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Medulloblastoma (?) with Epithelioid Features

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Summary. A midline cerebellar tumor in an 18-year-old male, on light microscopy composed of closely packed, small featureless cells with little cytoplasm, under electron microscopic examination showed distinct epithelial features. The cells were closely apposed and joined by zonula adherentes, puncta adherentia and classical desmosomes. The latter structure has not been described in unequivocal glial or neuronal tumors or in normal cells dervied from the neural tube in vertebrates, not even in ontogenesis. In many areas the tumor cells abut on extensive basement membranes. Although the majority of the cells were undifferentiated, we occasionally observed elements containing dense core vesicles, microtubules and cilia. In addition, typical astrocytes were identified. The presence of these features strongly favors the neuroectodermal origin of this neoplasm.

Key words: Medulloblastoma – Desmosomes – Dense core vesicles – Basement membrane – Ependymoma

Introduction

In considering the morphology of neuroectodermal tumors it remains useful to recognize that the Central Nervous System ultimately derives from the surface of embryonal epithelium and that many epithelial characteristics are retained, even in the mature tissue. Epithelial characteristics such as close apposition of cytoplasmic membranes, presence of several types of junctional devices and basement membranes are still consistenly present in neuroectodermal tumors, for instance choroid plexus papillomas (Carter et al. 1972), medulloepitheliomas (Pollak and Friede 1977), myxopapillary ependymomas (Rawlinson et al. 1973), but not ordinary ependymomas. In other tumors, however, only a few epithelial features may be expressed. Thus, junctional devices have been described in medulloblastomas (Hassoun et al. 1975), retinoblastomas (Choux et al. 1972), astrocytomas and glioblastomas (Tani and

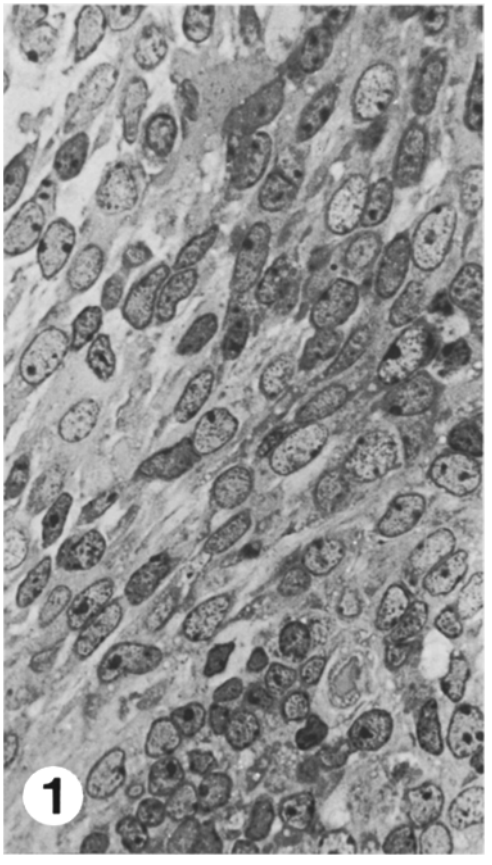

Fig. 1. Epon, 1 μm, Toluidine blue. Sheet of densely packed spindle cells with scanty cytoplasm, no distinct tissue pattern. × 250

