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A Marker for Primary Choroid Plexus Neoplasms

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Primary choroid plexus (CP) tumors are rare neoplasms that present in childhood or, less frequently, in adult life. The majority are benign and amenable to complete surgical excision, but occasionally more invasive variants are encountered. Although generally pathologically distinct, occasionally primary CP neoplasms may be difficult to distinguish from metastatic papillary carcinomas or papillary ependymomas. Conventional cytologic markers are not sufficiently specific to permit accurate diagnosis of primary CP tumors. The authors have reported that the CP is the unique site of synthesis within the brain of transthyretin (TTR, prealbumin), a transport protein for thyroxine and retinol. They therefore investigated the utility of TTR as a biochemical marker for CP tumors. They detected intense immunoreactivity for TTR at high dilutions of primary antiserum in the neoplastic epithelium of all of nine primary CP tumors (six papillomas and three carcinomas), but not in eight cellular or three papillary intracerebral ependymomas, meningiomas, oligodendrogliomas, astrocytomas, primary extracerebral papillary carcinomas (three thyroid, two breast) or five of six cerebral metastases from systemic papillary carcinomas. In one case of cerebral metastasis from papillary thyroid carcinoma, rare isolated immunoreactive cells were observed. Faint staining of the stromal–ependymal junction was seen in myxopapillary ependymomas of the filum terminale, which were otherwise nonreactive. By* in situ ***hybridization, TTR mRNA was abundant in neoplastic CP epithelium, confirming local TTR synthesis. The authors conclude that TTR is synthesized by neoplastic CP epithelium and is an excellent marker for primary CP neoplasms. (Am J Pathol 1990, 136:1317–1325)

Primary choroid plexus (CP) tumors are rare papillary neoplasms that present in childhood or, more rarely, in adult life.[1] They are usually intraventricular in location and may result in internal hydrocephalus. The majority are benign and amenable to complete surgical excision, but occasionally more anaplastic variants are encountered. Consistent with their epithelial nature, they exhibit the features of papillomas or carcinomas.

Although primary CP neoplasms are generally pathologically distinct, difficulties may arise in differential diagnosis.[2,3] Choroid plexus tumors occasionally may be confused with extracranial papillary epithelial neoplasms metastatic to brain, or with papillary ependymomas. The distinction between malignant CP papilloma and metastatic papillary carcinoma is a matter of considerable diagnostic, therapeutic, and prognostic importance. According to Rubinstein,[3] "the diagnosis of malignant CP papilloma must be made with great circumspection, especially in adults," and requires the concomitant presence of well-differentiated areas displaying the classic appearance of CP papilloma. The distinction from papillary ependymomas rests on the presence, in the latter, of cilia and blepharoplasts, and on the nature of the underlying stroma, which is neuroglial in ependymomas and fibrovascular in CP papillomas.

Several immunohistochemical markers for neoplastic CP epithelium have been described, including cytokeratin,[4–9] vimentin,[5–7] S-100 protein,[6,7,10] carcinoembryonic antigen (CEA),[6] and glial fibrillary acidic protein (GFAP),[5–9,11,12] but their utility has been limited by relative lack of specificity.[13,14] We[15,16] and others[17] have identified a selective product of the CP epithelium, transthyretin (TTR, prealbumin) and examined its synthesis in a series

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Table 1. *Primary Choroid Plexus Neoplasms, 1974–1988*

Case	Age	Sex	Location	Diagnosis
1	23	M	Fourth ventricle	Papilloma
2	0.5	F	L temporal horn and atrium	Papilloma
3	29	F	L lateral ventricle	Carcinoma
4	31	F	L lateral ventricle	Papilloma
5	2.5	F	L lateral ventricle Third ventricle	Papilloma
6	1	M	Not known	Papilloma
7	1.5	M	R lateral ventricle	Carcinoma
8	5.5	M	Fourth ventricle	Papilloma
9	2.5	M	Fourth ventricle	Carcinoma

of 55 brain tumors, including six CP papillomas and three CP carcinomas. We report that TTR is an excellent marker for primary CP neoplasms.

Materials and Methods

Pathologic Material

Cases were selected from the files of the Neuropathology department of the Columbia-Presbyterian Medical Center. Based on the reported diagnosis, we chose 50 brain tumors from the period 1974 to 1988, including all cases signed out as primary CP neoplasms. Five primary papillary carcinomas of systemic origin were obtained from the Division of Surgical Pathology. Blocks were retrieved from all cases and resectioned on a microtome. All slides were reviewed by two observers (JH and AJD).

