GANGLIOGLIOMA: A CASE WITH LONG HISTORY AND MALIGNANT EVOLUTION

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Ganglion-cell tumors of the central nervous system are both rare and controversial. There is much dispute over their definition, nomenclature and biological behavior. Most of them, however, fall within the general group of the gangliogliomas which, as implied in the term originally proposed by Ewing (1) and subsequently adopted by Courville (2), are relatively benign and slowly-growing neoplasms in which neurons and supporting neuroglial cells are the essential elements. The glia is, for the most part, astrocytic. However, as our own material and the examples reviewed in the literature (2, 3) make clear, the extent to which it displays a neoplastic evolution may vary from case to case: in some it is so scanty that the tumor may be called a pure ganglioneuroma; in others the glia may be so abundant that the first microscopic impression is that of an astrocytoma. Intermediate grades between these two extremes are, however, most frequently encountered. In such cases the cytological differentiation of one cell type usually parallels that of the other. But exceptions to this rule occasionally occur, and this variability is of importance when the biological potentialities of these tumors are assessed. We have suggested elsewhere (4) that when they undergo a malignant change it is in the glial and not the neuronal element that this is usually witnessed. The example reported here supports this view with particular clarity.

CASE REPORT

History: D.S. (NS/0107) was first seen by Hugh Cairns at The London Hospital in 1936 when she was 26 years old. Two years previously, when pregnant, she had noticed deterioration of vision. This progressed until she was almost blind in the right eye, and vision was becoming worse in the left. During the previous 16 months she had also suffered from severe morning headaches with occasional nausea and vomiting. She had received 3 courses of X-ray treatment elsewhere.

Examination: There was bilateral secondary optic atrophy, most severe on the right with a right nasal field defect, the left field being full. Apart from exaggeration of the right knee-jerk there were no further physical signs.

X-ray examination revealed enlargement of the pituitary fossa, with absence of the dorsum sellae. Cerebrospinal Fluid: The lumbar-fluid pressure was 300 mm. and contained 300 mg. of protein. In the lateral ventricles the pressure was 480 mm., the fluid being yellowish and containing 1050 mg. of protein (left) and 700 mg. (right). Ventriculography revealed a

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‡ The case to be described has been briefly mentioned by us (4, p. 167) as "alive and well" at the time of writing.

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Fig. 1. Original biopsy removed 23 years before death. a. Intraventricular tumor composed of neurons in a scanty glial stroma, separated from basal ganglia by ependymal cells (top left). Hematoxylin and Eosin stain; $\times$ 180. b. High power view. Atypical neurons. Hematoxylin and Eosin stain; $\times$ 330. c. Autopsy. Junction of ganglion-cell tumor (upper half) and highly fibrillary astrocytic glioma (lower half). Phosphotungstic acid-hematoxylin stain; $\times$ 33.

filling defect in the anterior two-thirds of the left lateral ventricle and blocking of the left foramen of Monro.

Operation (15 Dec. 1936): A left frontal craniotomy was performed. Part of the frontal lobe was excised and portions of an intraventricular tumor removed from the region of the basal ganglia.
Biopsy (SD/3204/36) (fig. 1 a and b). Microscopically, the bits received included a small amount of poorly to moderately cellular tumor, the accompanying grey and white matter showing no infiltration. The tumor contained neurons of varying size and shape, some with demonstrable Nissl substance. Occasional binucleate forms were present. There were no mitotic figures. The neurons were supported by a matrix of loose fibrillary tissue with pale areas of microcystic degeneration and containing scanty elongated glial cells, interpreted as pilocytic astrocytes. A number of somewhat larger cells with round or oval nuclei, displaying a well-defined nuclear membrane and a small conspicuous nucleolus, were also present, and were tentatively interpreted as immature ganglion cells. In one fragment, partly composed of basal ganglion, the tumor was clearly enroaching on the ventricular cavity (fig. 1a). Small caleospheres were scattered in the adjacent, otherwise normal, basal ganglia.

Course: Recovery from this operation was followed by right-sided spasticity and homonymous hemianopia. The patient was treated with two courses of radiotherapy in 1936 and 1937.

In 1938 and 1939 she had 2 attacks of unconsciousness which were interpreted as epileptic. No further events were recorded until 1949, when she had a further attack in which the head was rotated to the right.

In 1950 vision again deteriorated and, during the following 8 years, this was associated with dysphasia, dysarthria and progressive failure of memory. By July 1959 she was unable to walk on account of right hemiplegia. An angiogram then indicated a recurrence of the tumor. In the following month a second operation revealed discoloration and many small cysts in the region of the left motor cortex. A few bits of tissue examined microscopically showed, in places, a small amount of tumor resembling the original biopsy.

Subsequently the patient's condition steadily deteriorated, and she died on Dec. 28, 1959.