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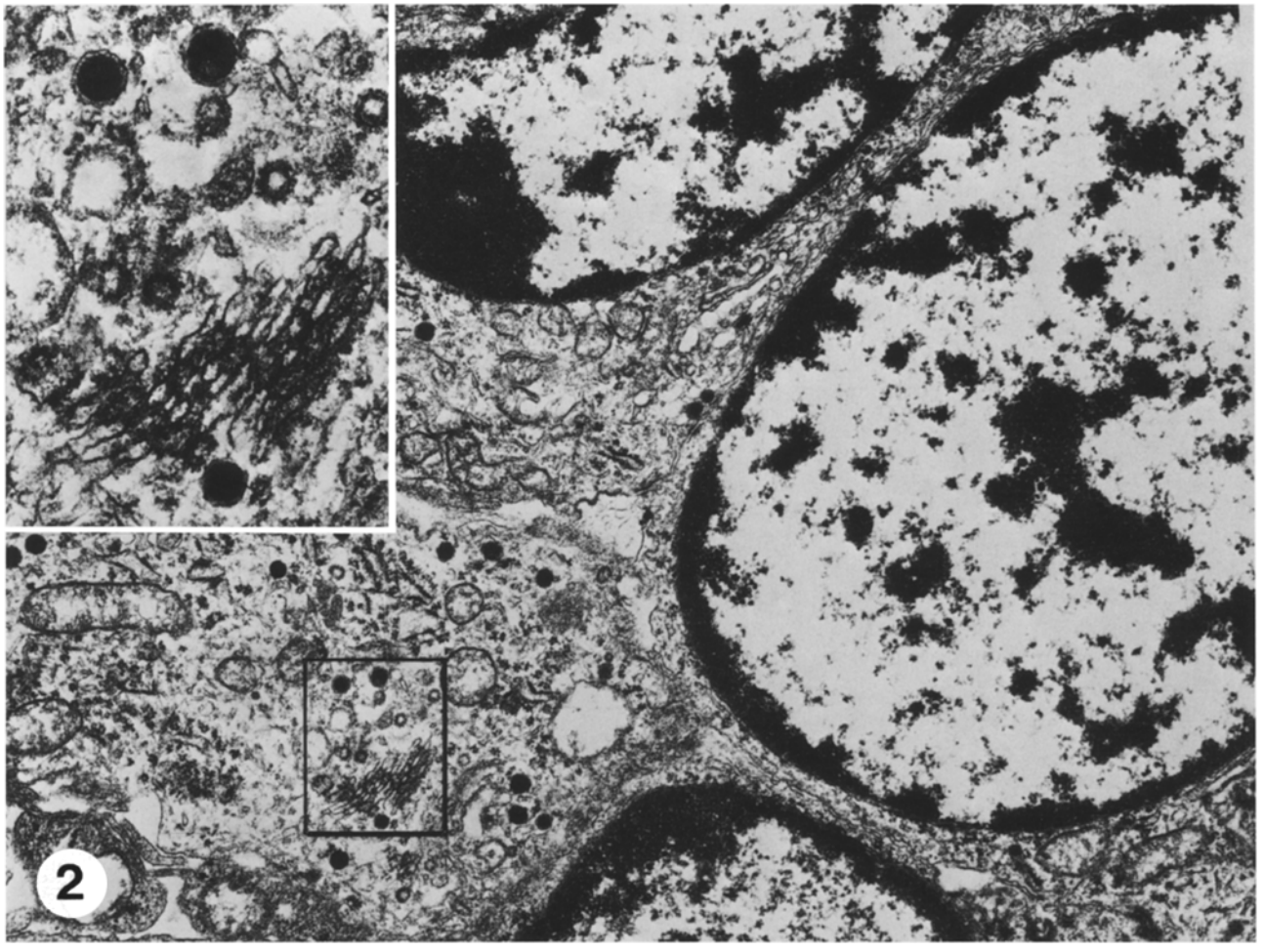

Fig. 2. Tumor cells with annulate lamellae and dense core vesicles. ×15,925. *Inset* ×45,700

Ametani 1971), oligodendrogliomas (Hirano 1975), ependymomas (Goebel and Cravioto 1972), ependymoblastomas (Hirano et al. 1973) and subependymomas (Azzarelli et al. 1977a). We present a case of small cell tumor of the cerebellar vermis, that ultrastructurally displays almost all known epithelial features, including uniquely desmosomes. Its neural tube derivation is discussed.

