Communications

Choroidal melanomata

Fluorescence angiographic and histopathological study

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This clinico-pathological study has been carried out on benign and malignant choroidal melanomata with the following objects in view:

- (1) To find out the fluorescent pattern on fluorescence angiography which would distinguish a pigmented choroidal malignant melanoma from other lesions of similar appearance in the fundus of the eye, *e.g.* pigmented benign choroidal melanoma or non-neoplastic pigmentation.
- (2) To study the pattern in non-pigmented malignant choroidal melanomata which could be confused with choroidal haemangiomata.
- (3) To find out the pathological basis of the fluorescent pattern seen in benign and malignant choroidal melanomata.
- (4) To find out the true nature of a benign choroidal melanoma, *i.e.* whether the pigmentation is always choroidal or is due in some cases to hyperplasia of the pigment epithelium.

MATERIAL AND METHODS

(A) FLUORESCENCE ANGIOGRAPHIC STUDIES

These were carried out in 38 patients who were seen with the following lesions at Moorfields Eye Hospital, City Road Branch, London:

- (i) Benign choroidal melanomata (fifteen patients);
- (ii) Flat pigmented malignant choroidal melanomata (fifteen patients);
- (iii) Very lightly pigmented or amelanotic malignant choroidal melanomata (five patients);
- (iv) Choroidal haemangiomata (three patients).

(B) HISTO-PATHOLOGICAL STUDIES

These were carried out at the Pathology Department at the Institute of Ophthalmology, London. The material included the following:

- (i) Benign choroidal melanomata (thirty eyes);
- (ii) Malignant choroidal melanomata (fifty eyes).

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OBSERVATIONS AND COMMENTS

(A) FLUORESCENCE ANGIOGRAPHIC STUDIES

I. Benign choroidal melanomata (BCM) (15 patients)

The pigmented lesion was noticed in the course of a routine ophthalmoscopic examination; it was situated at the posterior pole in all except two cases in which it was near the equator.

Fluorescence angiographic pattern (Fig. 1) During the transit of fluorescein, the background choroidal fluorescence in the area of the BCM is usually slightly less than elsewhere. During the late arterio-venous phase, the masking of the choroidal fluorescence is at its minimum at the site of the lesion. In one case, in which it was possible to outline the choroidal vascular bed during the very early stage of the transit, before the filling of the retinal arteries, the size of the lesion was found to be much greater than that revealed by ophthalmoscopy. As soon as the rest of the choroidal bed was filled, the non-fluorescent area diminished to a much smaller size (Fig. 1*b*). Late phases, 10–15 minutes after the injection of fluorescein, usually showed some degree of diminished fluorescence at the site of the lesion (Fig. 1*c*). In subjects with normally large amounts of pigment in the choroid, the BCM may show no significant diminution of choroidal fluorescence.

Drusen of variable number and size were seen in the lesion in only a third of the patients. These were usually outlined during the transit of the dye and in the late phase (Fig. 1*c*).

In one patient, the lesion was jet black and was due to hypertrophy of the pigment epithelium. It completely masked the background choroidal fluorescence. Thus, *when the pigmentation is in the choroid, it does not completely mask the choroidal fluorescence but reduces its intensity; however, when the pigmentation is in the pigment epithelium, it completely masks the choroidal fluorescence.*

II. Malignant choroidal melanomata (MCM)

(1) Flat-looking pigmented malignant choroidal melanomata

This group includes fifteen confirmed cases of MCM. The lesion in all of them was flat or only slightly raised. In the vast majority small yellowish-white non-pigmented patches were distributed in the dark grey pigmented lesion (Fig. 2*a* and 3*a*). The non-pigmented areas occurred more often in the peripheral part of the lesion, and quite often gave a striped appearance to the region of the tumour. Sometimes these patches were ill-defined. On follow-up, new non-pigmented spots appeared in previously pigmented areas as the tumour infiltrated at the periphery. The centre of the tumour in about a third had a greyish-white appearance and was usually more elevated than the peripheral areas.

Fluorescence angiographic patterns (Figs 2 and 3) During the transit of fluorescein through the vessels, the pigmented areas showed fluorescence which appeared in either the arterial or the early arterio-venous phase and tended to reach its maximum during the late arterio-venous phase, being less in the late venous phase. The non-pigmented areas showed either no fluorescence or much less fluorescence than that in the pigmented areas. Usually the difference in fluorescence of the pigmented and non-pigmented areas was quite marked. During the late arterio-venous phase or in the subsequent venous phase, small round discrete spots appeared in the lesion in all except two patients. These spots were more often situated in the peripheral part but could be seen anywhere in the lesion. Their number and fluorescence increased with the passage of time.