Diagnosis of primary CP neoplasm was considered established if unanimity of opinion existed among the pathologic diagnosis, the surgical diagnosis, and our diagnosis after review. During the period under review, 10 cases had been signed out as primary CP neoplasms. In nine of these, unanimity of opinion was obtained, and these were accepted as unequivocal examples of primary CP neoplasms. Case 9 had initially been signed out as a malignant ependymoma, but was later reclassified as a CP carcinoma. In one case, there was disagreement among neuropathologists over the diagnosis, and it was therefore excluded from the count of primary CP neoplasms.

Of the nine primary CP neoplasms, six were considered papillomas and three carcinomas (Table 1). The diagnosis of malignancy was according to Zulch,[2] and was based on poor preservation of papillary architecture, high cell density, cellular pleomorphism, numerous mitotic figures, and regional necrosis (cases 7 and 9). Although Russel and Rubinstein require for the unequivocal diagnosis of CP carcinoma both cytologic features of anaplasia and invasion of brain parenchyma, Zulch accepts the former criterion alone.[2] Moreover, Russel and Rubinstein also recognize intermediate stages in the malignant transformation of CP papillomas. Because brain parenchyma was not included in sections of any of the three CP carcinomas, we were unable to assess whether there was disruption of the ependymal lining or microscopical invasion of adjacent brain. We note that two of our cases classified as CP carcinomas developed recurrences after surgical resection.

Forty-six tumors carrying sign-out diagnoses other than primary CP neoplasm were examined. These included 11 intracerebral ependymomas, seven myxopapillary ependymomas of the filum terminale, six oligodendrogliomas, five astrocytomas, six meningiomas, six metastatic carcinomas to brain, and five primary papillary carcinomas (three thyroid, two breast). Of the 11 intracerebral ependymomas, three were papillary variants, and eight were cellular variants composed predominantly of solid sheets of neoplastic cells. Three of the latter contained, in addition, focal regions of papillary structure.

Immunohistochemistry

After removal, surgical specimens were fixed in unbuffered 10% formalin solution for 4 to 24 hours, processed through graded alcohols and xylenes, and embedded in paraffin. Sections were prepared at 8 μ on a microtome, mounted on gelatin-coated slides, and air-dried overnight in an incubator at room temperature or at 37°C. Baking of slides at 55°C, even for shorter periods, was found to result in attenuation or loss of TTR immunoreactivity. Transthyretin immunostaining of unfixed frozen sections was inconsistent, presumably because of loss of protein during tissue processing, whereas immunostaining of formalin-fixed and paraffin-embedded tissue yielded consistently reproducible results.

Immunohistochemistry was performed by a modification of the avidin-biotin-peroxidase technique of Hsu et al.[18] As primary antibody, we used rabbit antisera to human prealbumin from Boehringer-Mannheim (Indianapolis, IN) or from Dako Corporation (Santa Barbara, CA). Specificity of the primary antiserum was demonstrated by Western blotting, as reported previously.[16] The optimal dilution for both antisera was determined as 1:4000 by comparing serial dilutions applied to adjacent sections of postmortem human brain tissue containing choroid plexus. As reported previously,[16] staining of brain sections was limited to the choroid plexus epithelium (Figure 1A). As negative controls, we included adjacent sections from which the primary antiserum had been omitted from the incubation, and sections that were exposed to a 1:4000 dilution

