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The fine structure of gliomatosis cerebri*

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Summary. The ultrastructural features of five biopsies of gliomatosis cerebri (GC) are described. Four main types of tumour cells are seen: anaplastic astrocytes poor in organelles with a variable amount of glial microfilaments; atypical oligodendrocytes with scanty cytoplasm in which microtubules are present; intermediate forms with aboundant cytoplasm rich in organelles, with microtubules and microfilaments; and small cells with round nuclei and a very scanty rim of cytoplasm. In two cases several concentrically folded cytoplasmic lamellae of glial processes were arranged either around themselves or around the perikaryon of other cells. This ultrasructural study indicates that GC is a neoplastic process of small undifferentiated elements, transitional forms of astroglia (to oligodendroglia) and anaplastic cells of astrocytic origin in all stages of development.

Key words: Gliomatosis cerebri – Brain tumour – Ultrastructure – Glial cells

Introduction

Among the forms of gliomatous neoplasms in the CNS there is a variety in which the neoplastic elements are so diffuse and so widespread in their distribution that it has been designated gliomatosis cerebri (GC) (Nevin 1938). This condition is rare compared with other gliomas. Many aspects of its cytology and growth behaviour are unclear. Recently, we have reported a review of the clinical and pathological aspects and of the immunohistological findings in ten cases of GC (Artigas et al. 1985a, Artigas et al. 1985b). To our knowledge, ultrastructural studies in GC have not been reported previously, although we believe that the case of diffuse glioma reported by Mikol et al. (1975) may be an example of GC. We are therefore presenting our observations in 5 cases of GC.

Materials and methods

Table 1 gives an outline of the relevant clinical data. In all cases the diagnosis of GC was established according to the clinical features, CT-scan findings and histological study of brain biopsies (Couch and Weiss 1974, Kazner et al. 1981, Hayek and Valavanis 1982, Artigas et al. 1985). In three cases the diagnosis of GC was confirmed at autopsy. Two patients are still alive.

The samples of the intraoperative biopsies used in this study measured approximately 1 mm^3. The tissue was placed in a 3.5% buffered glutaraldehyde solution shortly after surgical removal and left in fixative for a period of 4 h. After rinsing in a 0.2 M cacodylat buffer solution, postfixation was performed for 2 h in 2% osmium tetroxide. Following dehydration the samples were embedded in Araldite (Merck, FRG). Ultrathin sections were studied with a Zeiss-EM-10 electron microscope.

Results

Four main types of tumour cells and intermediate forms are seen in all the cases studied.

The first cell type has nuclei rich in chromatin which is irregularly distributed throughout the nucleoplasm and tends to form aggregates. Nuclear profiles are very polymorphic without being bizarre. Nucleoli are prominent, sometimes multiple. These cells have aboundant cytoplasm of moderate to high electron density. They are poor in organelles, mitochondria being the most prominent and numerous. These are often deformed and have few or no cristae. The endoplasmic reticulum is scanty

* Dedicated to Prof. Dr. Lennert on occasion of his 65th birthday

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Table 1

Case	Duration of the illness	First symptoms	Brain biopsy	Clinical features
I 71y M	16 months	Seizures	Parietal right	Croniotomy; died 6 months after operation
II 30y M	17 years	Seizures	Frontal right	Seizures at the age of 13; paranoid behavior ten years later; at that time right amygdalofornico-comissural thalamotomy because of clinical diagnosis of paranoid psicosis; seven years later biopsy; died 3 days later
III 39y F	10 months	Headaches, weakness, dizziness	Parietal right	Two craniotomies because of diagnosis of malignant astrocytoma. Radiation (5400 rads). Died two days after second operation
IV 30y M	16 months	Seizures left hemiparesis	Parietal right	Brain stem signs. Stereotaxic biopsy; radiation (6000 rads); still alive 25 months after treatment
V 21y F	14 months	Left hemiparesis	Basal ganglia right	Several biopsies of the basal ganglia, not treatment; still alive after 14 months