FIG. 1 *Benign choroidal melanoma in a 57-year-old woman*

(a) Ordinary fundus picture; (b, c) fluorescence angiograms during early arterio-venous (b) and late (c) phases. Note fluorescent drusen in (c).

FIG. 2 *Flat diffusely infiltrating malignant choroidal melanoma*

(a) Ordinary fundus picture; (b, c) fluorescence angiograms during early arterio-venous (b) and late (c) phases.

FIG. 3 *Flat diffusely infiltrating malignant choroidal melanoma in a 45-year-old man*

(a) Ordinary fundus picture at the time of the first fluorescence angiogram (b); (b, c) fluorescence angiograms during late phases, (c) 4 months after (b). Note an increase in size of lesion in (c).

During the late phase 10–15 minutes after the last injection of the dye, the lesion showed fluorescence due to staining with fluorescein. The fluorescent area was quite often smaller than the pigmented area seen ophthalmoscopically. The fluorescence tended to be marked at this stage. The difference in the intensity of fluorescence seen during the transit of the dye in pigmented and non-pigmented areas of the lesion tended to be less distinct during the late phase because of a diffuse fluorescence of the lesion, although in some the pattern could still be made out. The peripheral part of the lesion in some tended to mask the background fluorescence (Fig. 3a, b). The small fluorescent spots were usually seen distinctly although in some these were not so clearly outlined because of diffuse fluorescence. The central white area, when present, was markedly fluorescent and in some cases was the only area showing significant fluorescence. During the transit of the dye such a central area usually showed less fluorescence and sometimes none.

In one case, haemorrhages in a lightly pigmented MCM produced a dark bluish-green colour with a non-pigmented area of the tumour in one part, confusing the lesion with a darkly pigmented MCM. In this case, the haemorrhage masked the fluorescence which was seen only in the non-pigmented area and became more marked in the later phases.

In contrast to the above-mentioned fluorescence pattern in MCM, in *non-neoplastic pigmented lesions of various aetiologies*, the pigmented areas were non-fluorescent while the non-pigmented areas fluoresced (Fig. 4)—a reverse of the MCM pattern. The intensity of fluorescence ran parallel with the choroidal fluorescence, reaching its maximum in the arterio-venous phase. During the late stages, after 10–15 minutes, the fluorescence was usually insignificant and, when present, was more marked in the non-pigmented areas. On the other hand, in MCM the late fluorescence was usually prominent and tended to be more marked in the pigmented areas except when there was a central whitish area which became markedly fluorescent.

There were, however, some pigmented non-neoplastic lesions in which the pigmented areas were more fluorescent than the non-pigmented areas (Fig. 5); this appearance resembled that of the MCM but the following points would differentiate the two lesions:

- (a) The pigmented area showed a granular type of fluorescence which ran parallel to the choroidal fluorescence, reaching its maximum in the arterio-venous phase (Fig. 5b).
- (b) The lightly pigmented or non-pigmented areas showed little or less fluorescence during the transit of the dye.
- (c) In late stages, the pigmented areas showed little fluorescence while the light or non-pigmented areas showed fluorescence (Fig. 5c).

Late fluorescence would thus differentiate them from the MCM, and whenever there was doubt about the nature of a flat pigmented lesion, I have attached great significance to the following distinguishing features in trying to differentiate the flattish pigmented MCM from other pigmented lesions:

- (a) In MCM the pigmented areas show fluorescence while the non-pigmented areas show much less or no fluorescence during the transit of the dye and usually in late fluorescence also.
- (b) In MCM discrete small, round fluorescent spots usually appear in the lesion, more often in the peripheral part. These usually appear in the venous phase and tend to become more prominent and numerous as time passes. In one case, repeated angiography showed that the old spots had disappeared and a new batch of spots had appeared (Fig. 3).

FIG. 4 *Non-neoplastic pigmentation of the fundus in a 60-year-old man*

(a) Ordinary fundus picture; (b, c) fluorescence angiograms during early arterio-venous (b) and late (c) phases.

FIG. 5 *Non-neoplastic pigmentation of macular region in a 41-year-old man*

(a) Ordinary fundus picture; (b, c) fluorescence angiograms during early arterio-venous (b) and late (c) phases. Note the leakage of fluorescein above and below the lesion due to abnormal retinal capillaries.