Case Report

An 18-year-old white male with an 11-month history of intermittent diplopia developed two months prior to his admission unsteady gait and transient episodes of vertigo, without headache or vomiting. Examination revealed divergent paresis of the eyes and gaze-evoked nystagmus. There was past pointing on the left with finger-to-nose testing, a positive Romberg sign and poor tandem gait. Rapid alternating movements were impaired bilaterally. The rest of the examinations was within normal limits, including a chest X-ray.

A CAT scan showed an enhancing midline lesion in the posterior medullary velum. A posterior fossa angiogram revealed an avascular mass within the same area. Upon posterior fossa craniotomy a midline cerebellar tumor was subtotally resected. Following surgery patient received cranio-spinal radiation (5580 rad) with Cobalt 60. Now, eight months after surgery, the patient remains symptomatic.

Description of the Tumor

For light microscopy, only small pieces of tissue were available and these were utilized for frozen sections. Small tissue blocks were fixed in 2.5% glutaraldehyde in cacodylate buffer postosmicated in osmium tetraoxide and embedded in Epon 812. One micron sections were stained with Toluidine Blue. Thin sections were stained with uranyl acetate and lead citrate. Pictures were taken in a Phillips 300 electron microscope.

On light microscopy the tumor is composed of a closely packed nuclei, varying but little in size and with an ill-defined, scanty cytoplasm in basically featureless masses. No rosettes, pseudorosettes or papillary formations are observed. There is no trending to the blood vessels. The cytoplasm is usually bipolar. The nuclei are ovoid, with finely dispersed chromatin and small nucleoli (Fig. 1, Epon block). Mitotic figures are occasionally identified.

On electron microscopy there are two types of cells.

I. Most common are spindle-shaped cells with a scanty to moderate amount of cytoplasm with distend-

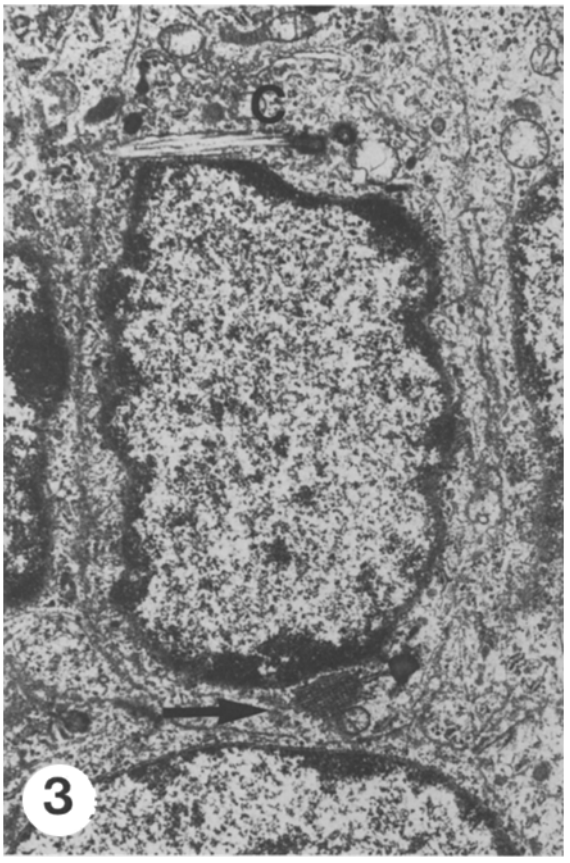

Fig. 3. Longitudinal section through a solitary cilium (*C*). Notice also the presence of annulate lamellae (*arrow*). × 8,970