Post Mortem Findings: (P.M. 517.1959). Death was due to bronchopneumonia and a pulmonary thrombotic embolus, but other significant findings were confined to the intracranial contents. No tumor was visible on the surface of the brain, but fullness of the gyri on the ventral aspect of the left frontal lobe and the medial aspect of the left occipital lobe suggested underlying growth.

Coronal sections disclosed the extension of this growth through the central parts of the cerebrum, with replacement of most of the corpus callosum, septum pellucidum and fornix, and obliteration of the body and anterior horn of the left lateral ventricle (fig. 2a). Posteriorly it fanned out into the medial halves of both occipital lobes, being more bulky on the left than the right (fig. 2b). On the left it also extended into the temporal lobe, replacing the ependyma.

For the most part the appearances suggested a classical glioblastoma multiforme with extensive necrosis and small hemorrhagic foci in a grayish, rather soft growth. Anterior to the splenium, however, the tumor was firmer, better defined and more homogeneous.

Microscopically, the main interest attaches to this anterior part which is composed of two types of tumor, in continuity with each other but distinctive cytologically.

Laterally, in the obliterated ventricle, it is essentially similar to the biopsy removed 23 years previously. Atypical neurons, often of large size, form the preponderant cellular element (fig. 3), but smaller, transitional forms are also included. Most are uninnucleate; occasionally two or three nuclei are present. In many, the Nissl substance is absent; in others it shows a variable distribution, presenting coarse, irregularly scattered, or peripherally aligned blobs (fig. 3e). In metal-impregnations by Bielschowsky's method the ganglion cells display a variable affinity for silver, but bizarre shapes are well brought out and, in many, dense dark tangles of cytoplasmic neurofibrils and numerous tortuous nerve fibers of varying calibre (fig. 3d) are present.

The stroma separating the neurons shows a variable degree of degeneration, being often spongy and vacuolated, with a scanty complement of small darkly staining cells. Occasional neuroglial fibrils are present, but pilocytic astrocytes are few; they become more prominent, however, as the border of the medially situated gliomatous portion is approached. There are scattered nests of lymphocytes and microglia, especially in the areas of degeneration and around the blood vessels. The latter are abundant in places, where they present an almost angiomatous appearance; they are mostly thin-walled, but some have undergone
marked acellular hyaline thickening. An extremely abundant reticulin network intersects the tumor widely; it is usually related to the intense vascularity and often separates large and small nests of ganglionic elements (fig. 3b). Ventrolaterally to the tumor, the uninvaded caudate nucleus shows beneath the ependyma a prominent band of calcospherites.

Fig. 2. Coronal sections of tumor at necropsy. a. Anterior part. Dark gray growth replaces the left anterior horn (mostly ganglionic microscopically) and is faintly demarcated from paler gray tumor infiltrating the pillars of the fornix and the corpus callosum (astrocytic). The paraventricular growth in the left temporal lobe is a direct extension from the more caudally situated glioblastoma. b. Posterior part of tumor. Necrotic glioblastoma in splenium and medial halves of occipital lobes.
This part of the growth shows no histological evidence of malignant change: focal cellular increases, anaplastic forms and mitoses are absent.

Medially, however, where it approaches the corpus callosum, septum lucidum and fornix, the tumor shows a fairly abrupt zone of transition (fig. 1c), merging into a widespread infiltration of these structures by fibrillary astrocytes exclusively: here the appearances are
indistinguishable from those of a diffuse astrocytoma. The cells are mostly piloid, sometimes stellate. Neuroglial fibers are conspicuous. Early malignancy, as witnessed by capillary endothelial proliferation and small foci of necrosis, is already evident, and mitoses with occasional giant cells are found as one proceeds more caudally along the densely cellular

![Image of histological sections showing anaplastic astrocytoma and glioblastoma in left temporal and occipital lobes.](http://jnen.oxfordjournals.org/)

**Fig. 4.** Anaplastic astrocytoma and glioblastoma in left temporal and occipital lobes. 

tumor infiltrating the corpus callosum. The neoplasm infiltrates the tela choroidea and the leptomeninges around the great vein of Galen. Progressive anaplasia of the glial element, with extensive necroses, is found in the splenium and the invaded left temporal lobe, where astrocytic elements with strongly staining neuroglial fibrils are still, however, recognizable (fig. 4a).

In the left occipital lobe, the cells, in considerable density, are mostly undifferentiated and polymorphic (fig. 4b). Recognizable astrocytes are relatively scanty. The tumor is very vascular, and many small and larger necroses are attributable to thrombosis. Typical pseudopalisades are also present (fig. 4c). The picture here is indistinguishable from a glioblastoma multiforme, as macroscopically evident.

Throughout this glial part of the tumor, reticulin is confined to the walls of blood-vessels, in strong contradistinction to the arrangement noted in the anterolateral ganglionic portion.

