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Papillary Ependymoma : Its differential diagnosis from choroid plexus papilloma

Sung Hye Park, Heum Rye Park, and Je G. Chi*

*Department of Pathology, Chung Ang Gil Hospital and Seoul National University College of Medicine**

Papillary ependymoma is a rare variant of ependymoma and often gives rise to confusion with choroid plexus papilloma because of topographic, light microscopic and ultrastructural similarities. Here, we report two cases of papillary ependymomas regarding their unique clinicopathologic features and differential points from choroid plexus papilloma. Brain MRI revealed a large mass in the left lateral ventricle in one case and a 3cm sized mass in the pineal area and the 3rd ventricle in the other. Microscopically, the tumor was characterized by papillary and tubular structures. Immunohistochemically, the tumor cells in both cases expressed cytokeratins(CK22 and CAM 5.2) but did not express glial fibrillary acidic protein(GFAP), vimentin, epithelial membrane antigen, and S100 protein. This is a very unusual immunohistochemical feature for papillary ependymoma. Ultrastructurally, the tumor showed a mosaic pattern of tumor cells with frequent intercellular microrosettes having a few stubby microvilli, a few cilia and zonulae adherentes. The cytoplasmic processes were markedly reduced compared to conventional ependymoma. The cytoplasm did not contain intermediate filaments. Interestingly, the mitochondria showed abnormal features with a pleomorphic shape and abnormal cristae in both cases. These ultrastructural features enabled differentiation between papillary ependymoma and choroid plexus papilloma in addition to the light microscopic findings.

Key Words : *Papillary ependymoma, Choroid plexus papilloma, Immunohistochemical study, Ultrastructural study*

INTRODUCTION

Ependymomas are glial tumors primarily of the brain and spinal cord. In 1937, Kernohan divided his large series of ependymomas into cellular, epithelial, myxopapillary and papilloma choroideum according to histologic pattern of growth(Kernohan and Fletcher-Kernohan, 1937). New WHO classifications have accepted the variants of ependymomas and they are cellular, papillary, epithelial, clear cell or mixed(Ringertz and Reymond, 1949 ; Friede and Pollak, 1978 ; Roessmann et al., 1980 ; Schiffer, 1993).

However, the papillary ependymoma has not been thoroughly described, except as having light microscopic differences from choroid plexus papilloma (Ringertz and Reymond, 1949 ; Russel and Rubinstein, 1989). Therefore, we report two cases of papillary ependymoma with regard to its clinicopathological, immunohistochemical and ultrastructural characteristics and differential points with the usual ependymoma and choroid plexus papillomas.

Address for correspondence : *Je G. Chi, M.D., Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea. Tel : (02) 760-2550, Fax : (02) 741-6195*

MATERIALS AND METHODS

Clinical findings were reviewed from the files of Seoul National University Hospital and Chung-Ang Gil Hospital. Light microscopical and ultrastructural findings were retrospectively reviewed.

Tissue samples obtained from both cases of papillary ependymoma were fixed in 10% formalin solution. They were processed routinely and embedded in paraffin, sectioned for 4μm, stained with hematoxylin and eosin(H & E), Masson trichrome, periodic acid Schiff(PAS) and mucicarmine.

Immunohistochemical staining was done on paraffin embedded sections using the biotin-avidin horseradish peroxidase method. Commercially available antibodies against glial fibrillary acidic protein(Dako corp.) ; cytokeratin(CK22, Dako corp. ; CAM 5.2 Dako corp.), epithelial membrane antigen(Dako corp.), S-100 protein (Dako corp.) and vimentin(Dako corp.) were used. Appropriate tissue sections were used as positive controls. Negative control sections were incubated with goat serum without primary antibody. For the electron microscopic study several pieces were sampled and fixed in 2.5% glutaraldehyde solution. They were postfixed in phosphate buffered 1% osmium tetroxide, dehydrated through graded concentrations of ethanol and propylene oxide, and embedded in epon. Thin sections were stained with uranyl acetate and lead citrate, and examined with a Hitachi H7100 electron microscope.