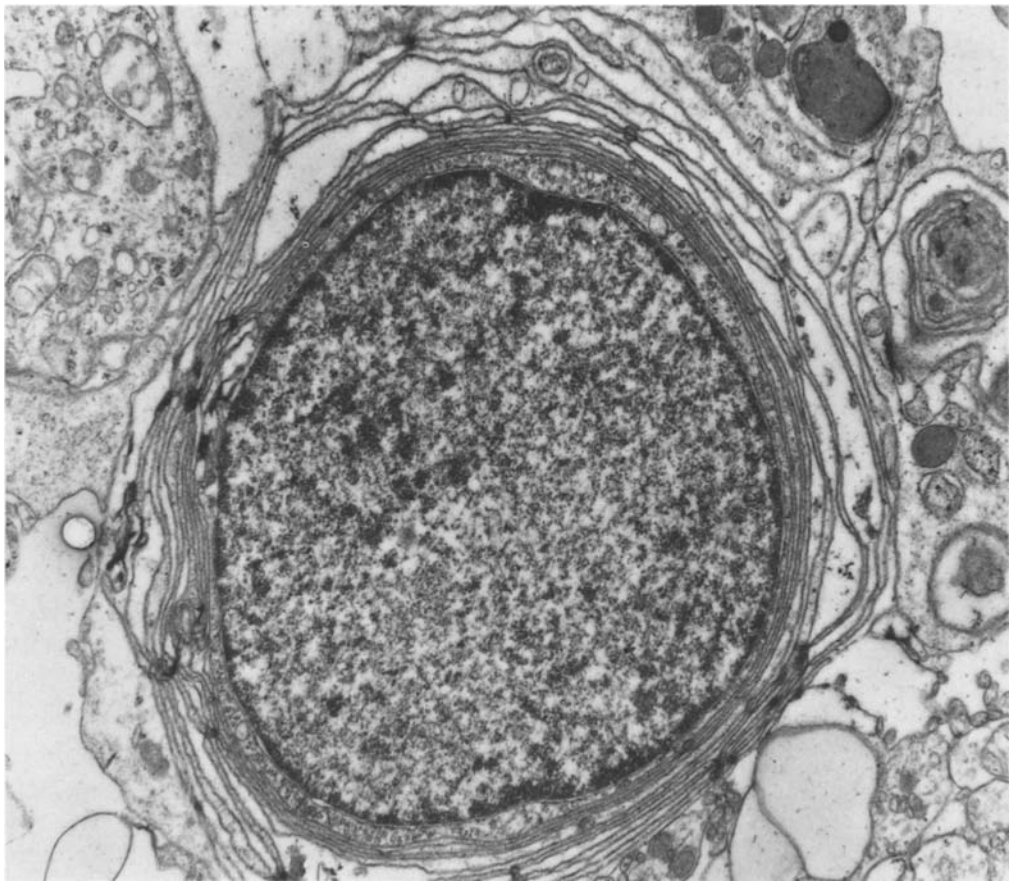

Fig. 1. Anaplastic astrocyte (Type I). Its cytoplasm contains bundles of glial filaments. Mitochondria are vacuolated. Chromatin is irregularly distributed in the nucleoplasm, forming aggregates

and dilated. Glial filaments 7 nm to 9 nm in diameter, sometimes running in bundles are found in the cytoplasm and in the cell proesses. Their density varies from cell to cell. Some cells are elongated and have several processes which are observed stretching out into the intercellular space for some distance before they ramify. More often they are short and plump.

The second type of cell seen is small to middle-sized and round to oval in shape (Fig. 1). The

