Choroid plexus papillomas and human choroid plexus

A light and electron microscopic study

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Choroid plexus papillomas and mature human choroid plexus were studied by light and electron microscopic techniques. The mature choroid plexus has three types of cells: Type I cells are cuboidal or columnar cells and line the villi; Type II cells are flat cells lining connective tissue adjacent to neural tissue; and Type III cells are flat cells lining crypts in connective tissue. The cells of benign papillomas were similar to the fully developed Type I cells. The cells of a malignant papilloma were similar to the underdeveloped-appearing Type III cells. A variant malignant papilloma had well differentiated mucus-secreting cells resembling goblet cells.

KEY WORDS • human choroid plexus • benign papilloma • malignant papilloma • mucus-secreting papilloma • ultrastructural study

It has been suggested that communicating hydrocephalus observed in association with choroid plexus papillomas is caused by overproduction of cerebrospinal fluid (CSF) by the tumor. In the normal choroid plexus, cell surface factors and organelles are considered to participate in the production of CSF. The hypothesis of overproduction of CSF by tumor cells in choroid plexus papillomas raises the question of whether a similar mechanism of CSF production exists in the tumor cells of these papillomas. Considerable interest has been focused on the fine structure of papilloma cells. There have been two recent electron microscopic studies of choroid plexus papillomas associated with communicating hydrocephalus.

It is of considerable importance to know whether the malignant choroid plexus papilloma does produce CSF, and at what developmental stage the normal choroid plexus resembles the malignant papilloma cells, if at all. It is suggested that a comparative study of the fine structure of normal human choroid plexus and the various choroid plexus papillomas could possibly elucidate the histological characteristics and function of these tumors. This paper presents the similarities and differences in fine structure histology of normal and neoplastic human choroid plexus. The relationship between the ultrastructure and function of each type of epithelial cell is discussed.

Normal Choroid Plexus

Ten specimens of normal human choroid plexus, obtained at the time of brain tumor resection, were fixed in 4% buffered glutaraldehyde, postfixed in 1% phosphate-buffered osmium tetroxide, and, after dehydration, were embedded in Epon 812. The thick sections for light microscopy were stained with toluidine blue, and the ultra-thin sections for electron microscopy were stained with uranyl acetate and lead citrate and observed under a Hitachi HS-9 electron microscope.

Choroid Plexus Papilloma

Choroid plexus papillomas were obtained from five patients at the time of surgery: Cases 1 and 5 at Fukuoka University Hospital, Case 2 at Kyushu Koseinenkin Hospital, and Cases 3 and 4 at Kyushu University Hospital. The clinical data are summarized in Table 1. The specimens for light microscopy were fixed in 10% formalin, embedded in paraffin, and sectioned. Hematoxylin and eosin, periodic acid-Schiff (PAS), and mucicarmine stains were employed. The specimens for electron microscopy were processed in the same manner as the normal choroid plexuses. In Case 5, periodic acid-thiosemicarbazide-silver protein stain (PA-TSC-SP stain) was used to observe the histochemical reaction.
Normal and neoplastic choroid plexus

TABLE 1
Clinical data for five patients with choroid plexus papillomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Anatomical Site</th>
<th>Hydrocephalus</th>
<th>Survival Time After 1st Op</th>
<th>Histological Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 yrs</td>
<td>F</td>
<td>lateral ventricle</td>
<td>communicating</td>
<td>alive &amp; well, 3 yrs 5 mos</td>
<td>benign</td>
</tr>
<tr>
<td>2</td>
<td>2 yrs 6 mos</td>
<td>M</td>
<td>third ventricle</td>
<td>communicating</td>
<td>alive &amp; well, 2 yrs 2 mos</td>
<td>benign</td>
</tr>
<tr>
<td>3</td>
<td>1 yr 11 mos</td>
<td>F</td>
<td>fourth ventricle</td>
<td>noncommunicating</td>
<td>alive &amp; well, 5 yrs</td>
<td>benign</td>
</tr>
<tr>
<td>4</td>
<td>5 mos</td>
<td>F</td>
<td>third ventricle</td>
<td>noncommunicating</td>
<td>died, 6 mos</td>
<td>malignant, ordinary type</td>
</tr>
<tr>
<td>5</td>
<td>46 yrs</td>
<td>F</td>
<td>cerebellopontine angle</td>
<td>noncommunicating</td>
<td>died, 1 yr 10 mos</td>
<td>malignant, variant type*</td>
</tr>
</tbody>
</table>