CASE HISTORY

Case 1 : A 24-year-old female had suffered from headache in the occipital area and dizziness for one year. Three months before this admission, she experienced loss of left visual acuity and it was associated with headache. Physical examination was unremarkable except for the fact that visual acuity of the left eye had decreased to 0.2. The magnetic resonance image of the brain revealed in the left lateral ventricle a large, irregular low signal-intensity mass with multiple high signal intensity spots in the center on T1 weighted image(Fig. 1A). Hydrocephalus and midline shift of the brain were also noted. The mass measured 8.0×6.5cm in its largest dimensions. On operation, the tumor showed easy bleeding and a friable nature. A limited removal was done because of uncontrollable tumor bleeding. The patient died 2 months after operation due to recurrent bleeding at the tumor site.

Case 2 : A 52-year-old male had suffered from intermittent headache and amblyopia of the right eye for the last 2 years. More recently, generalized seizure devel-

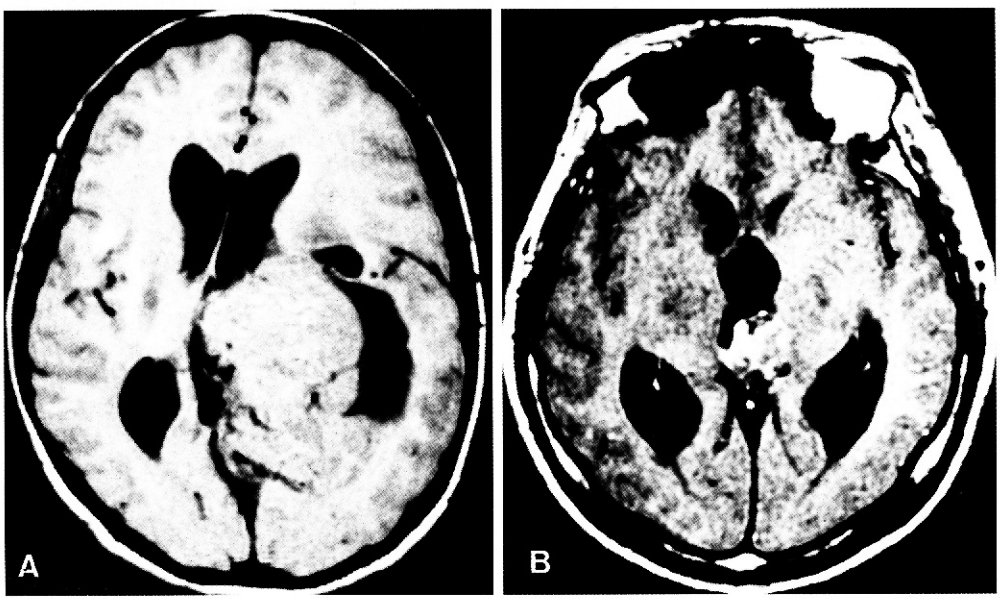

Fig. 1. Papillary ependymoma : **A (Case 1)** : T1 weighted MRI shows an irregularly outlined heterogeneous mass in the left lateral ventricle with high signal intensity spots in the center of the mass, **B (Case 2)** : Enhanced T1 weighted MRI shows a mildly enhanced, 3cm sized solid mass with calcification, mainly in the 3rd ventricle and pineal area, accomapanied with hydrocephalus.

oped which lasted for about 15 seconds. Since then he had taken minipress 1T/day, because the physician thought that his symptoms might have been caused by hypertension. On this admission, a physical examination revealed sluggish light reflex of the right eye with anisocoria. Brain magnetic resonance image showed a mildly enhanced, 3cm sized solid mass with calcification, located mainly in the 3rd ventricle and pineal area, accompanied with hydrocephalus on T1 weighted image(Fig. 1B). On operation, the tumor was a hard mass with gray purplish areas with calcification. Near total removal was done. The patient is relatively well 1 year and 6 months after operation.

Pathologic Findings

Histopathologically, both cases of papillary ependymoma showed identical features that consisted of papillary structures with multilayers of delicate fibrillated cells radiating around vascular cores(Fig. 2). Case 1 showed a rare tubule formation, but case 2 had a prominent tubule formation. On Masson trichrome stain, most areas were free of collagen, but the perivascular hyalinized areas with dystrophic calcifications were noted in focal areas. On mucicarmine stain, amorphous weakly positive extracellular material was noted. PAS stain did not reveal any basement membrane like structure.

