

Diffuse infiltrating retinoblastoma

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The term "diffuse infiltrating retinoblastoma" was introduced by Ashton (1958) to describe a form of retinoblastoma which did not produce a tumour mass within the retina. Although Manschot (1956) and Weizenblatt (1957) had described such cases previously, they did not recognize the condition as a distinct entity. Schofield (1960) described four cases of this type of retinoblastoma which presented with a hypopyon, and neoplastic cells were demonstrated in the anterior chamber paracenteses.

The purpose of the present paper is to describe a further case of this type of tumour, and to review the ten cases which have been seen in the Pathology Department of this Institute, including the four described by Schofield (1960).

Case report

CLINICAL FEATURES

A mentally defective boy aged 10 years was admitted to hospital with the history of pain in the right eye of several months' duration. There were no other complaints. Ophthalmological examination of the right eye showed a hypopyon, multiple whitish nodules on the iris, and white vitreous exudates; the left eye was normal. Radiographs of the chest showed no abnormality.

TREATMENT

Steroid therapy was begun, but glaucoma, corneal oedema, and an inferior limbal staphyloma ensued. The eye was enucleated.

PATHOLOGY

Macroscopical examination showed enlargement of the globe (antero-posterior diameter 32 mm; horizontal diameter 29 mm.). There was an inferior limbal staphyloma (Fig. 1, opposite), and exudate was present in the anterior chamber and the vitreous. The retina was diffusely thickened but there was no evidence of a tumour mass (Fig. 2, opposite). The optic disc was cupped.

Microscopical examination showed diffuse infiltration of the retina by a retinoblastoma, with no evidence of a tumour mass. The tumour was involving all the layers of the retina and was composed of cells having a little pinkish cytoplasm and hyperchromatic nuclei of varying shapes and sizes. Individual cell necrosis was seen and mitotic figures were fairly common, but there was no evidence of rosette formation (Fig. 3, opposite, and Fig. 4, overleaf).

Discrete foci of tumour cells were seen near the internal limiting membrane of the retina (Fig. 5, overleaf) and extension into the anterior vitreous had occurred, some of the cells at this site being viable but most of them being necrotic (Fig. 6, overleaf).

Posteriorly tumour cells had extended into the cupped optic disc but not into the nerve. Anteriorly extension had occurred on to the pars plana (Fig. 7) and ciliary epithelium (Fig. 8), into the iris leaf on one side, and on to both its anterior and posterior surfaces (Figs 9 and 10). Tumour cells had then extended on to the posterior surface of the cornea, the filtration angle on this side having

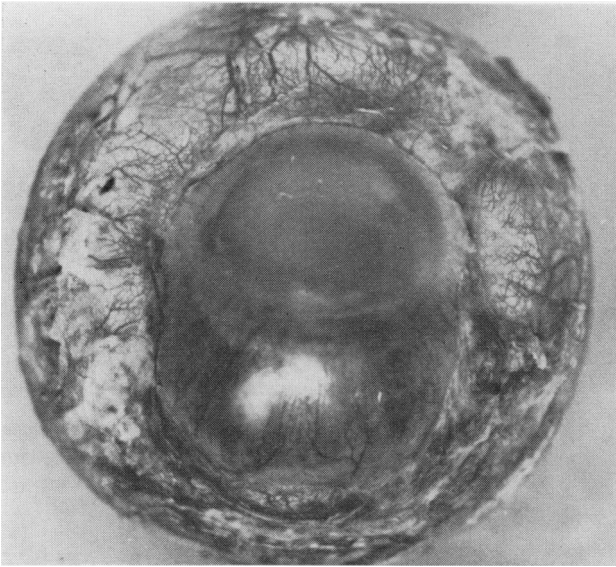


FIG. 1 Case 10, showing enlarged globe with inferior limbal staphyloma and exudate within the eye