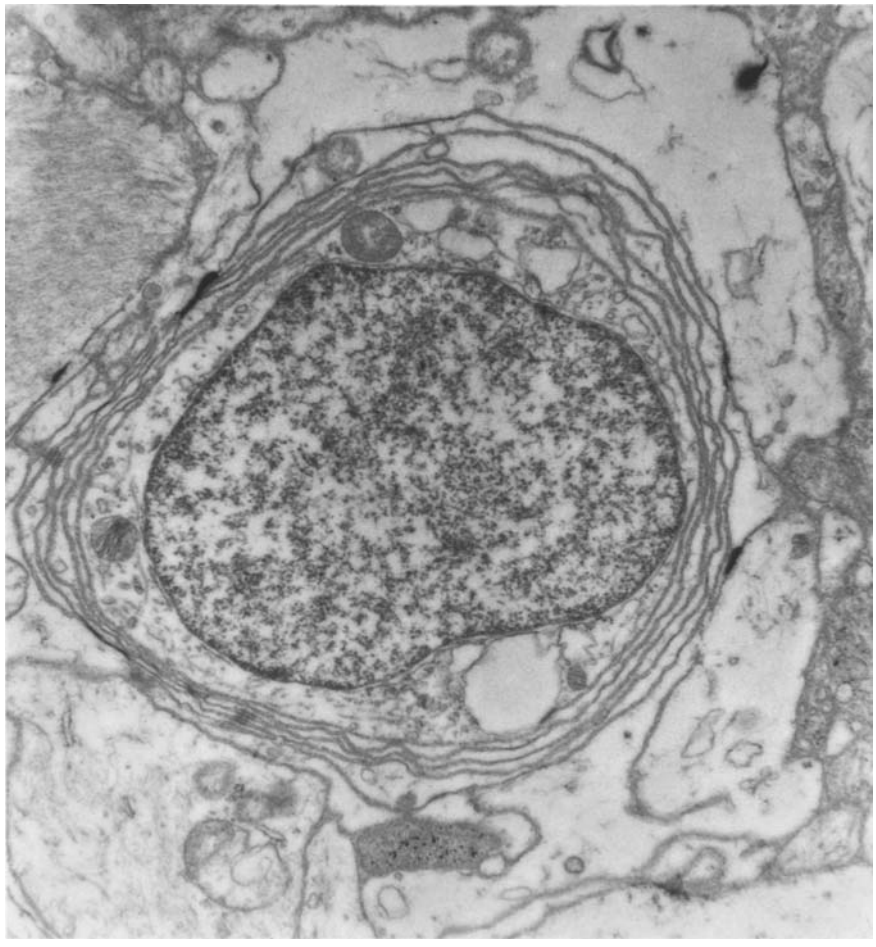

Fig. 2. Atypical oligodendrocyte very poor in cytoplasm (Type II cell) surrounded by a membranous whorl. Only polyribosomes can be recognized in the cytoplasma. Chromatin condenses under the nuclear membrane forming small aggregates

round-ovoid nucleus is fairly rich in chromatin which is, in general terms, homogeneously distributed throughout the nucleoplasm. In some cells, however, chromatin accumulates slightly along the nuclear membrane. Cytoplasm is generally scanty. Polyribosomes are dispersed throughout the cytoplasm. In the areas where cytoplasm is more aboundant mitochondria and microtubules are apparent (Fig. 2). Membranous whorls constituted by electron dense membranes separated by a variable and irregularly shaped space are seen around these cells (Fig. 2 and 3).

The third type of cell (Fig. 3) possesses aboundant cytoplasm of light to moderate electron density. The nuclei are round or oblong. Chromatin is present in moderate amounts and is regularly distributed throughout the nucleoplasm. Slight increases in density at the level of the nuclear membrane are seen. Nucleoli are often prominent. In a few cells fibrillary intranuclear inclusions are present. The cytoplasm contains microtubules, microfilaments, mitochondria many of them vacuolated, polyribosomes and dilated rough endoplasmic reticulum. Lysosomes are scarce. Only few cells have numerous lysosomes both in the cytoplasm and processes. Golgi apparatuses are not always seen. When present they are scanty and may be partially distended.

In addition, we have found small cells with a very scanty cytoplasm (Fig. 4). The nuclear/cytoplasm ratio is seldom less than 8:1. The nuclei are mostly round or oval, occasionally oblong and have a slightly irregular profile. Chromatin is irregularly distributed throughout the nucleoplasm forming disperse aggregates. Near the nuclear membrane sporadic aggregates are seen. In the cytoplasm there are rosettes of ribosomes and scattered mitochondria.

