in the second case with a funnel-like attachment of retracting posterior vitreous to the foveolar region (Figs. 4 and 5). In the zone of this attachment the vitreous contains a diffusely staining exudate and its arrangement indicates some vitreous pull on the central retina (comp. Wolter [5]).

Retroretinal exudate in the foveal retina in melanomas is usually continuous with exudate on or around the neoplasm (Wolter [6], Fig. 7), but the present case 2 shows, that the exudate can be separate. The foveolar retina in the center of this localized serous detachment exhibits the changes, that I consider typical for early CME [6]: elevation of the foveola with a vertical retinal fold, swelling and cystoid changes in Henle's fiber layer and degeneration of the central cones. The place of foveolar vitreous adhesion [5] and accumulation of prefoveal fibrinous exudate [5–8] is not as yet clear. Relatively broad vitreous adhesions to the foveal region, as they are seen in case 2 of the present paper, have also been demonstrated clinically in association with CME (Trempe, Takahashi and Topilow [9], Figs. 6 and 7).

The third case exhibits CME with a vertical fold of the outer retinal layers, swelling and microcystoid changes of Henle's fiber layer and detachment and early degeneration of central cones. This rather bizarre vertical infolding of outer retinal layers is not an artifact. It is known to occur in association with hypotony [10, 13] and probably represents a result of horizontal tension on the central retina with its fixation on the optic disk. Parallel wrinkling of the inner retinal layers at a higher "frequency" seen in the present case 3 reinforces my suspicion, that all this is a result of mechanical forces. The presence of "microwaves" in Henle's fiber layer [14] of this case further supports this view. Edema and cystoid changes in the fovea are usually associated with this retinal folding [11–13].

Involvement of the retina overlying choroidal melanomas has been studied clinically with the aim to differentiate choroidal nevi from active choroidal melanomas [15–17]. It has been found that retinal involvement can be used as an indicator for the malignancy of a choroidal lesion. Newell [18] has stated that "cystoid degeneration of the overlying retina suggests a malignant melanoma". Ignoring the direct retinal invasion in advanced melanomas with extension into the subretinal space, it has been concluded that this type of retinal involvement can be explained by interference with the nutritional functions of the choriocapillaris. The resulting retinal changes are typically limited to the outer retinal layers and they consist of degeneration of rods and cones, microcystoid or cystoid changes in the outer plexiform layer (see Karickhoff [15], Fig. 5) and diffuse loss of cells in the outer layers. All of the layers of the foveolar retina are dependant on the choroidal nutrition and are involved, of course.

Vascular congestion in the uvea is observed in most cases with active choroidal melanomas. Extensive enlargement of ciliary arteries in the choroidal sector with the neoplasm is common. Histologic evidence of a slight chronic anterior uveitis is also found associated with most active choroidal melanomas. These facts may be important in addition to the nutritional component for an explanation of the frequent association of choroidal melanomas with CME. The clinical occurrence of CME usually is obvious due to the resulting drop in central vision. The delicate fovea in the center of the retina, thus, is exposed to many direct and indirect influences – even in the relatively simple situation of an eye with a malignant choroidal tumor. The situation is much more complicated in posttraumatic or postoperative situations of the inner eye, I believe. The foveal reactions to choroidal melanomas, thus, can serve to give step by step insight into the pathologic mechanisms, that result in cystoid macular edema.

References

1. Spitznas M, Hogan MJ (1970) Outer segments of photoreceptors and the retinal pigment epithelium, Arch Ophth 84:810–819
2. Duke-Elder Sir St (1966) System of Ophthalmology, C.V. Mosby, St. Louis, Vol 9: p. 851
3. Naumann GOH (1980) Pathologie des Auges, Springer, New York, p. 458
4. Domarus D von, Hinzpeter EN (1978) Zystoides Maculaoedem über einem malignen Melanom der Aderhaut, Klin Mbl f Augenheilk 172:751–756
5. Wolter JR (1981) Cystoid macular edema in vitreo-retinal traction, Opth Surg 12:900–904
6. Wolter JR (1981) The Histopathology of Cystoid Macula Edema, Graefe's Arch Ophth 216:85–101
7. Wolter JR, Croasdale RE, Bahn CF (1980) Reactions to an anterior chamber lens – two years after implantation, Ophth Surg 11:794–800
8. Wolter JR (1982) Foveal pathology in ciliary body melanoma, Ophth Surg, in print
9. Trempe CL, Takahashi M, Topilow HW (1981) Vitreous changes in retinal branch vein occlusion, Ophth 88:681–687
10. Michels RG, Green WR, Maumenee AE (1971) Cystoid macular edema following cataract extraction. Ophth Surg 6:217–221
11. Wolter JR (1981) Vertical folds of central retina and choroid in sudden ocular decompression. Ophth Surg 12:190–194
12. Wolter JR (1981) Foveal pathology following anterior segment injury, Ophth Surg 12:661–665
13. Wolter JR, Expulsive hemorrhage: its nature and its effects on the foveal retina, 1982 Meeting of Amer Ophthal Soc submitted
14. Wolter JR (1981) Concentric "microwaves" of Henle's fiber layer: associated with horizontal folding, v Graefe's Arch Ophth 216:31–39
15. Karickhoff JR (1967) Loss of visual function and visual cells in 600 cases of malignant melanoma. Amer J Ophth 64:268–273
16. Naumann G, Yanoff M, Zimmerman LE (1966) Histogenesis of malignant melanomas of the uvea, Arch Ophth 76:784–796
17. Reese AB (1957) The differential diagnosis of malignant melanomas of the choroid, Arch Ophth 58:477–482
18. Newell FW (1978) Ophthalmology, 4th ed, CV Mosby St Louis p. 313

Received January 11, 1982