* Malignant papilloma with mucus-secreting cells.

of intracytoplasmic vesicles and coating material. This stain was devised by Thirry as a method for detecting polysaccharides by electron microscopy. In the control studies, this stain was also used in two cases of normal choroid plexus, in a benign papilloma (Case 2), and in an ordinary type of malignant papilloma (Case 4).

Normal Choroid Plexus

Light Microscopic Structure

The normal choroid plexus had papillary projections that were composed of a single epithelial layer abutting on a loose stroma with thin-walled blood vessels (Fig. 1). In four cases, tubules lined with flat epithelial cells were present in connective tissue adjacent to neural tissue. Epithelial cells lining villi appeared to continue on to the tubules forming crypts. Three types of cells were identified in the epithelial layer. The first (Type I) was cuboidal or columnar and lined the villi; the second (Type II) was a flat cell lining connective tissue adjacent to neural tissue; and the third (Type III) was a flat cell lining the crypts. In some preparations, there was a transition between these cells.

Electron Microscopic Structure

The three types of cells as seen by light microscopy showed the following ultrastructure.

**Type I Cells.** Type I cells varied from light to dark depending on their cytoplasmic density (Fig. 2). The ultrastructure was the same in all of these cells. A round or ovoid nucleus with diffuse chromatin and a clear nucleolus occupied the central area of the cell. Many mitochondria were concentrated in the apical and basal regions. Rough endoplasmic reticulum in a parallel array was noted, predominantly in the apical region, as was the Golgi apparatus in the paranuclear region. Numerous pinocytotic vesicles and coated vesicles were also seen. Glycogen deposits were few. Numerous microvilli and tufts of a few cilia were seen on the free surface. Most of the microvilli were club-shaped, while the others were symmetrically finger-like. Most of the cilia had microtubules of a "nine plus two" configuration, while in a few a "nine plus zero" arrangement was seen. Adjacent cells were attached apically by tight junctions, and the lateral cell membranes were closely apposed and slightly interdigitating. The basal cell membranes had various degrees of basal infolding, particularly remarkable at the basolateral portions, and were resting on a thick flat continuous basal lamina (Fig. 2B). In some portions, the surface of the basal lamina was undulant, and there the basal cell membranes were closely apposed, showing the same undulation.

**Type II Cells.** Type II cells were characterized by the flat shape of the cell and nucleus, many mitochon-
Type II Cells. Mitochondria, Golgi apparatus, and rough endoplasmic reticulum were less prominent than in Type I cells. Glycogen deposits were prominent and tended to accumulate. Spherical or dumbbell-shaped dense bodies were seen. The surface elaborations of the cell were not fully developed. A few irregular-shaped microvilli, tufts of two to six cilia, and a small number of pinocytotic vesicles and coated vesicles were present. A few of the cilia had microtubules of a "seven plus one" configuration. Tight junctions were present at the apical ends. The lateral cell membranes were relatively straight, even at the bases, and showed little interdigitation. Basal infolding was rarely seen, unlike the observation in the Type I cells.

The stroma consisted of fibroblasts, collagen fibers, and a vasculature characterized by fenestrated capillaries.