Immunohistochemically, the neoplastic cells expressed cytokeratins(CK22 and CAM 5.2) in diffuse pattern but did not express glial fibrillary acidic protein(GFAP), vimentin, epithelial membrane antigen, and S-100 protein in both cases(Fig. 3). GFAP and S100 protein were positive in positive control, i.e. the astrocytes of the included brain tissue.

Ultrastructurally, the tumor showed a mosaic pattern of tumor cell arrangement with frequent intercellular microrosettes with a few stubby microvilli and a few cilia (Fig. 4). The closely apposed cytoplasmic membrane did not have any junctions, except a luminal side where long zonulae adherentes were noted(Fig. 5). The cytoplasm contained rough endoplasmic reticulum, small Golgi apparatus, polyribosomes, and mitochondria. The mitochondria showed abnormal features with pleomorphic shape and abnormal cristae(Fig. 4). The cytoplasm had 20nm microtubules but did not contain intermediate filaments. The marginal cytoplasmic membrane of tumor cells apposed to perivascular connective tissue showed irregularity and was surrounded by basal lamina. There were no remarkable cytoplasmic process.

DISCUSSION

Histopathologically, the papillary ependymoma is distinguished from the choroid plexus papilloma by the frequent arrangement of cells in multiple layers, formation of tubules and the presence of the neuroglial stroma(Russel and Rubinstein, 1989)(Table 1). In both of our cases, histopathologic findings were identical; the tumor was characterized by papillary and tubular structures with multilayers of oval to elongated, uniform

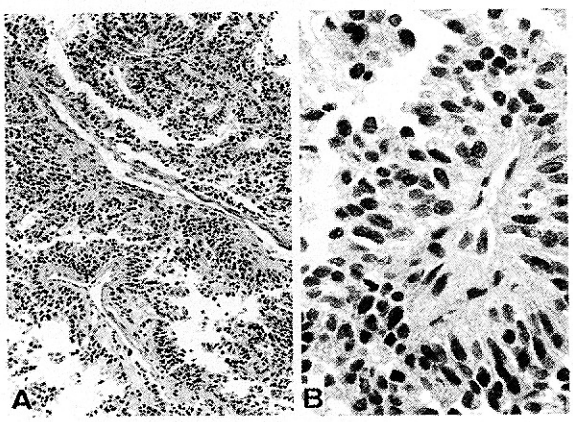

Fig. 2. Papillary ependymoma : A : Low power view of the tumor is composed of papillary structure with multiple layers of neoplastic cells and vascular cores.(H&E, ×100) B : The tumor cells have oval nuclei with coarse granular chromatin and indistinct cytoplasmic membrane. (H&E, ×400)

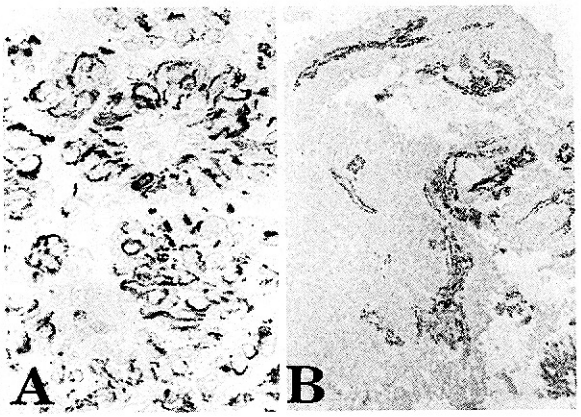

Fig. 3. Immunohistochemically, both papillary ependymomas express cytokeratin(CK22) and do not express GFAP and vimentin.
A : Cytokeratin(CK22, peroxidase antiperoxidase, ×100).
B : Vimentin (peroxidase antiperoxidase, ×100)