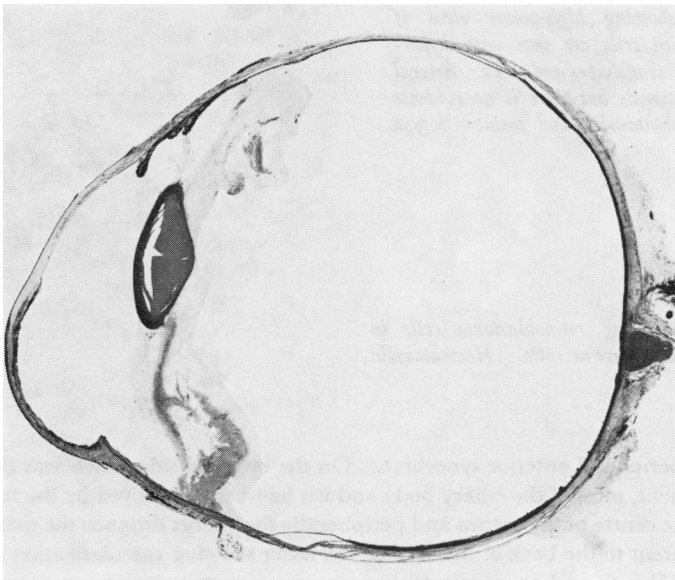


FIG. 2 Case 10, showing diffuse thickening of retina, exudate in anterior vitreous, occlusion of filtration angle, and inferior staphyloma

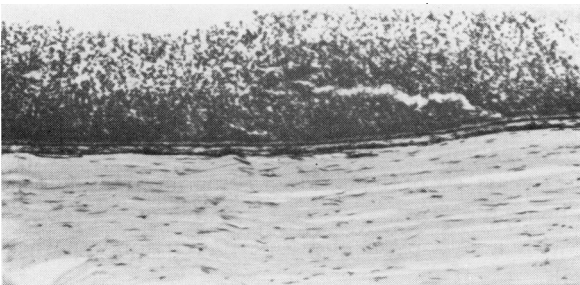


FIG. 3 Case 10, showing low-power view of tumour in which cells are involving all layers of retina. Haematoxylin and eosin. $\times 90$

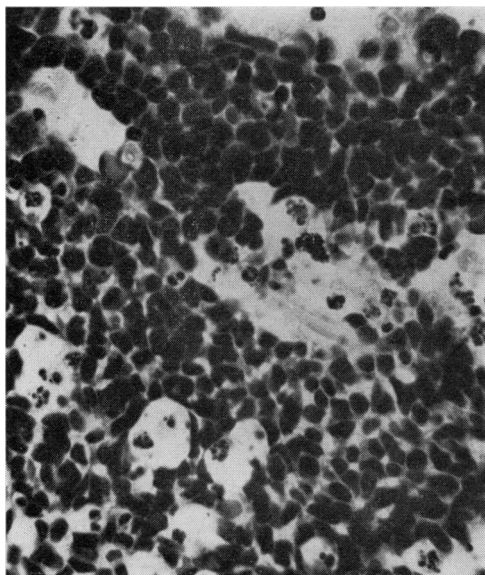


FIG. 4 Case 10, showing high-power view of retinoblastoma in which cells are seen with hyperchromatic nuclei of different shapes and sizes. Several cells are undergoing necrosis but there is no evidence of any rosettes. Haematoxylin and eosin. $\times 392$

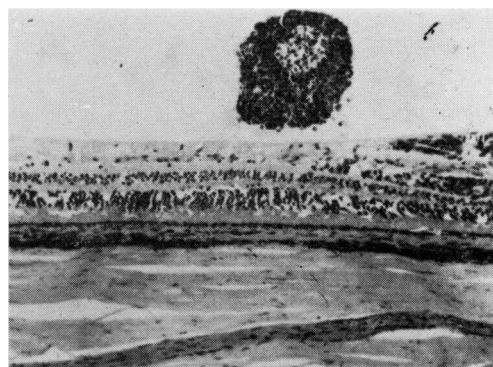


FIG. 5 Case 10, showing a single focus of tumour cells lying near internal limiting membrane of retina. Haematoxylin and eosin. $\times 90$

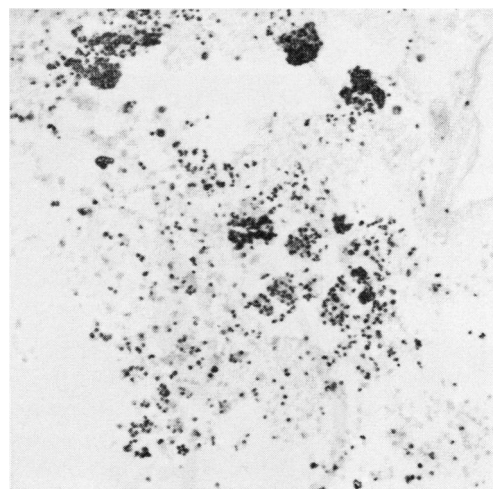


FIG. 6 Case 10, showing retinoblastoma cells in vitreous. Most of the cells are necrotic. Haematoxylin and eosin. $\times 90$

been occluded by peripheral anterior synechiae. On the opposite side which was the inferior part of the anterior segment, most of the ciliary body and iris had been destroyed by the tumour (Fig. 11, overleaf). Near the centre of the cornea and peripherally for a short distance the markedly atrophic iris was firmly adherent to the back of the cornea, the latter showing vascularization and infiltration by neoplastic cells (Figs 12 and 13, overleaf).