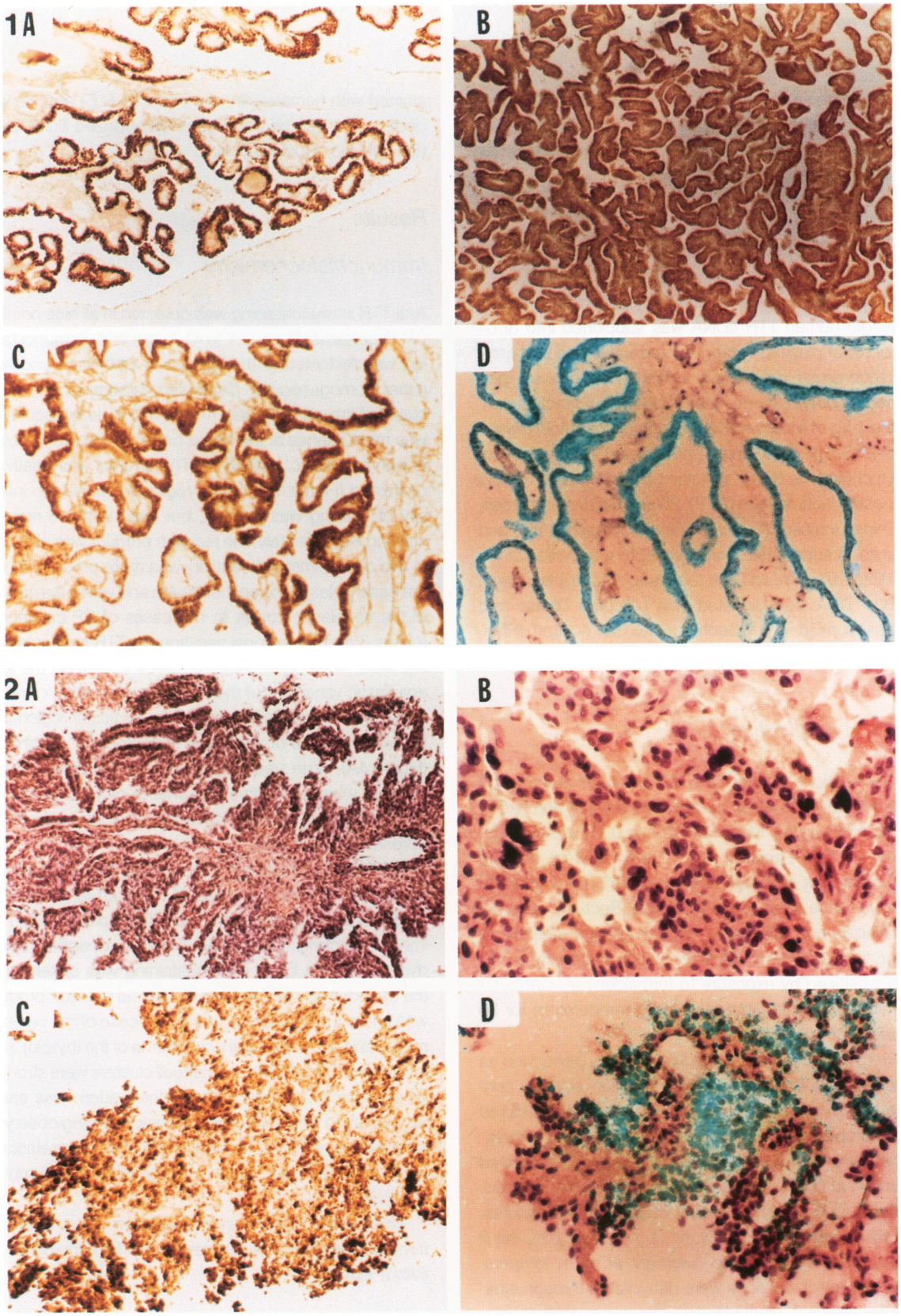


Figure 1. *Choroid plexus papillomas.* **A:** *Normal postmortem human brain, temporal horn of the lateral ventricle. TTR immunohistochemistry, no counterstain. Note the junction between CP epithelium and ependyma (×40).* **B:** *Case 6. TTR immunohistochemistry, no counterstain (×50).* **C:** *Case 4. TTR immunohistochemistry, no counterstain. Note abundant mucinous stroma (×54).* **D:** *Case 4.* In situ *hybridization, anti-message sense TTR cRNA probe. H & E counterstain. Silver grains appear green under epipolarized light (×54).* Figure 2. *Choroid plexus carcinoma.* **A:** *Case 7. (H & E, ×8).* **B:** *Case 7. Note cellular pleomorphism (H & E, ×190).* **C:** *Case 7. TTR immunohistochemistry, dilution 1:8000. No counterstain (×8).* **D:** *Case 7.* In situ *hybridization, anti-message sense TTR cRNA probe. Note variable distribution of silver grains (H & E, ×95).*

of nonimmune rabbit antiserum. In all cases, this entirely eliminated staining. In each experiment, postmortem human brain sections containing choroid plexus served as positive controls.