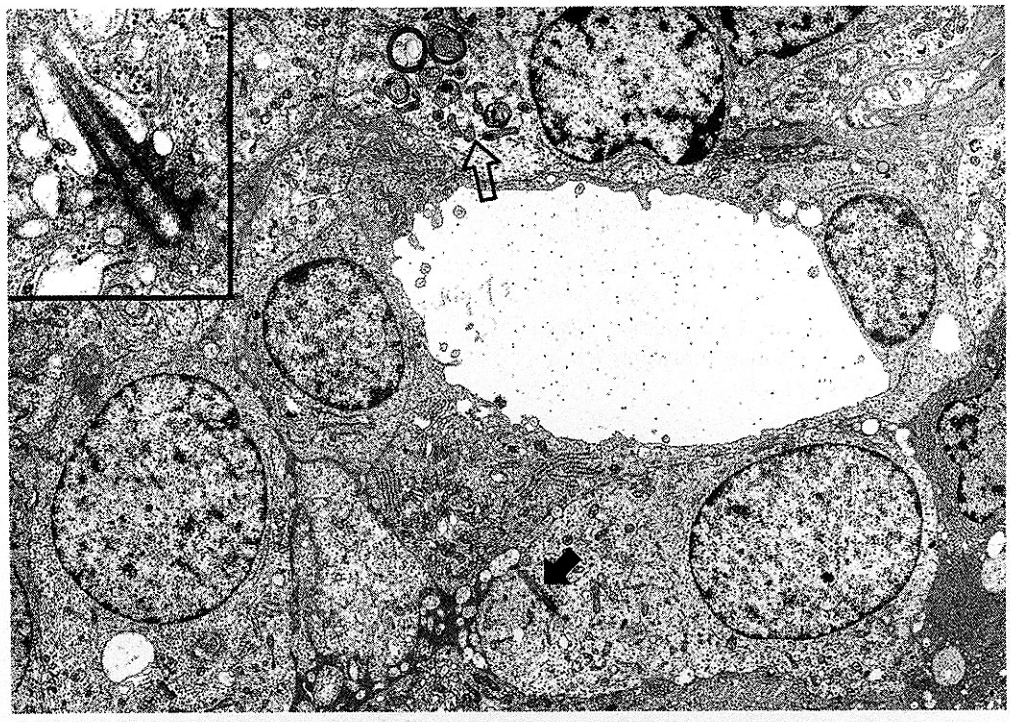

Fig. 4. Ultrastructurally, the papillary ependymoma shows mosaic pattern of neoplastic cells with microrosettes having stubby microvilli. The nuclei of the neoplastic cells show heterochromatin without prominent nucleolus and the cytoplasm devoid of intermediate filaments. Instead of glial type intermediate filaments, 20nm microtubules are easily seen. Occasionally, rudimentary cilium is projected in their cytoplasm(arrow and inset). Pleomorphic mitochondria are also noted (open arrows).(×5,400)

tumor cells without pleomorphism. In focal areas, prominent perivascular hyalinization with varying degrees of myxoid change was present in both cases and a mucicarmine stain revealed extracellular positive material, mimicking myxopapillary ependymoma of filum terminale or cauda equina.

Immunohistochemically, the neoplastic cells of papillary ependymomas in our study expressed cytokeratins(CK22 and CAM 5.2), while they did not express glial fibrillary acidic protein(GFAP), vimentin, epithelial membrane antigen, and S-100 protein(Table 2). This type of immunoreactivity is not typical of papillary ependymoma(Izukawa and Lach, 1988 ; Ang et al., 1990). In general ependymoma is variably positive for GFAP, but negative for cytokeratin(Coakham et al.,1985 ; Miettinen et al.,1986 ; Ng et al., 1988), although Mannoji and Becker(1988) reported that one half of papillary ependymomas(2/4cases) expressed cytokeratin. The absolute negativity for GFAP found in our cases is very unusual. Technical problem could be ruled out because internal control of normal glial tissue adjacent to the tumor expressed GFAP strongly. There are reports that nonpapillary ependymomas are negative for GFAP and positive for epithelial markers(Mannoji and Becker, 1988 ; Kaneko et al., 1990). S-100 protein has the same distribution as GFAP(Tabuchi et al., 1982). Unlike ependymoma, choroid plexus neoplasms coexpress cytokeratin and vimentin(Erlandson, 1993), and occasionally GFAP

Table 1. Light microscopic differential features of papillary ependymoma and choroid plexus papilloma