Choroid Plexus Papillomas

Light Microscopic Structure

The histological appearances in Cases 1, 2, and 3 of benign choroid plexus papilloma were similar to those seen in the normal choroid plexus (Fig. 5). On the other hand, the histological appearances in Cases 4 and 5 had characteristics of a malignant choroid plexus papilloma such as invasion of adjacent nervous tissue and loss of normal papillary structure, particularly at areas of invasion. There were also changes in the epithelium from a single-layered cuboidal to a pseudostratified columnar appearance, along with abnormal mitoses and considerable nuclear pleomorphism (Figs. 6 and 7). In Case 4, although an autopsy was not performed, the tumor...
Normal and neoplastic choroid plexus

FIG. 4. Electron micrograph of normal choroidal epithelial cells (Type III) obtained from the lateral ventricle of a 43-year-old woman. Note the small number of microvilli and organelles, little basal infolding, and prominent glycogen deposits. x 3900.

was diagnosed as originating from the choroid plexus since the patient was only 5 months old and the histological picture was similar to that of normal choroid plexus. In Case 5, autopsy indicated that the lesion was a primary brain tumor originating from the choroid plexus. No other neoplasm was found and there was an evident transition from normal choroidal epithelial cells to tumor cells. Material positive to PAS stain was found in tall columnar mucus-secreting tumor cells that resembled goblet cells. This case will be reported in detail in a separate study.

Electron Microscopic Structure

Benign Choroid Plexus Papilloma. Cases 1, 2, and 3 were found to have benign choroid plexus papillomas (Fig. 8). The tumor epithelial cells were dark or light. An oval nucleus with clear nucleolus occupied the central area of the cell. The chromatin tended to be clumped. The mitochondria were located more extensively in the apical and basal regions. As in Type I cells, the pinocytotic and coated vesicles, Golgi apparatus, and rough endoplasmic reticulum were seen. Unlike Type I cells, however, glycogen deposits were frequently observed, and in Case 3 they tended to accumulate. On the free surface were numerous microvilli, although somewhat fewer than seen in Type I cells; their shape varied from club-shaped to finger-like (Fig. 8 inset). Tufts of one to nine cilia were also noted. The apical ends of adjacent cells were attached by tight junctions and the lateral portions by slight interdigitation. Unlike Type I cells, the basal infolding was rarely seen. The basal lamina was not thick. The vasculature in the stroma was characterized by fenestrated capillaries.

Ordinary Type of Malignant Choroid Plexus Papilloma. Case 4 was an example of an ordinary malignant choroid plexus papilloma (Fig. 9). The tumor epithelial cells were very dark. The nucleus with one or

Fig. 5. Photomicrograph from a benign choroid plexus papilloma (Case 2). Papillary projections consist of a single cuboidal epithelial layer abutting on a loose stroma with thin-walled blood vessels. H & E, × 270.

Fig. 6. Photomicrograph from an ordinary type of malignant choroid plexus papilloma (Case 4) showing a pseudostratified columnar appearance and many abnormal mitoses (arrows). H & E, × 270.
FIG. 7. Photomicrograph from a variant type of malignant choroid plexus papilloma (Case 5). Papillary projections are composed of pseudostratified epithelial layer abutting on a stroma, and there are many abnormal mitoses (arrows) and some tubules. H & E, × 270.

FIG. 8. Electron micrograph from a benign choroid plexus papilloma (Case 1) showing oval nuclei, many club-shaped or finger-like microvilli, mitochondria, little basal infolding, and a thin basal lamina. × 4100. *Inset:* Higher magnification showing microvilli and tight junctions. × 7800.

TABLE 2

<table>
<thead>
<tr>
<th>Ultrastructural Characteristics</th>
<th>Normal Choroid Plexus Type I</th>
<th>Normal Choroid Plexus Type III</th>
<th>Benign Papilloma</th>
<th>Malignant Papilloma Ordinary</th>
<th>Malignant Papilloma Variant-like</th>
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</thead>
<tbody>
<tr>
<td>microvilli shape</td>
<td>club-shaped, finger-like</td>
<td>irregular</td>
<td>club-shaped, finger-like</td>
<td>irregular</td>
<td>finger-like</td>
</tr>
<tr>
<td>microvilli number</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>glyocalyx</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>junction at apical end</td>
<td>tight</td>
<td>tight</td>
<td>tight</td>
<td>extensive, elongated</td>
<td>tight</td>
</tr>
<tr>
<td>pinocytotic vesicles</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>basal infolding</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>mitochondria</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>glycogen deposits</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