Description of other cases

Ten cases of diffuse infiltrating retinoblastoma, including the case recorded in this paper, have been studied, and the findings are analysed in the Table (p. 605), which shows that in all cases the growth was entirely diffuse, there being no focal tumour mass. None of the tumours was bilateral. Seven patients were boys and three were girls. The age at onset varied between 1 year and 11 years, six of the children being more than 6 years old and the average age for the group being 6.2 years.

Six children presented with a hypopyon and anterior chamber paracentesis in four of these showed tumour cells,

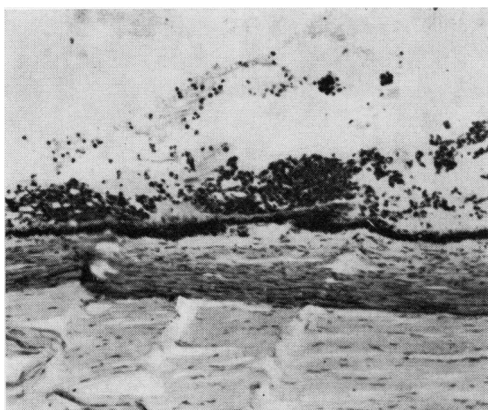


FIG. 7 Case 10, showing retinoblastoma cells on *pars plana*. Haematoxylin and eosin. $\times 90$



FIG. 8 Case 10, showing neoplastic cells on ciliary epithelium and surrounding a ciliary process. Haematoxylin and eosin. $\times 90$

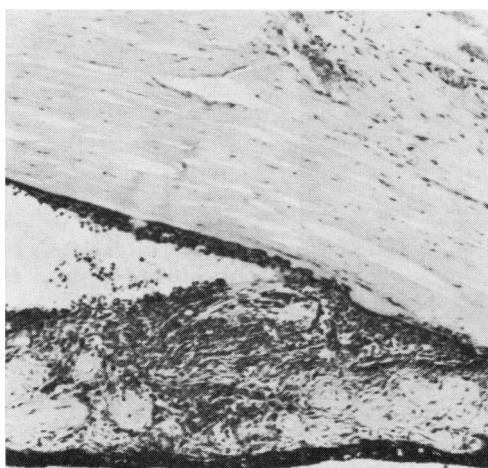


FIG. 9 Case 10, showing infiltration of iris stroma by neoplastic cells which are also present on anterior iris surface and posterior corneal surface. Haematoxylin and eosin. $\times 90$

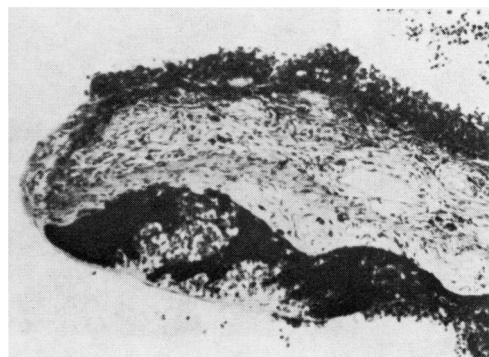


FIG. 10 Case 10, showing tumour cells on both surfaces of iris. Haematoxylin and eosin. $\times 90$

Histological examination of the eyes showed in every case that all layers of the retina were involved by a diffuse infiltration of closely packed cells with little cytoplasm and hyperchromatic nuclei of varying shape and size. Mitotic activity and cellular necrosis were moderate, and there was no evidence of rosette formation. Infiltration of the ciliary body, iris, and anterior chamber had occurred in eight cases, with extension into the trabecular meshwork in four of them. Neoplastic cells were seen in the vitreous in every case, in the optic nerve head in four cases, and in the optic nerve and choroid in one case.

At the present time all ten patients are alive and well, the survival times varying between 2 and 17 years (average 9.3). The apparently good prognosis is illustrated by the fact that Case 3 (Table) has survived for 14 years without recurrence or metastases despite infiltration of the trabecular meshwork by tumour cells, and that Case 7 has survived for 8 years despite invasion of the choroid.