Preparation of cRNA Probes

The *Eco*RI insert of plasmid pHTT1[15] containing an almost full-length human TTR cDNA was subcloned into SP64 (Riboprobe) plasmid vector in message-sense and anti–message-sense orientations. Transcription was performed as previously described[19] in a 10-μl reaction containing 1 μg of linearized DNA template, 25 μmol/l (micromolar) ^{35}S-UTP, 500 μmol/l (micromolar) each of guanosine triphosphate (GTP), cytidine triphosphate (CTP), and adenosine triphosphate (ATP), 20 units of human placental RNase inhibitor (Promega Biotec, Madison, WI), and 20 units of appropriate polymerase, to a specific activity of 10^8 to 10^9 cpm/μg DNA template. After transcription, residual DNA was digested with ultrapure DNase and probes purified on a Sephadex G-100 column (Pharmacia, Piscataway, NJ).

In Situ *Hybridization*

Paraffin sections were cut at 6 to 8 μ on a microtome and mounted on glass slides coated with poly-L-lysine hydrobromide (50 μg/ml; Mr > 300,000) in 0.1% diethyl pyrocarbonate (DEP)-treated water. Sections were dried at 40°C overnight and then heated to 50°C for 6 hours to improve tissue adhesion to the slides. Sections were deparaffinized and rehydrated through graded ethanols to water, treated in 0.2 N HCl at room temperature for 5 minutes, postfixed by exposure to formaldehyde vapors for 30 minutes, and incubated at room temperature for 30 minutes in 1 μg/ml proteinase K.

Prehybridization and hybridization were performed as described previously.[19] The hybridization solution contained 50% formamide and 3×10^6 cpm of denatured cRNA probe per ml. Sections were overlayered with approximately 100 μl hybridization solution and incubated overnight at 50°C. The next day, sections were washed, treated with 60 μg/ml RNase A at 37°C for 45 minutes, and then washed stringently in 0.1 × SSC at 50°C for 3 hours. Washing continued overnight at room temperature, after which sections were dehydrated through ethanols containing 0.3 mol/l (molar) ammonium acetate, vacuum-dried, and exposed to x-ray film for 5 to 10 days. Sections then were dipped in NTB2 nuclear track emulsion (Kodak, Rochester, NY) and stored in the dark at 4°C for 2 weeks. After developing, sections were counterstained with hematoxylin and eosin (H & E) and viewed under combined brightfield and epipolarized illumination (E. Leitz, Inc., Rockleigh, NJ).

Results

Immunohistochemistry

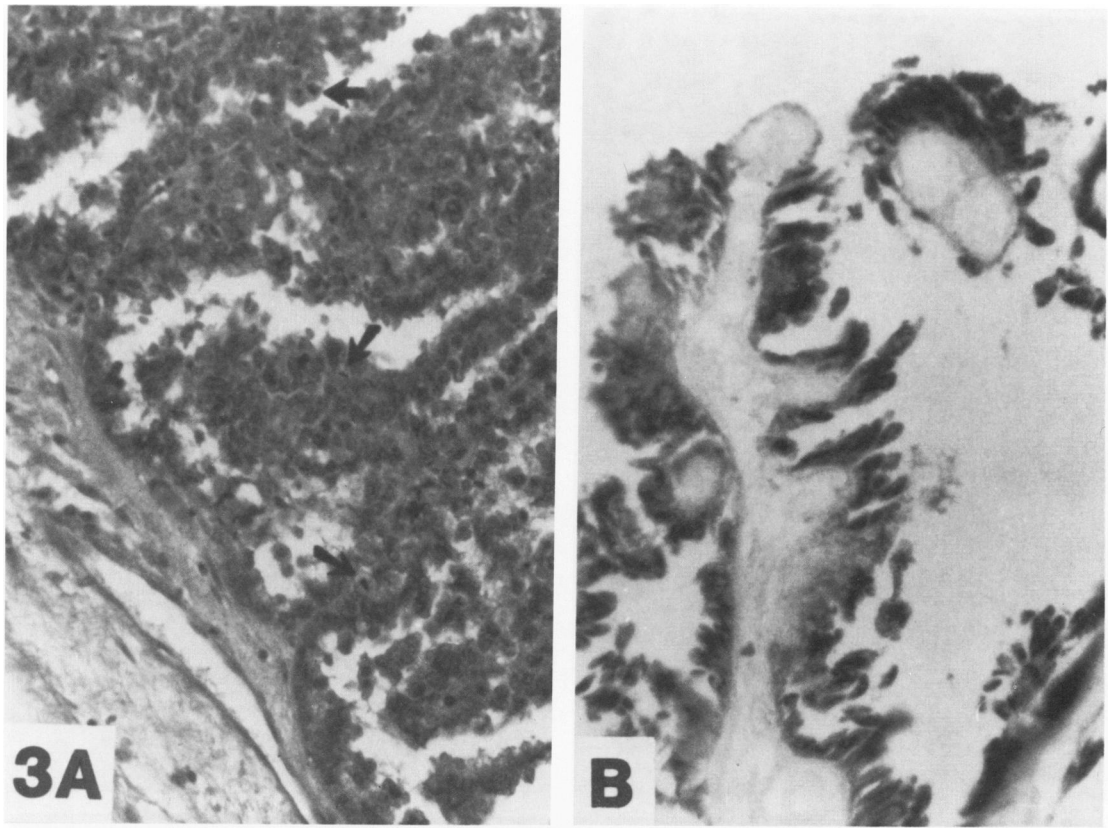
Anti-TTR immunostaining was detected in all nine primary CP neoplasms (Figures 1 to 4). In general, immunostaining was restricted to the neoplastic epithelium and was either homogeneously distributed throughout the cytoplasm of the epithelial cells (Figure 1B) or, less frequently, was more intense at the apical poles, as has been noted in non-neoplastic epithelium. The stroma was relatively unstained (Figure 1C). Some regional variability in intensity of staining was present, but even in those regions staining less intensely, the reaction product was obvious. In two cases, immunoreactivity was more pronounced at the basal poles of the epithelial cells and within the stroma of the neoplastic fronds. In two cases of CP carcinoma (cases 3 and 7), regional variations in TTR immunostaining were more pronounced (Figures 2, 3) than the less anaplastic variants, but there was no obvious correlation between TTR immunoreactivity of a particular region and histologic degree of anaplasia. In another CP carcinoma (Figure 4A), large areas of perivascular necrosis were unstained, whereas intervening sheets of tumor cells arranged in a perivascular distribution were intensely immunoreactive (Figure 4B).