In the anterior left temporal extension of the tumor, a few large atypical neurons are found beneath the ependyma, amidst the glioma cells. They display no cytological evidence of malignancy, and their location suggests an independent heterotopia of maldevelopmental origin. No other ectopic ganglion cells were found in any other part of the gliomatous area.

**DISCUSSION**

This case is of interest and importance in the long survival of the patient (23 years) from the time of her first operation. The tumor must already have been long established even then, from the radiographic appearance, verified post mortem, of her sella turcica. This feature, as well as the long post-operative course, are consistent with the relatively benign biological character of the original growth. The late progressive clinical course and the terminal pathological findings constitute clear evidence of an ultimate anaplastic change.

The malignant evolution of a ganglioglioma might theoretically take place along the lines of neuroblastic dedifferentiation of the ganglion-cell elements, or anaplasia following proliferation of the glial cells. An objective assessment, from the literature, of the frequency of this evolution is extremely difficult, owing to the diagnostic problems presented in the identification of ganglion-cell tumors in general (4), and the tendency of several workers (5–9) to label, as malignant ganglion-cell tumors, growths in which the nuclei assume a superficial resemblance to neuronal nuclei and which appear to be giant-cell glioblastomas. In such tumors Nissl substance and neurofibrils cannot, in our experience, be demonstrated in the component cells, and all transitional forms to anaplastic cells of neuroglial origin can usually be traced.

Acceptable ganglion-cell tumors in which the anaplastic element appears solely referable to more primitive neuroblastic forms have occasionally been recorded (10, 11). Such cases showed all transitions from neuroblasts to mature ganglion cells. In an unpublished example, examined by us, in a boy aged 5 years, a large cystic left fronto-parietal tumor was composed largely of small neuroblasts with many young differentiating neurons, only a few reactive astrocytes being demonstrated. Following a good postoperative recovery, recurrence of the tumor 5 years later ultimately led to its seeding throughout the lateral ventricles and to death of the patient. The histological picture recapitulated that seen at the time of the original biopsy. The biological behavior of the tumors in this group, to which the term “differentiating neuroblastoma” seems appropriate, appears, therefore, completely unpredictable. Case 1 of Kernohan
et al. (12) is of particular interest, in that a 6 years' interval elapsed between the transformation of a primitive neuroblastoma into a mature ganglieneuroma. The case recently reported by Liss (13), in which an interval of 13 years separated the surgical removal of a recurrent tumor regarded as a parietal neuroblastoma, may possibly belong to this group.

Other, apparently genuine, ganglion-cell tumors exhibiting both biological and histological evidence of malignant change, such as rapid growth and many mitotic figures, include Case 3 of Kernohan et al. (12) and Case 4 of Tönß and Züleh (14). Here, however, the available documentation leaves open the question whether the more anaplastic elements were unequivocally of neuroblastic or glial origin. Similar difficulties of interpretation apply, in our opinion, to the examples reported more recently by Fletcher and Bailey (15) and by Courville and Abbott (16). Fletcher and Bailey's case, described as a neurogliogenic tumor of the diencephalon, includes unquestionably highly abnormal neoplastic neurons, but their Figure 5 recalls, as in the present case, the typical pseudo-palisades found in a glioblastoma multiforme; moreover, other areas of the brain exhibited a diffuse glioblastomatous process. Courville and Abbott, on the other hand, expressed the definite view that in their case the anaplastic features were referable solely to the neuronal element.

From our knowledge of the potential activities of these two types of cell, and by analogy with the known behavior of many cerebral astrocytomas, it might, however, be supposed a priori that anaplastic changes in the glia would be more probable. In two examples of ganglioglioma from our own material we have noted anaplastic features which appeared to be entirely referable to the glial element; no equivalent malignant change was observed in the neurons. The present case confirms this hypothesis. The clinical symptomatology, manifested episodically over a span of 25 years, and the pathological findings disclosed on two widely separated occasions permit a reconstruction of the lines of the tumor's evolution; they would indicate that extremely slow growth, with possibly long intervals of arrest and accompanied by continuous differentiation of the neuronal element, was the cardinal feature of the original centrally located ganglioglioma. The presence of a few heterotopic neurons beneath the left temporal ependyma, independent of the main tumor, suggests that its origin was essentially that of a hamartoma. It is clear, however, that this benign evolution was overtaken, in the later stages, by a widespread acceleration of the neoplastic process, now accompanied by anaplasia, in which participation of only the glial element was demonstrated. The picture of a massive glioblastoma multiforme was thus ultimately produced.

SUMMARY

A case of ganglioglioma is described, in which anaplastic change of its astrocytic component into a glioblastoma multiforme took place 23 years after the original biopsy. The original ganglionic tumor was readily identified at necropsy. The neurons played no part in this malignant evolution of the growth.
REFERENCES