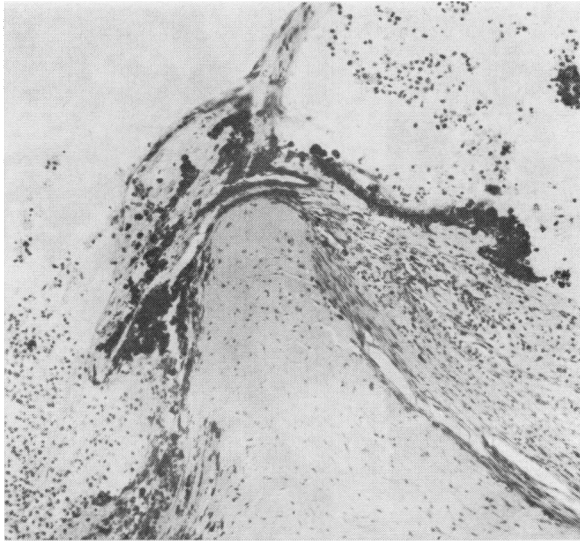


FIG. 11 *Case 10, showing extensive destruction of ciliary body and iris by tumour. Haematoxylin and eosin. $\times 90$*

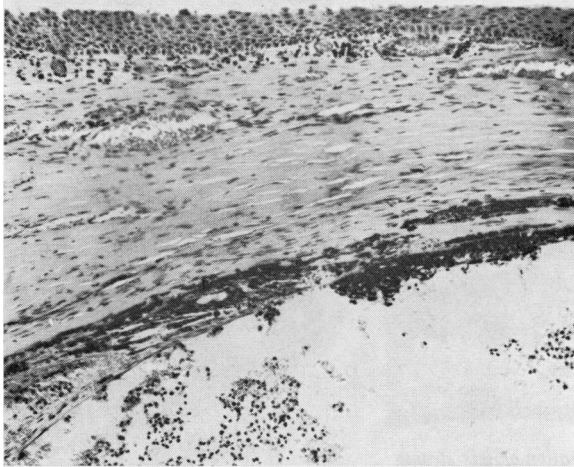


FIG. 12 *Case 10, showing markedly atrophic iris leaf firmly adherent to back of vascularized cornea. Haematoxylin and eosin. $\times 90$*

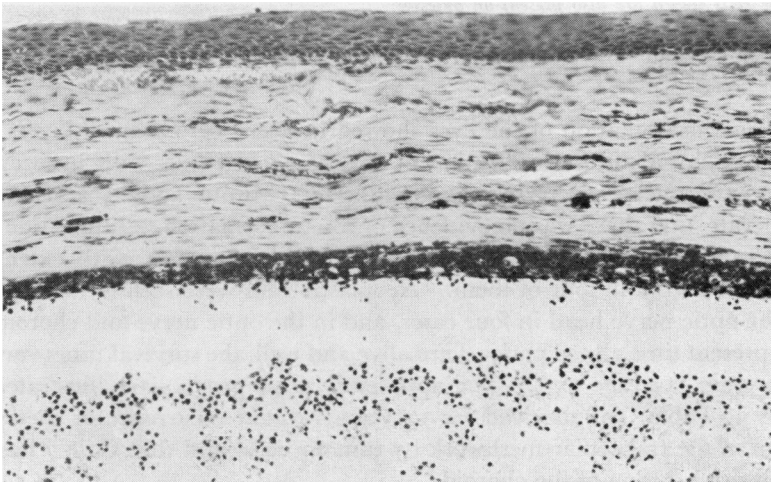


FIG. 13 *Case 10, showing infiltration of cornea by neoplastic cells. Haematoxylin and eosin. $\times 130$*