Of the 46 undisputed nonchoroidal tumors, only the myxopapillary ependymomas of the filum terminale and a solitary metastatic lesion (Figure 5) displayed any TTR immunoreactivity. In the case of the myxopapillary ependymomas, faint linear immunostaining was observed at the ependymal–stromal junction, but no reaction product was present within tumor cells. In the case of the cerebral metastasis (from a papillary carcinoma of the thyroid), rare isolated malignant cells or small cell clusters were strongly immunoreactive (Figure 5B), but this pattern was easily distinguished from the diffuse epithelial staining observed in the primary CP tumors. All other primary and metastatic papillary carcinomas failed to demonstrate TTR immunoreactivity.

None of the 11 intracerebral ependymomas, including three papillary variants, displayed any TTR immunoreactivity (Figure 6).

In Situ *Hybridization*

Sections from all nine primary CP tumors, six meningiomas, and the solitary TTR-immunoreactive metastatic thy-



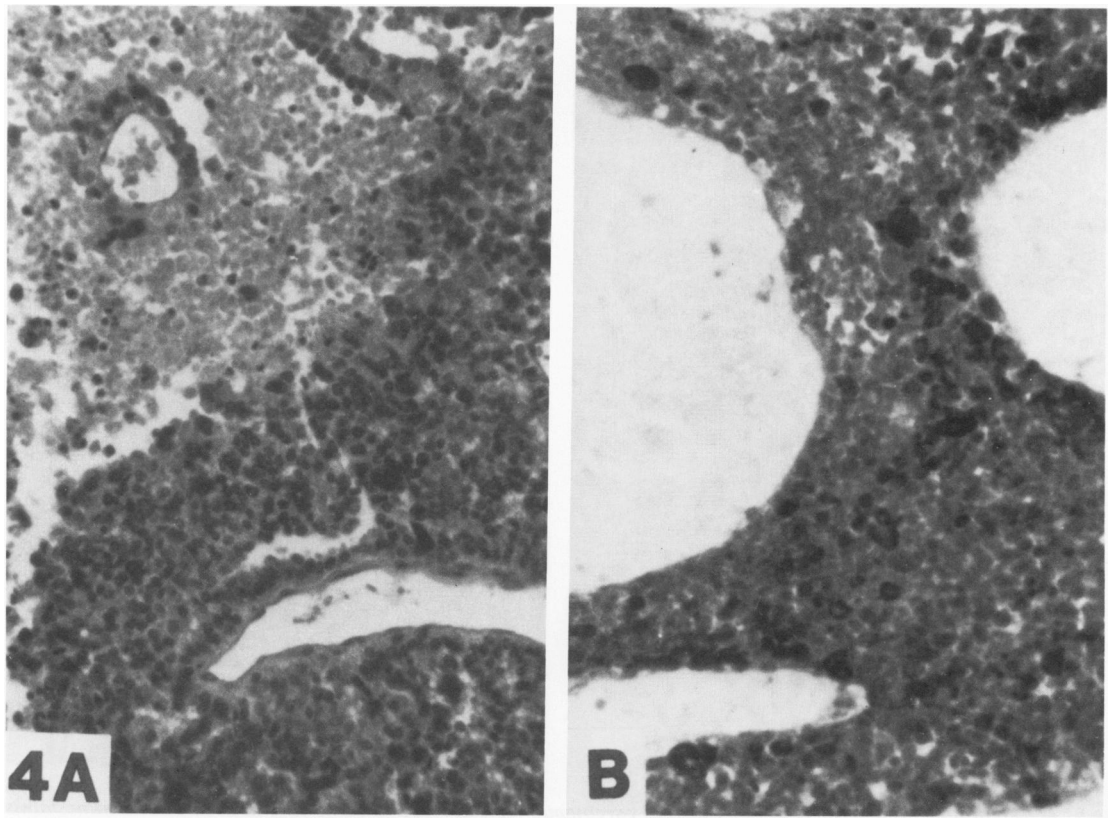
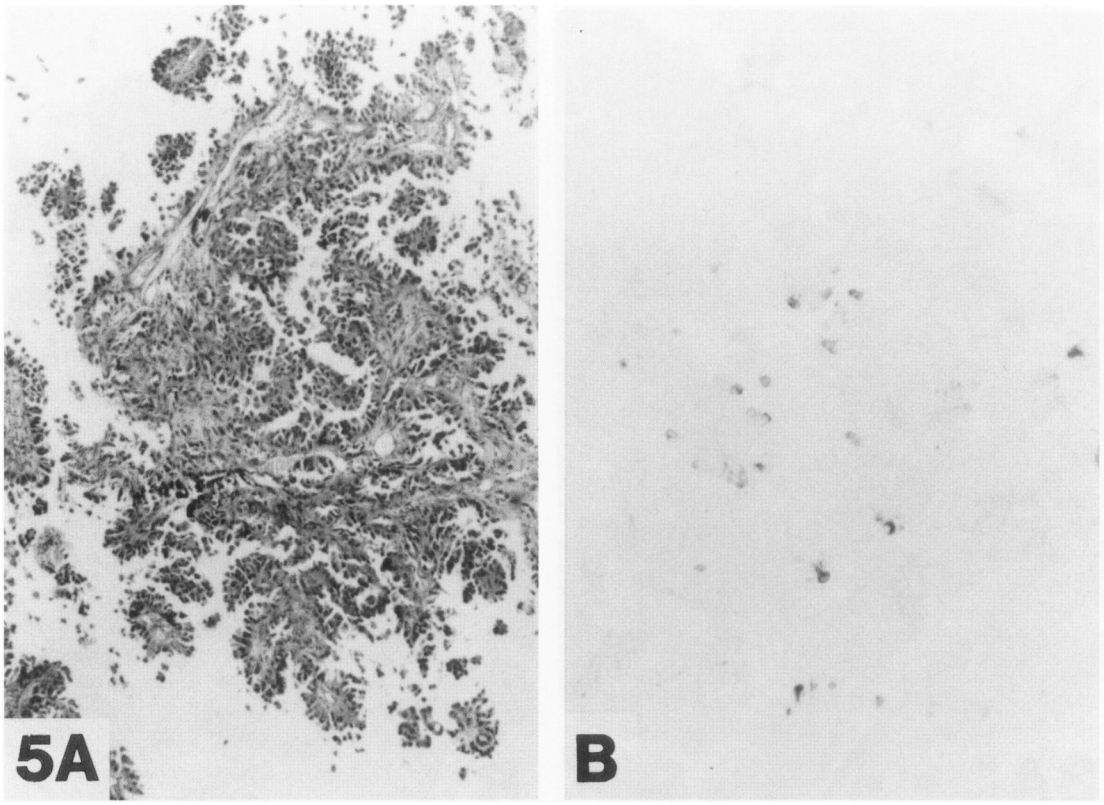


Figure 3. **A:** *Case 3. CP carcinoma. In this region the papillary structure is still evident. Arrows indicate mitotic figures (H & E, ×240).* **B:** *Case 3. TTR immunohistochemistry, no counterstain. (×240).* **Figure 4.** **A:** *Case 9. CP carcinoma initially misdiagnosed as malignant ependymoma. Note regional perivascular necrosis and numerous mitotic figures (H & E, ×220).* **B:** *Case 9. TTR immunohistochemistry, no counterstain. Areas of necrosis are unstained (×220).*