(2) *Non-pigmented malignant choroidal melanomata*

This group consists of five cases with large non-pigmented tumours projecting into the eye. Histopathological examination confirmed that all were MCM. The tumour surface was pink or white in colour or a mixture of the two, with white areas scattered on the surface. In four cases prominent choroidal vessels were visible on some part of the surface of the tumour (Fig. 6); they had perforated Bruch's membrane and the pigment epithelium as was shown by histopathology.

Fluorescence angiographic pattern (Fig. 6) During fluorescein transit, the fluorescence of the lesion was seen to be more marked in the pinkish areas than in the white areas. The fluorescence tended to appear with the arterial phase of the retinal circulation. On rare occasions the tumour became fluorescent only gradually and progressively. With the passage of time, the fluorescence increased. The prominent vessels seen on the surface beneath the retinal vessels filled at the same time as the retinal arteries or a little before, or at the same time as the retinal veins. This may depend upon the nature of the vessels, *i.e.* whether they are arterial or venous in nature. These abnormal vessels were choroidal and the larger ones were found to be markedly permeable to the dye, so that fluorescein leaked out rapidly (Fig. 6*b*), giving them a feathery appearance. This demonstrates the mechanism responsible for staining the tumour tissue on fluorescence angiography. In these amelanotic MCM, if light grey patches were seen on the surface, they were non-fluorescent in contrast to the pigmented MCM.

The lesion showed marked late fluorescence of a diffuse nature (Fig. 6*c*), the pure white lesions being much more fluorescent in late pictures than during the transit.

The tumours could be confused with choroidal haemangiomata or a secondary tumour deposit in the choroid.

A pink tumour showing patchy fluorescence during the pre-arterial phase of retinal circulation would favour the diagnosis of choroidal haemangioma. Other clinical signs would assist in such a differentiation. The choroidal haemangioma is usually located close to the optic disc (Fig. 7); it is lighter in colour than the remainder of the fundus with no pigment in it, and is lighter than the remaining fundus on retroillumination, and shows sector-shaped field defects. Some of the secondary deposits are non-fluorescent, and when they are fluorescent their fluorescence pattern tends to be of a different type.

III. *Choroidal haemangiomata*

This group includes only three cases which may seem too few for definite conclusions to be drawn. One was an almost exact replica of another, *i.e.* they were both situated superiorly and close to the optic disc, were moderately elevated, and had pinkish surfaces and big whitish irregular patches (Fig. 7). The third was seen in a young woman aged 20 years; it was nasal to the disc and much larger than the other two, having a pink colour with white patches on the surface. Unlike the amelanotic tumours there was a gentle slope from the swelling to the adjoining normal retina. No retinal detachment was seen in any of these cases.

Fluorescence angiographic pattern (Fig. 7) During the fluorescein transit these choroidal haemangiomata showed patchy fluorescence before the dye reached the retinal arteries, and it was much more intense as the transit of the dye progressed. The white patches masked the fluorescence of the lesion to some extent, so that the pink areas were more fluorescent than the white areas. No choroidal vessels were seen.

FIG. 6 Malignant choroidal melanoma in a 52-year-old man which has perforated Bruch's membrane and the pigment epithelium

(a) Ordinary fundus picture; (b, c) fluorescence angiograms during arterio-venous (b) and late (c) phases.

FIG. 7 (a) *Fluorescence angiogram of choroidal haemangioma in a 20-year-old woman during pre-arterial phase of retinal circulation.* (b, c) *Choroidal haemangioma in a 49-year-old man. (b) Ordinary fundus picture. (c) Fluorescence angiogram during late phase*

In the first two cases, on the slope of the retina at its margins, the retinal capillaries, which were prominent and dilated, leaked fluorescein as the dye was passing through them. This produced a spotty fluorescence around the haemangioma.

Late pictures, 10–15 minutes after injection, showed fluorescence of the lesions; in the first two cases this was less in the white than in the pink areas, and around the lesion there was a small rim of minor fluorescence which was surrounded in turn by a band of patchy fluorescence caused by the leakage from the retinal capillaries (Fig. 7c).

Some may be of the opinion that these lesions could be amelanotic melanomata. The third patient in this group has been followed for nearly 15 years since she was 5 years old, and has esotropia in this eye. In the first patient, the lesion was once treated with light coagulation; this immediately collapsed the tumour which is unlike a MCM. The second patient came from Cyprus and I have lost contact with her, but I presume that the tumour was a haemangioma, being an exact replica of the first in all respects.

(B) HISTO-PATHOLOGICAL STUDIES

These have been carried out in the hope of discovering the pathological basis of the fluorescence patterns described above.