	Papillary Ependymoma	Choroid Plexus Papilloma
Arrangement of cells	multiple layers	single layer
Tubular structure	occasional or common	never
Stroma	neuroglia	fibrocollagenous
Basement membrane on PAS preparation	prominent	lack

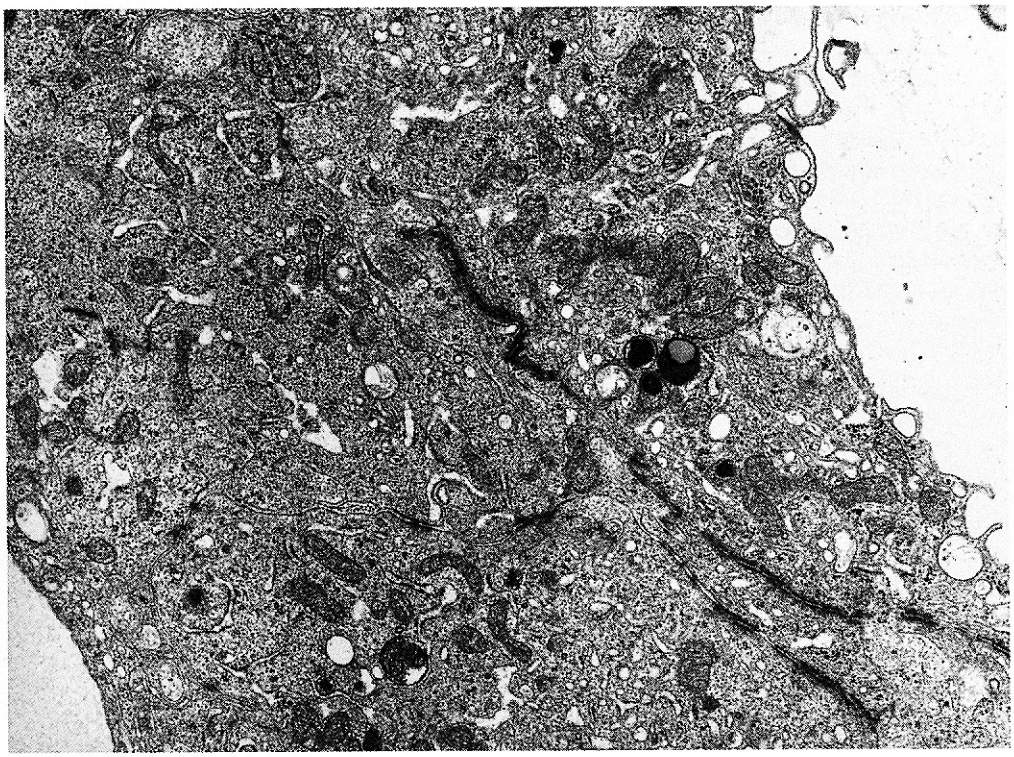

Fig. 5. The microrosettes of papillary ependymoma is composed of several ependymal cells joined by junctional complexes.(×13,500)

positive cells were found in them(Paulus and Janisch, 1990). Therefore, immunohistochemical studies were not helpful to differentiate between papillary ependymomas and choroid plexus papillomas.

In humans, from the 15th week of gestation to birth, the ependymocytes express GFAP. However, adult ependymocytes do not express GFAP(Deck et al.,1978 ; Velasco et al.,1980). In order to explain the presence of GFAP in developing ependymal cells and its absence in adult cells, it was proposed that either the synthesis of detectable amounts of GFAP occur only at a stage of ependymal cell maturation, or that the intermidiate filaments assembled in developing ependymal cell are antigenically distinct from those of the mature cells (Roessmann et al., 1980). We thought that cytokeratin expression with negativity of GFAP, may be a specific finding of some papillary type ependymoma and histogenetically, this type of ependymoma may be a prototype of adult ependymocytes.