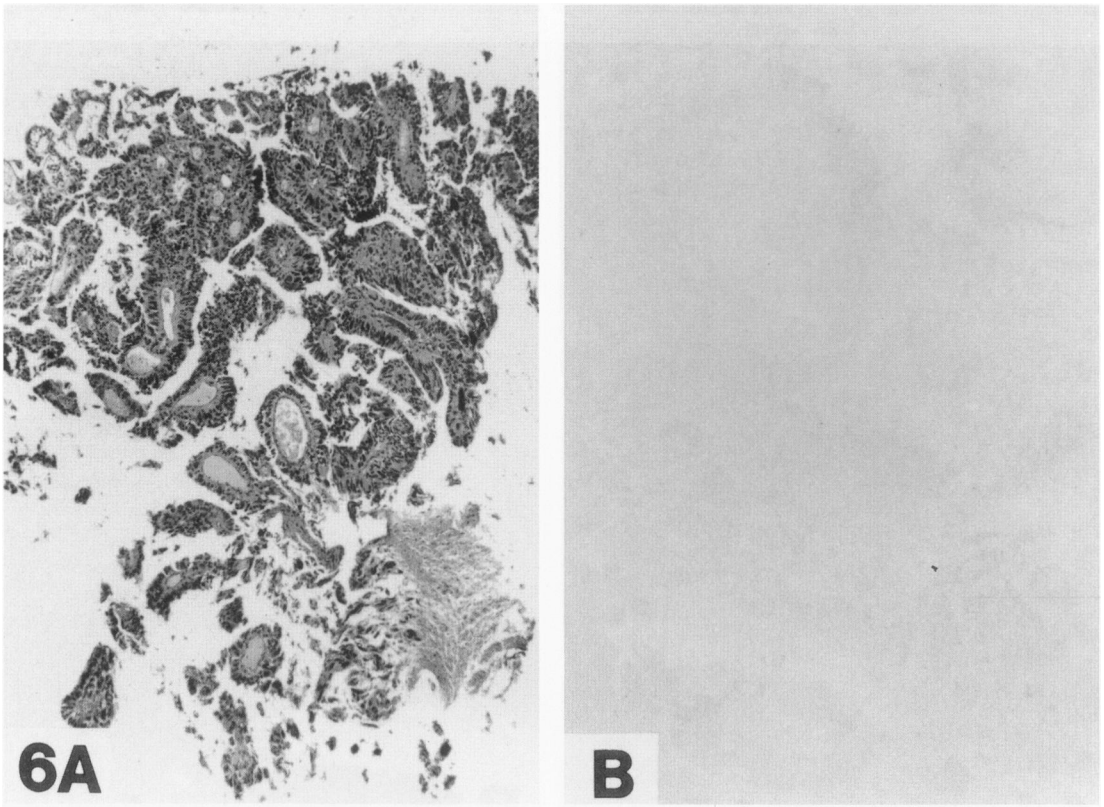


Figure 5. A: *Cerebral metastasis from papillary thyroid carcinoma. (H & E, ×12).* B: *Same case as in* A. *TTR immunostaining, no counterstain. Note scattered immunoreactive tumor cells (×24).* Figure 6. A: *Papillary ependymoma. (H & E, ×15).* B: *Same case as in* A. *TTR immunostaining, no counterstain (×18).*

roid carcinoma were hybridized to TTR cRNA probes prepared in both orientations. All primary CP tumors were labeled intensely with silver grains when hybridized with the anti-message sense probe (Figures 1C, 2D). With the message-sense probe, silver grains were not detectable above background levels in the CP tumors (not shown). As with the immunoreactive product, labeling was distributed homogeneously over the cytoplasm of neoplastic epithelial cells. In the case of the three CP carcinomas, silver grains were distributed more variably over neoplastic tissue (Figure 2D) but, once again, there was no obvious correlation with histological atypia. None of the other cases studied by this technique hybridized specifically to either probe.