A striking finding, in two cases, was the disposition of glial cell processes in a laminar pattern. Three or more membranous layers are concentrically arranged or overlap each other (Fig. 1, 2 and 5). Some of these processes seem to embrace either the perikaryon of the cell from which they are derived or other cells by forming semicircular or circular folds around them.

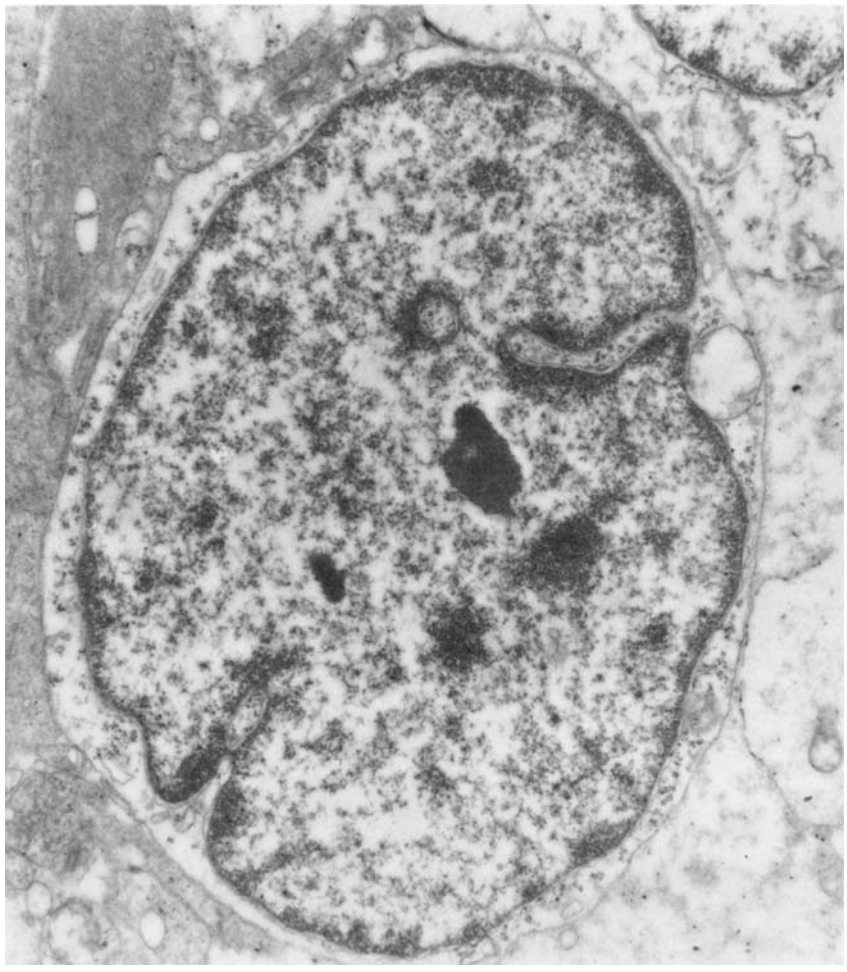

Fig. 3. Type II cells. Atypical oligodendrocyte with scanty cytoplasm surrounded by a membranous whorl. Few Mitochondria, microtubules and dilated endoplasmic reticulum

All types of neoplastic cells are intermingled with neurons and neuroglial cells in the cortex and white matter. Their density varies within the infiltrated areas with the normal brain tissue being relatively well preserved.

Discussion

Light microscopical and immunohistological studies of GC reveal, in most cells, the usual features of glial cells (Artigas et al. 1985a; Artigas et al. 1985b). The cytoplasm of most neoplastic cells and numerous stout cell processes contain GFAP-positive fibrils which at the ultrastructural level consist of typical intracellular glial filaments measuring 70 A to 90 A in diameter. The variable amounts of glial filaments may explain the variations in GFAP positivity observed in our previous immunohistological studies (Artigas et al. 1985a).