ed cisternae of rough endoplasmic reticulum, unexceptional amounts of ribosomal rosettes, a few mitochrondria and a regular size Golgi apparatus. Some cells (Fig. 2) show frequent annulate lamellae (Fig. 2, also inset; Fig. 3, arrow), microtubules, and dense core vesicles, 120 – 160 nm in external diameter (Fig. 2, inset). There are centrioles and occasional cilia (Fig. 3). Nuclei are ovoid with finely dispersed chromatin and an occasional small, eccentric nucleolus. The cells are closely apposed and joined by no less than three types of junctional devices. The most characteristic device is formed by parallel segments of apposing membrane re-inforced by dense plaques and separated by an interspace of 30 – 36 nm which is bisected by a thin dense line. These are desmosomes (Figs. 4a arrow, 4b). These structures were fairly numerous, constituting the most common junctional device in this tissue. The second type is formed by membranes which course parallel to each other for 100 to 1,000 nm, separated by a space of 10 – 20 nm (Fig. 5). Typically, the cytoplasm immediately under such a membrane is electron dense. These are Zonula adherentes. The third type, the puncta adherentia consists of a small area where the membranes actually appear to fuse across the intercellular space (Fig. 6). The adjacent cytoplasm, as usual, is electron dense. Basement membranes also often make an appearance, defining extracellular spaces (Fig. 4a, E) with collagen fibers. The tumor cells are often separated from the basement membrane by thin, strongly fibrillated cytoplasmic processes, presumably astrocytic (Fig. 4a marked by "A"). In the case of direct contact the tumor cell cytoplasmic membrane may show focal densities on reaching the basement membrane.

II. The second cell type is larger, irregular in shape, with long processes (Fig. 6, Fig. 4a, "A"). The cytoplasm is filled with filaments, 80 – 90 nm and contains a few scattered cisternae of rough endoplasmic reticulum, minimal numbers of ribosomes and only a few mitochondria. The nucleus is irregular in shape, sometimes indented, with the chromatin in clumps, frequently resting on the inner nuclear membrane. A small nucleolus may be present. These cells are interpreted as astrocytes.

Characteristic Weibel-Palade bodies are often seen in the blood vessels.

Discussion

The epithelial cell is characterized by, firstly, its close apposition to its neighbor cells; secondly, to insure this close contact, the presence of junctional complexes, and thirdly, its insertion onto a basement membrane. In the development of nervous tissue some of these features are modified or totally lost. The close mutual cell contact is always maintained, with little or no extracellular space in the central nervous system. Then, in the case of the basement membrane, only the outermost cells remain seated on a basement membrane, such as the surface astrocytes and the choroid plexus cells.

Of the four commonly listed junctional devices, zonula occludens are observed in between ependymal (Brightman and Palay 1963), choroidal cells (Doolin and Birge 1969) and between adjacent myelin lamellae (Robertson 1957). The nexus or gap junctions are commonly seen between ependymal cells, between neuroglial cells and between certain neurons (Peters et al. 1976). Zonula adherentes occur between ependymal cells (Brightman and Palay 1963); a variation of this junction is the punctum adherens, commonly found between neurons and between neuroglial cells (Peters et al. 1976). Desomosome-like contact has been described between ependymoblasts (Tennyson 1970), but classic desmosomes are never seen (Peters et al. 1976), not even during the ontogenesis of the vertebrate central nervous system (Tennyson 1970).

Fairly widespread basement membrane has been seen in neuroectodermal tumors, particularly in cho-

