Malignant optic nerve glioma

Report of a case with electron microscope study

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Optic nerve gliomas are rare, being responsible for 1 per cent. of intracranial tumours (Russell and Rubinstein, 1971) and 3 per cent. of unilateral orbital lesions (Reese, 1963). 75 per cent. of patients are under the age of 10 years (Chutorian, Schwartz, Evans, and Carter, 1964) and the association with neurofibromatosis is well established (Davis, 1940; van der Hoeve, 1925; Tym, 1961). The benign glioma has been described as a 'congenital non-neoplastic hamartoma-like lesion with a distinctive self-limiting pattern of growth and morbidity' (Hoyt and Baghdassarian, 1969).

In contrast to this benign group, a malignant glioma with acute onset simulating optic neuritis and a rapidly progressive course has also been reported (Martin and Cushing, 1923; Saebø, 1949; Mattson and Peterson, 1966; Condon and Rose, 1967).

The present case, which exemplifies this malignant group, is reported with electron microscope findings.

Case report

A 50-year-old farm manager presented at Moorfields Eye Hospital on August 9, 1968, with a history of the accidental projection of pig meal into his right eye 10 days previously. The following day an unspecified conjunctival foreign body was removed at another hospital, and since that time he had experienced pain and blurred vision.

Examination

The visual acuity was perception of light in the right eye and 6/5 in the left. The right eye was tender to palpation and showed an afferent pupillary defect. A diagnosis of retrobulbar neuritis was made. Investigations, including a full blood count, erythrocyte sedimentation rate, Wassermann reaction, and skull x ray were all normal.

3 weeks later there was no perception of light in the right eye and systemic prednisolone, 20 mg. daily, was commenced. X rays of the optic foramen were reported to be normal.

Course

2 months later right proptosis was observed and the patient was admitted for investigation. There was 4 mm. of proptosis on the right with pain and limitation of movement in all directions—particularly on elevation and abduction. The right disc was swollen, with peripapillary haemorrhages which extended to the periphery along the retinal veins. The visual acuity in the left eye was still 6/5, though at this time a left temporal hemianopia was recorded. A diagnosis of an orbital lesion with chiasmal involvement was made and the patient was transferred to the National Hospital, Queen Square, under the care of Dr. Ross Russell.

By December 2, 1968, the visual acuity in the left eye had deteriorated to 6/24 and the dosage of steroids was increased to 120 mg. prednisolone daily. A lumbar puncture, air encephalogram, and carotid angiogram were all normal.

Fluorescein angiography of the right eye showed slow retinal transit with marked leakage at the disc and perivenous leakage extending to the periphery (Fig. 1).

FIG. 1 Fluorescein angiogram at 5 minutes, showing leakage of dye from optic disc and along retinal veins

A provisional diagnosis of a granulomatous lesion or a nasopharyngeal tumour was made. Examination by an oto-rhino-laryngologist revealed no abnormality and x rays and biopsy of the postnasal space were also negative. However, x rays of the optic foramina showed that the right was larger than the left (Fig. 2).

FIG. 2 Photograph of x rays, showing enlarged right optic foramen and normal left optic foramen

Operation

Exploration of the chiasm on December 18, 1968 (Mr. Lindsay Symon) showed that the right optic nerve and optic tract were thickened and grey. The bony roof of the optic canal was absent. A biopsy was taken and this showed the histological features of a Grade III astrocytoma. Steroids were consequently stopped and radiotherapy instituted.

Progress

Over the subsequent months the sight of the left eye deteriorated further and on June 25, 1969, the patient developed acute pain in the right eye. Examination revealed corneal oedema, rubeosis iridis, and an intraocular pressure of 50 mm. Hg. A diagnosis of thrombotic glaucoma was made and despite a retrobulbar injection of alcohol the pain persisted and the eye was enucleated. The optic nerve was found to be markedly thickened (see Fig. 3).

FIG. 3 Enucleated right eye showing thickened optic nerve

Termination

By August, 1969, the left eye was blind. The patient became confused and disorientated and he died one month later. Permission for a *post mortem* examination was refused, so that only the enucleated eye was available for study.

Pathological studies

GROSS APPEARANCE

The eye, fixed in 10 per cent. formol saline and opened parasagittally, showed a mild degree of disc oedema with surrounding deep exudates and numerous haemorrhages in the posterior retina.

HISTOPATHOLOGY

Apart from peripheral anterior synechiae and some cystic changes in the ciliary epithelium, the principal findings were related to the posterior segment. The optic nerve, immediately behind the lamina cribrosa, was thickened and largely replaced by glial tissue (Figs 4 and 5, overleaf).