Table 2. Immunohistochemical differences between papillary ependymoma and choroid plexus papilloma

	PE	CPP	Our cases of PE
GFAP	+(-)	-(+)	-
Vimentin	+(-)	+	-
Cytokeratin	-	+	+
EMA	-	+	-
CEA	-	+(-)	-
S-100 protein	+	+	-

PE : Papillary ependymoma
CPP : Choroid plexus papilloma
GFAP : Glial fibrillary acidic protein
EMA : Epithelial membrane antigen
CEA : Carcinoembryonic antigen
( ) : Uncommon feature

Although the fine structures of myxopapillary ependymoma have been studied by many authors(Luse, 1960 ; Wolff et al.,1972 ; Rawlinson et al.,1973 ; Specht et al.,1986), we could not find any specific ultrastructural description of papillary ependymoma. The ultrastructural features of usual ependymoma are those of normal ependyma, i.e, intracellular or intercellular microrosettes (lumina) with cilia and microvilli on the luminal surface. The lateral surfaces of the cytoplasmic membrane are joined close to the luminal surface by junctions, almost

exclusively of the zonulae adherentes type, while the zonulae or maculae occludentes seen in normal ependyma are sparse(Brawer,1972 ; Tani and Higashi,1972). The nuclei are large, the nucleoli are rope-like, and the mitochondria are clustered. The endoplasmic reticulum and ribosomes are scarce, and only a few Golgi apparatus are found. There are variable amount of 9nm diametered intermediate filaments and 20nm diametered microtubules in the cytoplasm. Cilia projection outside the cells, intracytoplasmic cilia and scattered basal bodies(blepharoplasts) are common.

Ultrastructural features of choroid plexus papillomas that are shared with ependymoma, are the microvilli and cilia. However, the cilia are seldom found and the microvilli and cilia are seen on the apical border of cytoplasmic membrane. These two structures may not be seen in carcinoma. The choroid plexus papillomas show apicobasal polarity of epithelial cells with a generally smooth basal surface and continuous basal lamina at the vascular pole. The tumors are composed of dark and light cells, according to the different state of cell hydration. The cytoplasm contains abundant mitochondria, parallel RER, pinocytotic vesicles and pools of glycogen, which are sometimes lost during processing. The apicolateral cytoplasmic membrane is joined by junctional complexes including zonula adherentes and desmosomes. The apposed lateral cytoplasmic membrane shows complex interdigitations with no junctions, reminiscent of normal choroid plexus papilloma. The choroid plexus epithelium, like normal ependyma, contain intermediate filaments as well as rare microtubules in their cytoplasm(Wolff et al., 1972).

Both of our cases showed identical ultrastructural features ; a mosaic pattern of tumor cell arranged in frequent intercellular microrosettes having a few stubby microvilli, a few cilia and basal bodies. The closely apposed cytoplasmic membrane did not have any junctions except on the luminal side where long zonulae adherentes were noted. The cytoplasm contained a slender tubular RER, small Golgi apparatus, mitochondria and polyribosomes. The mitochondria showed abnormal features with a pleomorphic shape and abnormal cristae in both cases. There were haphazardly arranged microtubules, but cytoplasm did not contain intermediate filaments, that corresponded to the immunohistochemical negativity for both GFAP and vimentin. The marginal side of tumor cells, in the vascular pole, showed some irregularity of the cytoplasmic membrane with basal lamina, but long cytopasmic processes were not seen.

Main differential points in ultrastructural findings, between papillary ependymoma and choroid plexus papilloma are summarized in table 3. Although papillary ependymoma cannot be differentiated from choroid plexus papilloma by immunohistochemical expression pattern of intermediate filaments, ultrastructural features make us possible to distinguish one from another. Although exceptional examples of myxopapillary ependymoma, originating in a lateral ventricle have been reported(Sato et al., 1983 ; Maruyama et al., 1992 ; Warnick et al.,1993), we thought papillary ependymomas are clearly different form myxopapillary ependymoma in their light microscopic and ultrastructural features.

It seems appropriate to say that papillary ependymoma has its own histological and ultrastructural characteristics which are quite different from choroid plexus papilloma and conventional ependymoma.

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Table 3. Ultrastructural differential features between papillary ependymoma and choroid plexus papilloma

	Papillary ependymoma	Choroid plexus papilloma
Pattern	mosaic with no polarity	apico-basal polarity
Microrosettes	present	absent
Microvilli	in microrosettes	on apical free surface
Cilia	frequently seen	rarely seen
Basement membrane	beneath perivascular cytoplasmic membrane	beneath the basal cells
Junctions	zonular adherens in luminal side	apical junctional complexus
Pinocytotic vesicles	absent	present

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