* +++ = many; + = few; ± = occasional; = = none; ? = uncertain.

two nucleoli was large, elongated, and irregular in shape. Prominent chromatin was usually clumped. Unlike the observation of benign papillomas, the cytoplasm was filled with abundant polyribosomes (Fig. 9B), and the numbers of mitochondria and Golgi apparatus were small. Pinocytotic vesicles and coated vesicles were not apparent. As in the case of Type III cells, glycogen deposits were prominent and accumulated in the apical and basal regions (Fig. 9C). The underdeveloped surface elaborations were also similar to those of Type III cells. Only a few short and irregular microvilli and a few tapering cilia were present (Fig. 9A and B). One of the most prominent features was an extensive and elongated junctional device near the apical ends (Fig. 9B). At the lateral and basal portions of the cell membranes, either interdigitation or infolding was hardly seen (Fig. 9C). The basal lamina was thin and flat. The capillaries showed fenestrations.

**Variant Type of Malignant Choroid Plexus Papilloma.** A variant type of malignant choroid plexus papilloma with mucus-secreting cells was seen in Case 5 (Fig. 10). The tumor epithelial cells were dark. The nucleus with one or two nucleoli was large, elongated, and irregular in shape. Prominent chromatin was usually clumped. The cytoplasm contained prominent polyribosomes and glycogen deposits, and many mitochondria, rough endoplasmic reticulum, and Golgi apparatus (Fig. 10A). Pinocytotic and coated vesicles were not observed. The specific characteristics in this case were intracytoplasmic vesicles and surface coating over the microvilli. Numerous vesicles of 700 to 3000 Å in diameter, probably secretory granules, were seen.
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Fig. 9. A: Electron micrograph from an ordinary type of malignant choroid plexus papilloma (Case 4) showing large and elongated nuclei, few irregular-shaped microvilli, and accumulations of glycogen deposits in the apical and basal regions. × 6400. B: High magnification of the surface area showing irregular-shaped microvilli, extensive and elongated terminal attachments, and prominent polyribosomes. × 20,000. C: High magnification of the basal region showing accumulations of glycogen deposits, little basal infolding, and a thin basal lamina. × 16,000.

in the apical region (Fig. 10B and C). Many microvilli that were uniform in length and diameter were erect in a closely parallel array and were coated by a fibrous and granular electron-dense material, glycocalyx (Fig. 10B and C). Cilia were absent. The apical ends of adjacent cells were attached by tight junctions and the lateral portions by many desmosomes and prominent interdigitations (Fig. 10A). Basal infolding was hardly seen. The basal lamina was flat and thick. The capillaries in this case also showed fenestrations. On PA-TSC-SP staining, the intracytoplasmic vesicles and the surface coating material of the microvilli were revealed to be positive (Fig. 10C). However, in other controls, the positive material was limited to the glycogen deposits and lysosomes.

The characteristics in the fine structure of epithelial cells in normal and neoplastic choroid plexuses are tabulated in Table 2.

Discussion

The choroid plexus of various mammalian species has been extensively examined, but the ultrastructure of the human choroid plexus has been reported less extensively. In the present study, Type I cells are
FIG. 10. A: Electron micrograph from a variant-type of malignant choroid plexus papilloma (Case 5) showing a round nucleus, many uniform microvilli, prominent interdigitation, many desmosomes, numerous intracytoplasmic vesicles, many Golgi apparatuses, and rough endoplasmic reticulum. × 13,000. B: High magnification of the surface area showing many uniform microvilli coated by fibrous and granular material, tight junctions, and many vesicles in the apical region. × 20,000. C: Electron micrograph of the surface area stained with PA-TSC-SP. Glycocalyx, intracytoplasmic vesicles, and glycogen deposits are revealed. × 28,000.