Table Summary of ten cases of diffuse infiltrating retinoblastoma

Case no.	Age (yrs)	Sex	Clinical features and ancillary investigations	Pathology	Treatment	Follow-up
1	9½	M	4 mths' history of uveitis with hypopyon Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in ciliary body, iris, anterior chamber, and vitreous	Enucleation	Alive and well without recurrence or metastases 17 yrs after onset
2	1	M	Presented with hypopyon and buphthalmos Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in subretinal space, ciliary body, iris, vitreous, and anterior chamber	Enucleation	Alive and well without recurrence or metastases 13 yrs after onset
3	6½	M	Presented with hypopyon, subluxated cataractous lens, and raised intraocular pressure Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, anterior chamber, and trabecular meshwork	Enucleation	Alive and well without recurrence or metastases 14 yrs after onset
4	4½	F	Cobalt treatment for retinoblastoma 2 yrs before onset of hypopyon and cataract Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, and anterior chamber Calcification of retina at site of original lesion	Enucleation	Alive and well without recurrence or metastases 14 yrs after onset
5	11	F	Hypopyon for 3 mths with raised intraocular pressure ESR, WR, and radiograph of globe normal	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, anterior chamber, trabecular meshwork, a scleral channel, subretinal space, and optic nerve head	Enucleation	Alive and well without recurrence or metastases 3 yrs after onset
6	7	M	"Peculiar-looking" eye for 3 mths in a mentally backward child Dense grey lesion almost completely covering fundus	Diffuse involvement of retina with no rosettes Tumour cells in vitreous	Enucleation	Alive and well without recurrence or metastases 10 yrs after onset
7	3	F	Mother noticed white pupil 2 yrs previously Signs of iritis and cataract on examination Chest x ray and ESR normal	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, anterior chamber, trabecular meshwork, optic nerve, and choroid	Enucleation	Alive and well without recurrence or metastases 8 yrs after onset
8	6	M	Treated as a case of "retinal haemangiomas" 10 mths previously Recently developed iris deposits and aqueous flare	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, subretinal space, ciliary body, iris, anterior chamber, trabecular meshwork, and optic nerve head	Enucleation	Alive and well without recurrence or metastases 7 yrs after onset
9	3½	M	White pupil noticed by mother for several wks	Diffuse involvement of retina with no rosettes Tumour cells in vitreous and optic nerve head	Enucleation	Alive and well without recurrence or metastases 5 yrs after onset
10	10	M	Endophthalmitis and hypopyon for 8 mths Inferior staphyloma for 1 mth with secondary glaucoma Child mentally defective	Diffuse involvement of retina with no rosettes Tumour cells in ciliary body, iris, anterior chamber, vitreous, and cupped optic disc	Enucleation	Alive and well without recurrence or metastases 2 yrs after onset

ESR = erythrocyte sedimentation rate
WR = Wassermann reaction

Discussion

Of 720 cases of retinoblastoma examined histologically in the Department of Pathology of this Institute between the years 1949 and 1970, only ten (1.4 per cent.) have been diagnosed as diffuse, infiltrating tumours. Several interesting features have emerged from the study of these ten cases. The average age of the patients is higher than that of the usual type of retinoblastoma which presents with a tumour mass, and none of these tumours was bilateral. Patients frequently present with a hypopyon so that examination of an anterior chamber paracentesis for neoplastic cells is an important diagnostic procedure. Rosettes are not a feature of this tumour, and as far as this small series of cases is concerned the tumours have a good prognosis.

The tumour originates either as a simple diffuse growth or as multiple foci of growth which coalesce. Spread may then occur through the ciliary body and iris and extend into the anterior chamber, and may in some cases invade the trabecular meshwork. Tumour cells may grow into the vitreous or upon the pars plana and ciliary processes. Invasion of the choroid or optic nerve occurs in some cases.

In seven of the ten cases presenting with this tumour, the age of the patient was 4½ years or over, suggesting that the neoplasms arise at a later age than the usual type of tumour. In three of the cases, however, the age at onset was 1 year (Case 2), 1 year (Case 7), and 3 years (Case 9) respectively, which shows that the tumour can arise at an earlier age and that some (Cases 2 and 9) may grow more rapidly than others, although there were no histological features to account for this. On the whole, however, the rate of growth is slow, as illustrated by Case 4 in which the original lesion was treated by cobalt irradiation 2 years before the onset of a hypopyon, and by Case 7 in which the mother noticed a white pupil 2 years before bringing the child to hospital. A rapidly-growing tumour would be expected to produce an expanding growth within the area of the retina while a slowly-growing tumour would be more likely to spread through the retina. There seems to be little doubt that the tumour must have a low malignant potential which would explain the apparently favourable prognosis of this uncommon neoplasm, for in spite of invasion of the trabecular meshwork in four cases (Cases 3, 5, 7, and 8) and of the choroid in one (Case 7), the patients have survived with no evidence of recurrence or metastases for periods varying between 3 and 14 years after enucleation. The question whether or not the low malignant potential is due to the tumours' origin from more highly differentiated tissue is not clear, because the rosettes seen in the better differentiated retinoblastomas were not observed in the ten cases of this series. It is possible, however, that they were absent because the tumour did not produce a mass, and there was insufficient space within the retina for their development.

Summary

Ten cases have been described of a type of retinoblastoma which is both diffuse and infiltrating, and which does not form a tumour mass; four of these cases have been reported previously (Schofield, 1960). The average age of the patients is higher than that found in the usual type of retinoblastoma, and the majority present for the first time with a hypopyon. Bilaterality was not a feature, and rosette formation was not seen. The prognosis after enucleation appears to be good.

I am most grateful to Prof. Norman Ashton for his advice during the preparation of this paper.

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