I. Benign choroidal melanomata

These included cases in which the eye was removed for some other ocular lesion, the BCM being an incidental finding. Thirty cases were studied to find out the site of the pigment deposition. In all these, the pigmentation was situated in the outer layers of the choroid and extended inwards to a variable extent, sometimes approaching the pigment epithelium (Fig. 8). However, a gap was always discernible between the choroidal pigmentation and the pigment epithelium. In none of these was hypertrophy of the pigment epithelium seen. In the vast majority the lesion was in the posterior half of the globe, mostly at the posterior pole. The presence of colloid bodies over the lesion was a rare finding (Fig. 8). In some, the area of the lesion showed a vascular choroid with prominent choroidal vessels. Such a lesion would obviously be slightly elevated. The pigment epithelium and the retina over the lesion were normal in all cases where no other pathological lesion, unassociated with BCM, was considered to be responsible for changes in these.

II. Malignant choroidal melanomata

Histological sections from fifty cases with MCM were studied. The investigation was primarily concentrated on a study of the state of the pigment epithelium over the tumour in order to find out the factors responsible for the fluorescence pattern of the MCM. In all cases the pigment epithelium overlying the tumour was abnormal, showing degenerative and disintegrative changes in some places and being totally absent in others (Fig. 9a). In about half the cases, the pigment epithelium showed one or more small patches of thickening of the pigment epithelium over the tumour, usually near its periphery. Some of these seemed to be due to hypertrophy and others to aggregation of the pigment (Fig. 9a). In some places hyaline degeneration was seen in the pigment epithelium. Rarely, a few small tumour pieces which were separate from the main tumour mass could be seen between the retina and the pigment epithelium. The overlying Bruch's membrane showed colloid bodies in some cases. Small localized areas of subepithelial and/or sub-retinal exudation were also seen over the tumour.

In some of these cases, the tumour tissue lay in the centre with a mantle of choroidal pigment around it, as if the malignant change started in the centre of a BCM and its growth

FIG. 8 Photomicrograph of a benign choroidal melanoma; note the two drusen on Bruch's membrane

FIG. 9 (a) Photomicrograph of malignant choroidal melanoma from the tumour seen in Fig. 2, showing aggregation of pigment at one site with degenerative changes at other sites in the pigment epithelium.

pushed the original pigment outwards around it. Thus, at its peripheral margins, there was a considerable amount of the BCM type of pigmentation which may have been responsible for the reduced or absent background choroidal fluorescence at the periphery of the tumour.

From these histopathological studies, the following interpretations of the fluorescence pattern of the BCM and MCM could be postulated:

(1) In BCM it is the deposition of pigment in the choroid which is responsible for the ophthalmoscopic picture of the lesion. On fluorescence these choroidal lesions are partially but not completely non-fluorescent; the degree of non-fluorescence depends upon the extent of the involvement of the choroid by the pigment. If the pigment involves only the external part, it may show normal fluorescence or only slightly reduced fluorescence as compared with the surrounding fundus. When the pigment involves most of the thickness of the choroid, the fluorescence is markedly reduced; fluorescein in the chorio-capillaris is responsible for some fluorescence still present. In contrast, when there is hypertrophy of the pigment epithelium, there is a complete masking of the choroidal fluorescence and no partial fluorescence of the lesion is seen. From the histological sections, it was not possible to determine the exact extent of involvement of the chorio-capillaris. I feel that when the pigment does not involve the chorio-capillaris, the lesion will not be associated with any field defect. But when it involves the overlying chorio-capillaris it leads to field defects. Such visual field defects with BCM have been recorded by Tamler and Maumenee (1959: in 38 per cent.), by Naumann, Yanoff, and Zimmerman (1966), by Karickhoff (1967: in 21 per cent.), and by Flindall and Drance (1969: in 85 per cent.). Flindall and Drance (1969) speculated that the field defects were due to derangement of the pigment epithelium or outer segments of rods and cones without microscopical changes. The incidence of drusen over a BCM, so much stressed in the literature, is not common, as is shown by both the fluorescence and the histological studies. Naumann, Zimmerman, and Yanoff (1966) recorded, in 41 per cent. of their cases, changes in the overlying tissue, which included narrowing or obliteration of the chorio-capillaris, changes in the pigment epithelium, drusen, and retinal lesions. In the present series, no significant changes were seen in the pigment epithelium and the retina apart from the occasional drusen.

(2) The fluorescence of the lesion in the MCM is due to two factors:

(a) Disintegration or even complete absence of the overlying pigment epithelium leads to unmasking of the background fluorescence of the choroid.