Whorl membranes found in our material have been reported in oligodendrogliomas (Robertson and Vogel 1962; Cervos-Navarro and Pehlivan 1981; Cervos-Navarro et al. 1981). Mikol et al. (1975) found these structures in a diffuse glioma, which, from the original description could be considered to be a GC. These have also been observed in organotypic cultures of the central nervous system (Raine and Bornstein 1974). They may, therefore, be regarded as an inherent and specific characteristic of neoplastic oligodendroglial cells. We agree with Cervos-Navarro et al. (1981) who interpreted these membranous whorls as the manifestation of a capacity to form myelin by the tumour oligodendroglia, while the more primitive folding systems are a remnant of this capacity. These structures could be the ultrastructural substratum for the myelin basic protein positive neoplastic cells present in GC (Artigas et al. 1985b). Cervos-Navarro et al. (1968) described similar structures in neurinomas, the stem cell of which are Schwann cells that have a similar function in the peripheral

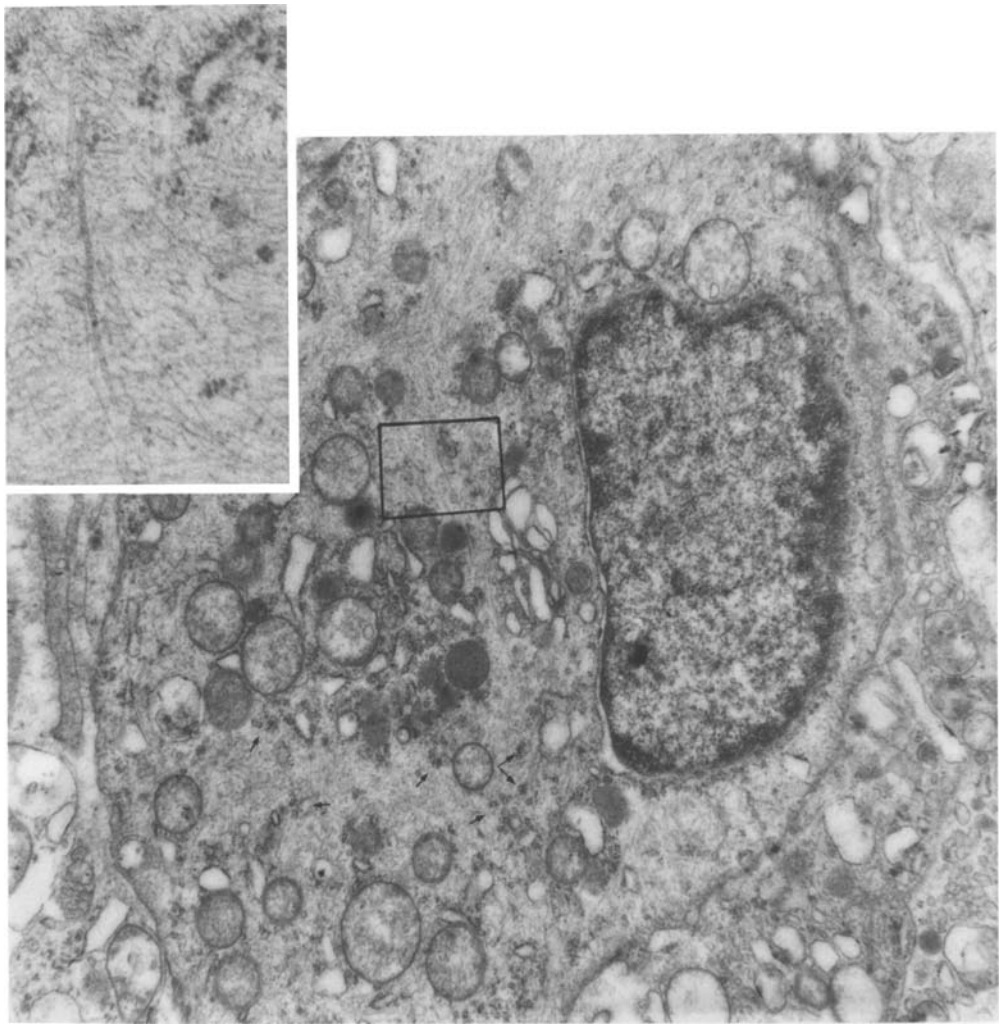

Fig. 4. Type III cells fairly rich in cytoplasm and in organelles. Mitochondria of the crysta and tubular type are seen as well as rosetts of ribosomes. The rough endoplasmic reticulum is slightly dilated. Microtubules and microfilaments are seen (Inset)

nervous system to that of oligodendrocytes in the central nervous system. These findings corroborate the observation of Robertson and Vogel (1962) indicating that under certain circumstances glial cells have the capacity to form sheath like structures by concentric lamination of several processes, rather than by the spiraling of a single process.