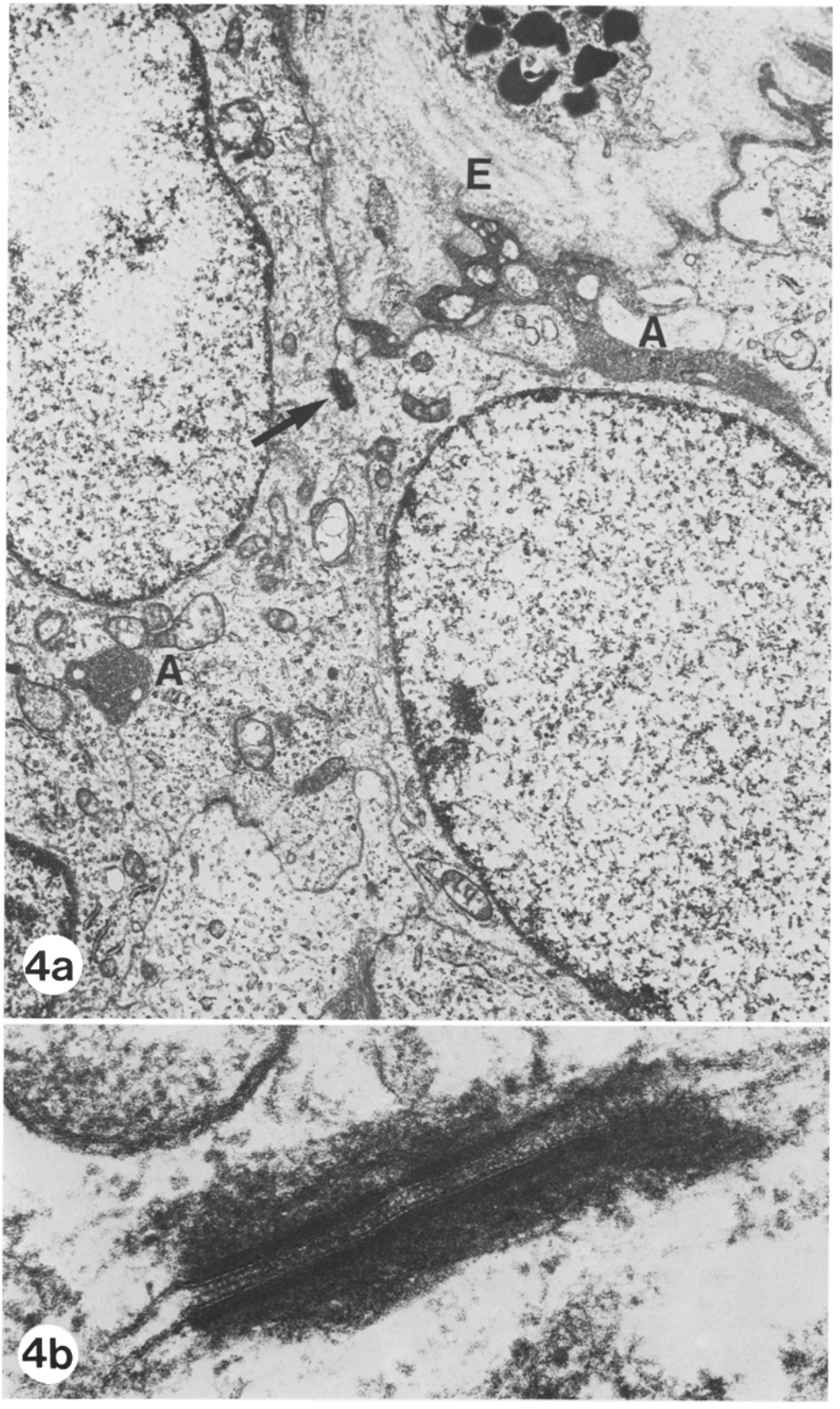

Fig. 4. **a** Several tumor cells abut a large extracellular space (*E*). A continuous basal lamina partially invests the cell perimeter. Astrocytic processes insinuate themselves between the tumor cells (*large arrow*) and beneath the basal lamina. A desmosome is marked with a *small arrow*. × 11,466. **b** High magnification of typical desmosome (from another field). × 66,090