(b) The tumour is usually very vascular. When a tumour perforates Bruch's membrane and the pigment epithelium, so that tumour tissue is clearly visible through the clear retinal tissue, a large number of prominent vessels are almost always seen. Moreover the vessels in the tumour are abnormal (Fig. 9b) and abnormally permeable to fluorescein, leading to a marked outflow of fluorescein from the vessels into the tissue.

Thus, in MCM, the characteristic fluorescence of the lesion is due to increased vascularity, abnormally permeable choroidal vessels, and disappearance of the overlying pigment epithelium. In patients with MCM treated by cobalt plaque by Mr. M. A. Bedford at Moorfields Eye Hospital, I have carried out fluorescence angiography both before and after treatment. Although a large amount of the pigment is left at the site of the lesion after treatment, fluorescence is completely absent all along. In fact, no vessels are seen in that area and for some distance surrounding the lesion after the cobalt radiation treatment; for some distance beyond it only the very large choroidal vessels are seen. This seems to

FIG. 9 (b) Photomicrograph of malignant choroidal melanoma, showing one of the abnormal vessels seen in Fig. 6

indicate that the fluorescence of the MCM is due to its abnormal vascularity and that the pigment itself has no part in it.

(c) In most of the pigmented MCM of this series, there were non-pigmented patches in the pigmented parts, producing a mottled appearance. It is not possible to be definite about the nature of these patches, but the histological studies suggest that they may be caused by a patchy thickening of the pigment epithelium. This is further supported by the observation that these non-pigmented patches remain non-fluorescent when the pigmented part becomes fluorescent after the injection of fluorescein. Such a hypertrophy of the epithelium was not seen in histological sections over a benign melanoma.

(d) The exact nature of the small round discrete fluorescent spots observed in the pigmented tumours is not clear. They may be due to small localized areas of subretinal/subepithelial exudation or to drusen in Bruch's membrane, or they may possibly be caused by extension of the tumour tissue which comes to lie between the pigment epithelium and the retina. The last phenomenon, *i.e.* extension of the tumour, was only very rarely seen in histological sections in the present study; it was much less frequent than the spots seen in fluorescence angiography. Moreover, the number and site of the spots changed at successive examinations, suggesting that they represented small localized exudates under the retina or the pigment epithelium.

The MCM are always accompanied by a localized visual field defect. I feel that this may be due to changes in the pigment epithelium which is always involved in MCM, and to involvement of the chorio-capillaris in the tumour. At a later stage the complete absence of Bruch's membrane and of the pigment epithelium and the associated retinal degeneration and detachment, would make the field defect more pronounced. Later still the defect would be due to invasion of the retinal tissue by the tumour.

CONCLUSIONS AND SUMMARY

This study has been carried out by fluorescence fundus angiography in 38 patients and histopathological examination in eighty eyes with benign or malignant choroidal melanoma.

On fluorescence angiography, the benign choroidal melanoma showed a variable degree of masking of the background choroidal fluorescence which depends upon the extent of infiltration of the choroid by the pigment.

A flat diffusely infiltrating malignant choroidal melanoma (MCM) has small yellowish non-pigmented patches scattered on its surface, more at the periphery. On fluorescence angiography, the pigmented areas are fluorescent and the non-pigmented areas are non-fluorescent. Usually, these also show numerous small round discrete fluorescent spots. Non-neoplastic lesions of similar appearance show two types of fluorescence pattern. In the first group, the pigmented areas are non-fluorescent and non-pigmented areas are fluorescent. In the second group, during the transit of the dye, the pigmented areas are fluorescent and non-pigmented areas are non-fluorescent, but during the late phase the pigmented areas are non-fluorescent or faintly fluorescent but the non-pigmented areas are markedly fluorescent.

In an amelanotic choroidal melanoma, the pink areas fluoresce more than the white areas during the transit of the dye and the reverse occurs during the late phases. Abnormal choroidal vessels, when seen, usually show a marked leakage of fluorescein. The lesions are markedly fluorescent.

In choroidal haemangioma, patchy fluorescence is seen during the pre-retinal-arterial phase, with leakage of fluorescein at a later stage.

Histopathologically, the pigment epithelium over the malignant choroidal melanoma was never normal. The epithelium was either degenerate or absent. In about half the cases examined a few small patches of thickened pigment epithelium were seen. In the benign choroidal melanoma, no change was seen in the pigment epithelium over the area of choroidal pigmentation; the latter involved the choroid to a variable thickness extending from the periphery inwards. A thin layer of chorio-capillaris was usually not involved by the pigment.

Fluorescence of the malignant choroidal melanoma is due to the partial or complete absence of the pigment epithelium over the tumour, marked vascularity, and abnormally permeable vessels in the tumour.

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