Discussion

Transthyretin (TTR, prealbumin) is a 55-kd tetrameric protein consisting of four identical subunits.[20] Plasma TTR is synthesized in the liver[21] and plays an important role in the plasma transport of retinol (vitamin A)[22,23] and thyroxine.[24] In addition, TTR is synthesized by the yolk sac endoderm[25] and the retinal pigment epithelium.[26,27] Within the brain, TTR is synthesized uniquely within the CP epithelium[15-17] and secreted into the cerebrospinal fluid (CSF).[28,29] Transthyretin appears to be a major biosynthetic product of the CP, accounting for approximately 20% of all newly synthesized protein.[28] In the embryo, TTR is synthesized within the primordial CP even before morphogenesis of the plexus,[30,31] suggesting that TTR may play a role in brain development. Transthyretin is thus a specific and early marker for CP epithelium.

We have taken advantage of this property to investigate the utility of TTR as a histopathologic marker for neoplastic CP epithelium. Although previously we[32] and others[33] reported that TTR expression in CP neoplasms was inconsistent, we have since found that TTR antigenicity in tissue sections is sensitive to heat and to the method of fixation and embedding.[34] After appropriate methodologic modifications, we now report consistently positive TTR immunostaining in primary CP neoplasms.

All of nine CP tumors reported here stained strongly with a commercial polyclonal antiserum to TTR at high dilutions. To determine whether this was due to intratumoral TTR synthesis or to uptake of TTR from the CSF or across the blood–brain barrier, we performed *in situ* hybridization studies with radiolabeled cRNA probes prepared from a cloned human TTR cDNA. Transthyretin mRNA was easily detected in all cases, indicating that at least some of the protein detected by immunochemical methods is a biosynthetic product of the neoplastic epithelium.

In general, staining of CP papillomas was homogeneous. In the three CP carcinomas, while most epithelial cells were immunoreactive, intensity varied (Figure 2C, D). However, this variability could not be related to histologic degree of anaplasia. Matsuhima et al[35] described TTR immunostaining in five CP papillomas, but, unlike our cases, two CP carcinomas in that study were unreactive. Our immunohistochemical results, which were confirmed by *in situ* hybridization, prove that at least some anaplastic CP tumors synthesize TTR, and raise questions about the diagnosis of CP carcinoma in other reported cases.

Choroid plexus carcinomas constitute a minority of all primary CP papillomas (approximately 20%, according to Lewis[36]), and their occurrence in adults is particularly rare. However, the problem of distinguishing CP carcinoma (or even papilloma) from metastatic papillary carcinomas is not uncommonly encountered in diagnostic pathology.[1-3] In these cases, a definitive diagnosis based on histologic criteria often cannot be made. In this study, we were unable to detect TTR in five of six adenocarcinomas metastatic to brain. A solitary metastasis showed scattered, individual immunoreactive cells, easily distinguished from the pattern seen in primary CP tumors. In that case, we failed to demonstrate TTR mRNA in the individual tumor cells by *in situ* hybridization, suggesting that the rare immunoreactive cells have taken up TTR from the plasma or CSF rather than synthesized TTR *de novo*. Thus, TTR immunoreactivity is extremely useful in distinguishing primary CP neoplasms from intracranial metastases of systemic papillary carcinomas.

Another cause of diagnostic difficulty may occasionally be the differentiation between CP papilloma and papillary ependymoma.[1,2] In the present study, TTR immunohistochemistry was negative in three cases of intracerebral papillary ependymoma. A separate subgroup of spinal ependymomas—the myxopapillary ependymoma of the filum terminale—showed faint linear TTR immunoreactivity at the stromal–ependymal junction, but neoplastic cells themselves were not labeled and there was no difficulty in distinguishing these tumors from primary CP tumors.

Transthyretin immunoreactivity also has been reported in most carcinoid tumors[37] and in endocrine tumors of the pancreas.[38] Because these neoplasms seldom metastasize to the CNS and because they are not likely to be confused with CP neoplasms morphologically, this should not affect the utility of TTR immunostaining in neuropathologic evaluation. In addition, metastases to brain may express antigens specific to the tissue of origin, eg, thyroglobulin in thyroid carcinoma, thereby facilitating their distinction.

Previous immunocytochemical studies have identified

several other cytologic markers for CP epithelial cells, the most consistent of which have been cytokeratin,[4–9] vimentin,[5–7] S-100,[6,7,10] CEA,[6] and GFAP.[5–9,11,12] However, the relative lack of specificity of these markers greatly limits their diagnostic usefulness.[13,14] Transthyretin immunostaining, however, appears to be an excellent biochemical marker for CP epithelium. While larger numbers of tumors of all classes will have to be studied before the precise limits of the specificity and sensitivity of TTR immunostaining can be determined, at present this is the best available marker for CP neoplasms.

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