FIG. 4 Section showing fibrillary astrocytes in which there is a moderate degree of pleomorphism. There is also considerable endothelial hyperplasia in the capillary blood vessels. Haematoxylin and eosin. $\times 185$

FIG. 5 (a) High-power view, showing fibrillary astrocytes, some of them with hyperchromatic and giant nuclei. Haematoxylin and eosin. $\times 370$

(b) Another part of the tumour, showing prominent hyperplasia of the capillary endothelium. Haematoxylin and eosin. $\times 370$

Though most of the cells were recognizable as fibrillary astrocytes, there was a degree of pleomorphism and many cells had giant hyperchromatic nuclei which were occasionally multilobulated. Mitotic figures were also present. The tumour had a somewhat open texture in places with the spaces containing an acid mucopolysaccharide which was both Alcianophilic and periodic acid-Schiff positive. Endothelial cell hyperplasia was a prominent finding in the majority of the blood vessels coursing through the tumour, though many capillaries within the pre-existing fibrous septa of the nerve were normal. Neoplastic cells had invaded both the arachnoid and dural sheath and infiltrated the optic nerve head, where several large thrombosed and recanalized vessels could also be seen. Occluded branch veins in the retina were associated with numerous superficial haemorrhages and occasional serous exudates in the outer layers. The peripheral retina showed marked cystoid degeneration.

Digest preparations of a portion of the retina stained with oil red O showed lipid in some veins and capillaries; staining with haematoxylin and eosin showed several capillary microaneurysms, occasional arterio-venous shunts, and widespread endothelial cell degeneration.

ULTRASTRUCTURE

A portion of the optic nerve excised at operation was fixed in 2.5 per cent. glutaraldehyde for electron microscopical examination. After post-fixation in 1 per cent. osmium tetroxide and embedding in araldite, semi-thin sections were cut and stained with toluidine blue. Light microscopy of these sections showed a few Rosenthal fibres, but were otherwise identical to the paraffin sections.

Electron microscopy of thin sections stained with uranyl acetate and lead citrate showed closely packed polyhedral cells with oval or bizarre multilobulated nuclei. Nucleoli were prominent and usually multiple and there was some marginal condensation and clumping of the nucleoplasm (Fig. 6, overleaf). The cytoplasm was rich in organelles and included small mitochondria, dilated cisternae of endoplasmic reticulum filled with flocculent material, occasional lipid inclusions, abundant free ribosomes, and prominent Golgi systems. In some cells there was a well-developed smooth surfaced endoplasmic reticulum arranged in a whorled concentric fashion (Fig. 7, overleaf). The cytoplasmic processes of these neoplastic astrocytes were short and stubby and contained delicate filaments arranged in whorls and parallel bundles along the axis.

The filaments often encircled the nucleus (Fig. 8, overleaf) while occasional cells were apparently devoid of filaments. A few glial processes, corresponding to the Rosenthal fibres of light microscopy, were characterized by focal irregular condensation of the intracytoplasmic filaments, the latter in some instances having been superseded by granular disintegration of the electron dense aggregates (Fig. 9a, b).

The endothelium of many capillaries was hyperplastic and bulged into the lumen, giving individual cells a somewhat columnar appearance (Fig. 10). The cells were rich in organelles and an isolated example of mitotic activity was seen. Vessels within the fibrous septa of the nerve were surrounded by collagen fibrils which mingled with the more amorphous component of the basement membrane. Though there was a definite basement membrane separating the neuroglial tissue from the fibrovascular septa, neoplastic astrocytes and their processes were often seen within the septa. Glial processes were frequently present within the collagenous basement membrane of the septal capillaries. Occasional non-astrocytic cells (probably histiocytes), having lipoidal inclusions, were also seen.

FIG. 6 *Electron micrograph, showing prominent nucleus with marginal condensation of nucleoplasm. The extracellular spaces are filled with flocculent material. $\times 15,000$*

Discussion

Malignant glioma of the optic nerve should be suspected when an adult presents with unilateral optic neuritis which progresses to complete blindness and is associated with disc swelling as part of a venous occlusive process.

Fluorescein angiography performed in the case described showed the typical features of a venous occlusive process with marked perivenous leakage of dye. This technique may

FIG. 7 *Electron micrograph, showing whorled endoplasmic reticulum, some with dilated cisternae, and an abundance of ribosome granules. $\times 25,000$*

exclude the diagnosis of optic neuritis. Cases with similar clinical patterns have been reported by previous authors (Meadows, 1949; Saebø, 1949; Horland and Ellis, 1966), and with progression to thrombotic glaucoma by Meadows (1949).

Confirmation of the rapid spread of a malignant process is obtained when x rays reveal an enlarged optic foramen, or when a temporal hemianopia develops in the contralateral eye.