The cell populations of GC is mainly composed of three types. Two of them (Type II and III) resemble the two populations found by Cervos-Navarro et al. 1981 in oligodendrogliomas. These populations are characterized either by cells with scanty cytoplasm surrounded by membranous lamellae or by cells which are rich in cytoplasm. Organelles such as variably atypical mitochondria of the crista type, rosettes of ribosomes, dilated endoplasmic reticulum and microtubuli and microfilaments are typical of these cells. The nuclei are round or oval and contain irregularly distributed chromatin which aggregates under the nuclear membrane. The more polymorphic cells, with irregular cytoplasm and nuclear shape, which present with bundles of glial microfilaments in their cytoplasm and processes (cell type I) is also found in astrocytomas (Luse 1960; Dufell et al. 1963; Ebhardt 1979) and in astroblastomas (Kubota et al. 1985).

In GC evidence of a glial tumour origin is overwhelming. Our findings are in aggreement with histological and immunohistological findings (Artigas et al. 1985a; Artigas et al. 1985b) showing that GC is composed of neoplastic cells of astrocytic origin and of transitional forms of oligodendroglia and astroglia.

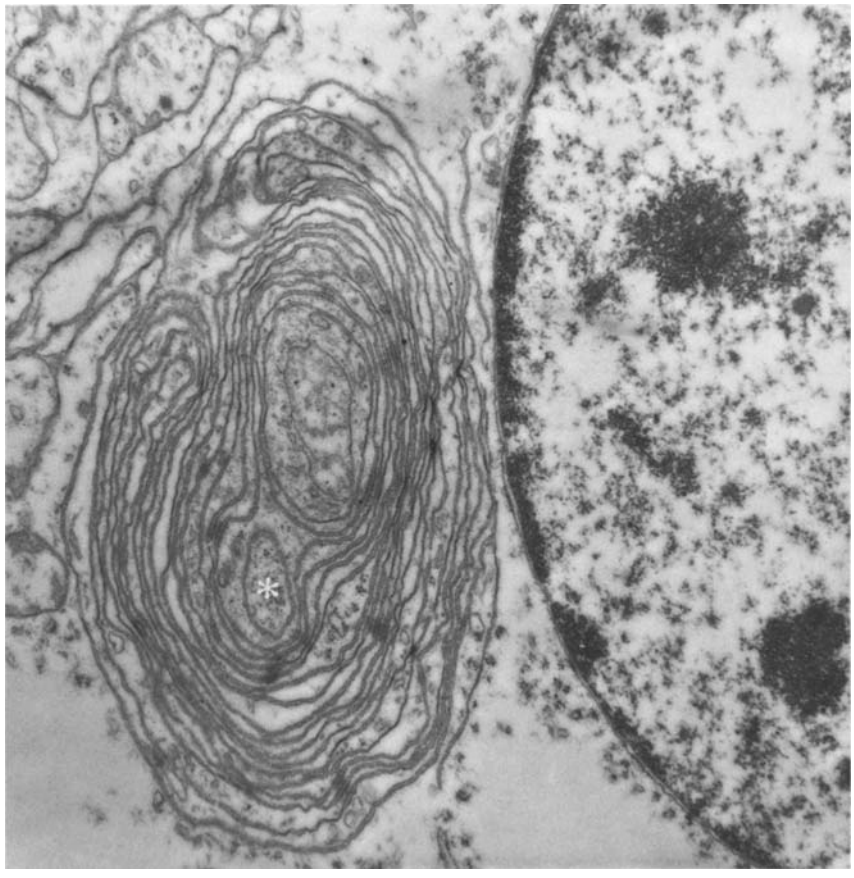

Fig. 5. Membranous whorl formations concentrically disposed around an axon

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