similar to the normal choroidal epithelial cells already reported. These Type I cells have many microvilli and prominent basal infolding. To the author's knowledge, the fine structure of the flat cells lining the crypts (Type III cells) has never been reported. In a light microscopic study, cells of this type were reported by Shuangshoti and Netsky.26 These have characteristics similar to those observed in the choroid plexus in early embryonic stages, as reported by Tennyson and Pappas.28 Their report describes the elongated microvilli with incipient folding of the basal surfaces of adjacent cells and the increased number of organelles. It appears, therefore, that the Type I cell is fully developed while the Type III cell is underdeveloped. The relationship between Type I and Type III cells resembles that seen between the epithelium covering the villi and that lining the crypts of Lieberkühn in the intestine. In the depths of the crypts, less clearly differentiated cells are seen and here new cells are thought to be formed.4 Pease23 has proposed that the microvilli and the basal infolding provide for increasing the surface area, and that increased surface area might be important in fluid transport mechanisms. If such is the case, the fully developed Type I cell would seem capable of producing CSF while the Type III cell does not. The developmental stage and functions of the Type II cell could not be clarified.

The fine structure of 23 neoplasms originating from the choroid plexus has been reported by several investigators.3,5,6,10,11,14,16,17,19,20,23,31–34 Sixteen were apparently benign. At present, the benign papilloma is considered by most to be similar to a normal choroid plexus.19,20,23,32,34 In the present study, findings in the three benign papillomas were also similar to the fully developed normal choroid plexus. Ghatak and McWhorter10 and Milhorat, et al.,19 have described the ultrastructure of choroid plexus papillomas associated with communicating hydrocephalus and overproduction of CSF. Ghatak and McWhorter10 emphasized that the specific features in their case were tubular bodies in the endothelium and well developed pericytes. Two of the benign papillomas in the present study were associated with a communicating hydrocephalus. This may
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be due to an excess population of tumor epithelial cells capable of producing CSF. In Case 1, overproduction of CSF by the tumor was suggested because the hydrocephalus regressed after total excision of the tumor. The ultrastructure in this case had no specific features, unlike that reported by Ghatak and McWhorter.10

Lewis12 reported the following characteristics of malignant choroid plexus papillomas: 1) invasion of adjacent nervous tissue; 2) departure from the normal cellular patterns with abnormal mitoses and nuclear pleomorphism; and 3) extensive necrosis and metastases in the cerebrospinal axis. Russell and Rubinstein24 did not include metastasis in the cerebrospinal axis as evidence of malignancy, because it was also found in some cases of benign papillomas. In this study, Cases 4 and 5 were diagnosed as malignant papillomas, using the criteria of Lewis13 and Russell and Rubinstein.24 Gullotta and de Melo11 reported the case of an ordinary type of malignant choroid plexus papilloma. There were no specific ultrastructural features. The poorly differentiated characteristics in Case 4 were similar to those seen in the underdeveloped-appearing Type III cells of normal choroid plexuses, and were also similar to those of the choroid plexus in early embryonic stages, as reported by Tennyson and Pappas.28 It is possible, because of poor differentiation, that the epithelial cells of the ordinary type of malignant papillomas do not participate in CSF production.

Six cases of the variant type of choroid plexus papilloma with peculiar mucus-secreting cells have previously been studied by light microscopy.1,7,12,24,27,28 The light microscopy study of Case 5 in the present report showed a transition from normal choroid plexus epithelium to columnar mucus-containing tumor cells resembling goblet cells. The electron microscopic study revealed characteristics of differentiation, such as numerous secretory granules and the glycoalyx.

Acknowledgments

I am grateful to Prof. K. Kitamura, Prof. J. Tateishi, and Associate Prof. M. Ohta, Neurological Institute, Kyushu University, for pertinent advice and continuous encouragement, and to Prof. M. Tomonaga and Dr. T. Fukushima, Fukuoka University, Dr. T. Soejima, University of Occupational and Environmental Health, and Dr. C. Kirumatsu, Kyushu Kindai Hospital, for permission to study their patients. I am also thankful for Dr. A. Hirano, Montefiore Hospital and Environmental Health, and Dr. C. Kuromatsu, Kyushu Koseienken Hospital, for critical reading of this manuscript.

References


Manuscript received July 21, 1982.
Accepted in final form June 27, 1983.

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