FIG. 8 *Electron micrograph, showing central nucleus encircled by filaments; the peripheral cytoplasm contains dense inclusions and dilated endoplasmic reticulum. $\times 28,000$*

(a) Focal irregular condensation of intracytoplasmic filaments; (b) More obvious condensation. $\times 32,000$

FIG. 9 Electron micrograph, showing stages in morphogenesis of Rosenthal fibres.

Presentation with a retrobulbar neuritis and later evidence of both disc and chiasmal involvement, as in this case, support the concept that these tumours arise within the optic nerve and rapidly spread proximally and distally. Biopsy of the optic nerve in a blind eye seems essential in order to establish the histological features and if, in this way, early

FIG. 10 *Electron micrograph of part of a blood vessel within a fibrous septa; the latter is infiltrated with fibrillary astrocyte processes, and the lumen (L) shows compressed endothelial cells giving a columnar appearance. $\times 10,000$*

diagnosis becomes possible, excision may conceivably prevent spread. It is our experience that sudden and often bilateral visual loss may be due to other conditions involving the optic nerve and chiasm such as carcinomatous infiltration or sarcoidosis.

The progressive unremitting retrograde spread of this tumour produced death 13 months after presentation and similar histories were given in other reported cases.

The morphological features which gave grounds for believing that this optic nerve glioma was malignant were cellular pleomorphism, nuclear irregularity including multilobulated glial forms, hyperchromatism, and some hypoplasia of most cytoplasmic processes. Comparable findings have been described in malignant astrocytomas of the brain at both light and electron microscopical levels (Russell and Rubinstein, 1971; Luse, 1960; Raimondi, Mullan, and Evans, 1962). Mitotic activity was also increased, and ultrastructurally some cells showed margination of the nucleoplasm indicative of nuclear exhaustion similar to that reported by Raimondi (1966) in cerebral glioblastoma multiforme. In a patient in his fifth decade, such proliferative activity cannot be regarded as hamartomatous and must be seen as neoplastic growth with sinister implications. The degree of malignancy corresponds most closely to the Grade III astrocytoma described in the classification introduced by Kernohan, Mabon, Svien, and Adson (1949).

Clinical diagnosis on initial presentation has in most cases been that of optic neuritis due to the sudden visual loss, often with pain and proptosis. Recently it has been suggested that this might be due to increase in tumour size related to accumulation of mucinous material rather than to any proliferative activity (Anderson and Spencer, 1970). The present tumour contained extracellular mucosubstance and presented cytological features, such as Golgi system hypertrophy and dilated cisternae of the endoplasmic reticulum filled with flocculent material, which might justifiably be construed as evidence of enhanced mucopolysaccharide production. The amount of mucosubstance, however, seemed insufficient to cause significant increase in tumour size and certainly did not give rise to the microcystic appearance described in a case by Anderson and Spencer (1970).

Invasion of the fibrous septa of the nerve by astrocytes is occasionally seen in benign gliomas (Anderson and Spencer, 1970), but when it is as prominent as in the present case it must indicate the invasive potential of the tumour. Capillary endothelial cell proliferation was most prominent and, though not specific for malignancy, should raise suspicion in an otherwise benign lesion (Russell and Rubinstein, 1971). The cause of the proliferation is unknown but it is interesting to speculate that it might in some way be related to the observed infiltration of the collagenous adventitia and basement membrane of the vessel by neoplastic glial processes.

Rosenthal fibres were a common finding among the tumour astrocytes. Tissue culture (Gluszczyk, Giernat, Habryka, Alwasiak, Lach, and Papierz, 1971) and ultrastructural studies (Herndon, Rubinstein, Freeman, and Mathieson, 1970) uphold the impression current since their original description by Rosenthal (1898) that they are probably a degenerative phenomenon in dysplastic glial processes. Thus, from proliferated and frequently matted intracytoplasmic filaments, focal condensations of thickened filaments develop, which later aggregate into electron dense bodies and eventually disintegrate into coarse granules. They are not specific for neoplasia but are an indication of disordered astrocyte metabolism.

The electron microscopical findings are therefore indicative of a growing tumour with evidence of retrogressive ischaemic change. The neuronal changes in the optic nerve could possibly be attributed to ischaemia, resulting from vascular endothelial cell hyperplasia and attendant changes in capillary calibre, or direct compression by the tumour.

Summary

A case is reported of a malignant glioma of the optic nerve in a 50-year-old man. This case exemplified certain important diagnostic features of this group of neoplasms:

- (1) Initial diagnosis of typical neuritis.
- (2) Progression to visual loss in the contralateral eye.
- (3) Venous occlusive process in the ipsilateral eye progressing to thrombotic glaucoma.
- (4) Intracranial spread of the tumour to cause death about 1 year after onset.

Electron microscope studies showed invasion by tumour of neighbouring structures and endothelial cell hyperplasia, and the clinical pattern is related to these findings.

We should like to thank Dr. R. W. Ross Russell for allowing us to study his case.

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