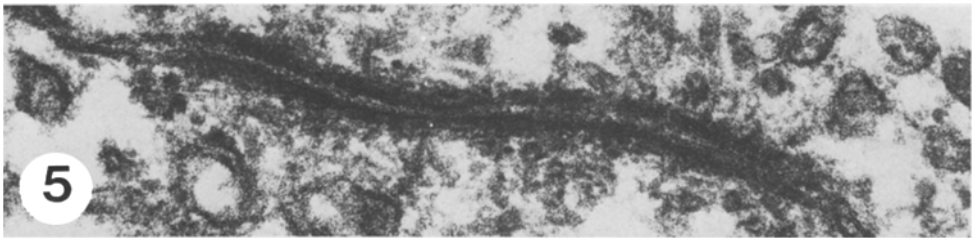

Fig. 5. Zonula adherens. × 102,000

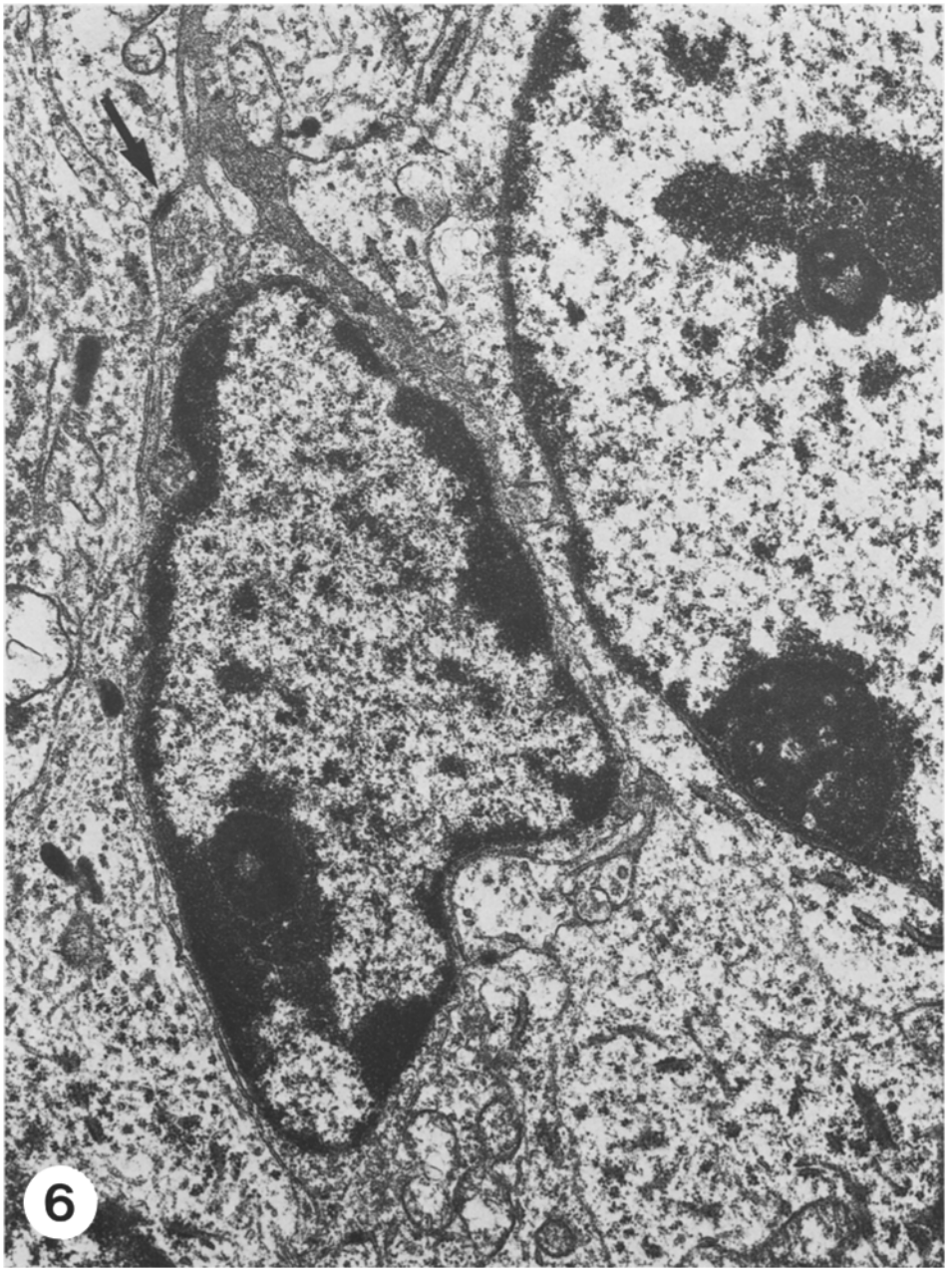

Fig. 6. Strongly fibrillated cell (astrocyte) joined by a punctum adherens with adjacent cell processes (*arrow*). × 17,250

roid plexus papillomas, myxopapillary ependymomas of the cauda equina, medulloepitheliomas, in colloid cysts (Coxe and Luse 1964) and in the supratentorial intracerebral epithelial (ependymal) cysts (Friede and Yasargil 1977). They also have been occasionally reported in medulloblastomas (Soejima 1970).

Desmosomes are consistently seen in colloid cysts (Coxe and Luse 1964) and in the supratentorial intracerebral epithelial (ependymal) cysts (Friede and Yasargil 1977). Occasionally they have been reported in ependymomas, but the published photographs are of low magnification and the identification of these junctions as desmosomes perhaps remains in doubt (Hirano 1975; Goebel and Cravioto 1972; Miller and Torack 1970). They have not been seen in any other neural tube derived tumors. If the pure neurotubular derivation of the colloid and the "ependymal" cysts be questioned, as it has (Hirano and Ghatak 1974; Ghatak et al. 1974), the simplifing statement that desmosomes do not occur in normal central nervous system tissue or its tumors can stand. In tumors derived from the neural crest, such as meningiomas, desmosome are common (Luse 1960; Kepes 1961, 1982). In that light, the documentation of desmosomes in our tumor is a unique finding.

There are some other unusual features. First are the dense core vesicles (DCV) 120–160 nm in diameter, similar to the catecholamine containing structures in the adrenal medulla (DeRobertis and Ferreira 1957) and in peripheral neuroblastomas (Greenberg et al. 1969). In the latter, there is correlation to chemically determined catecholamine levels (Greenberg et al. 1969). In central neuroblastomas as well, dense core vesicles correlate with high cerebrospinal fluid levels of catecholamines (Azzarelli et al. 1977b). In medulloblastomas DCV are quite uncommon (Ermel and Brucher 1974). DCV also has been reported in an otherwise typical ependymoma of the filum terminale (Miller and Torack 1970). A secretory role is clearly limplied, although final proof is lacking.

Second, the annullate lamellae, so striking in our case, are however common to many embryonal tissues and tumors; they lack specificity (Ghadially 1975).

Thirdly, cells with a single cilium are occasionally observed. The exact type could not be determined on account of their longitudinal orientation. Although cilia are most frequently observed in cells of ependymal derivation, they can also be found, although rarely, in all CNS cell types including the meninges (Dahl 1963; Duncan et al. 1963; Tso et al. 1969; Cervos-Navarro and Vazques 1966).

The second cell population in this tumor is composed of astrocytes. But whether they are reactive or neoplastic could not be determined.

By location, posterior medullary velum, roof of the fourth ventricle as well as by the age of this patient (18 years), the likelihood is that of an ependymoma. The presence of cilia and numerous junctional complexes are in favor of this. The light microscopical observations -- featureless cells, almost naked nuclei packed closely together, without a vestige of architectural sophistication such as rosettes, papillary structures, angiothropism, anuclear zones – do not support this possibility. Also there is much independent basement membrane around, this is only found in myxopapillary ependymomas (Rawlinson et al. 1973) but occasionally (Soejima 1970) also is seen in medulloblastomas. If the astrocytes present indeed are neoplastic, not easy to ascertain (Burger and Vogel 1982), this would also favor medulloblastoma (Soejima 1970).

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