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PAPILLOMAS AND CARCINOMAS OF THE CHOROID PLEXUS

Histological and immunohistochemical studies and comparison with normal fetal choroid plexus

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ABSTRACT - *Background*: Choroid plexus tumors are rare. Results on immunohistochemical features are scanty and controversial even regarding normal plexus. *Method*: Thirteen cases of choroid plexus tumors and five samples of normal fetal choroid plexus were submitted to immunohistochemical study using a panel of epithelial, neuronal and stromal markers. *Results/Conclusions*: Relevant histological findings were presence of clear cells in 3/5 papillomas (PP) and 7/8 carcinomas (CA) and all 5 fetal plexuses; rhabdoid cells, desmoplasia and vascular proliferation were found respectively in 3, 4 and 5 cases out of 6 poorly differentiated CA and were absent in PP and well differentiated CA. Pancytokeratin AE1/AE3 was strongly positive in all 13 cases, even in the undifferentiated component of poorly differentiated CA, where reactivity was focal in 3 and diffuse in 3 cases. Low molecular weight cytokeratin (35βH11) was not expressed in any of the 8 CA, but was present in all 5 PP. In 4 of 6 poorly differentiated CA there was reactivity for smooth muscle actin (1A4) in 10 to 30% of the cells. This was true also for one case lacking rhabdoid cells. Laminin was undetectable in all 6 cases of poorly differentiated CA but was present in 4 PP and 2 well differentiated CA. All 5 fetal plexuses expressed GFAP.

KEY WORDS: choroid plexus tumors, normal fetal choroid plexus, immunohistochemistry, central nervous system.

Papilomas e carcinomas do plexo coróide: estudo histológico e imuno-histoquímico e comparação com plexo coróide fetal normal

RESUMO - *Contexto*: Os tumores do plexo coróide são raros. Os resultados de dados imuno-histoquímicos são escassos e controversos, o mesmo valendo para o plexo coróide normal. *Método*: Treze casos de tumores do plexo coróide e cinco exemplares de plexo coróide fetal normal foram submetidos a estudo imuno-histoquímico, utilizando-se marcadores para antígenos epiteliais, neurais e estromais. *Resultados/Conclusão*: Os achados histológicos mais relevantes foram células claras em 3/5 papilomas (PP) e 7/8 carcinomas (CA) e em todos os 5 plexos fetais; células rabdóides, desmoplasia e proliferação vascular foram encontradas, respectivamente, em 3, 4 e 5 casos de 6 CA pouco diferenciados, mas não nos PP e CA bem diferenciados. A pancitoqueratina AE1/AE3 foi fortemente positiva em todos os 13 casos, mesmo no componente indiferenciado do CA pouco diferenciado, em que a reatividade foi focal em 3 casos e difusa em outros 3. A citoqueratina de baixo peso molecular (35βH11) não foi expressa em nenhum dos 8 CA, mas estava presente em todos os 5 PP. Em 4/6 CA pouco diferenciados houve reatividade para actina de músculo liso (1A4) em 10-30% das células. Este achado ocorreu também em um caso sem células rabdóides. Laminina não foi detectada em nenhum dos 6 CA pouco diferenciados, mas estava presente em 4 PP e em 2 CA bem diferenciados. Todos os 5 plexos fetais expressaram GFAP.

PALAVRAS-CHAVE: tumores do plexo coróide, plexo coróide fetal normal, imuno-histoquímica, sistema nervoso central.

Choroid plexus tumors are infrequent (0.4-1% of central nervous system (CNS) tumors)[1-5] and their immunohistochemical pattern is still controversial, in part due to the paucity of cases available for study, particularly among the malignant variants. Choroid plexus cells are truly epithelial in nature as demonstrated by ultrastructural and immunohistochemical studies[6-15]. Most studies report

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reactivity to cytokeratins (CK), especially of low molecular weight, vimentin, epithelial membrane antigen (EMA), transthyretin (TTR), S100 protein, glial fibrillary acidic protein (GFAP) and neuron specific enolase (NSE), but the frequency of reaction varies greatly[6,9-11,13,14,16-21]. In contrast, normal choroid plexus, fetal or adult, has been described as constantly negative to GFAP, with rare exceptions[7-15].

Poorly differentiated choroid plexus CA, especially in pediatric patients with posterior fossa neoplasms, must be distinguished from other anaplastic tumors with solid diffuse pattern and undifferentiated cells, such as the rare and controversial atypical teratoid / rhabdoid tumor (AT/RT)[22-25]. In these situations an immunohistochemical panel may be helpful.

The variation of results in the literature concerning the immunohistochemical patterns in choroid plexus tumors and in the normal choroid plexus prompted us to study their immunoreactivity using a panel of epithelial, neuronal and stromal markers. It was also intended to compare these findings with the normal fetal choroid plexus to evaluate whether neoplastic cells may show immunohistochemical features of fetal cells.

METHOD

Cases of choroid plexus tumors occurring in patients up to the age of 25 years between 1966 and 1999 were selected from the files of the Department of Anatomic Pathology, State University of Campinas, São Paulo, Brazil. This study was approved by the Ethics Committee of the Faculty of Medical Sciences of our institution. Only those cases in which paraffin embedded tissue was available for immunohistochemical study and the amount of tissue was large enough (at least 1.5 cm in largest diameter) were included. Age and sex of patients and topography of the tumors were recorded. Archival slides stained with H&E were reviewed for diagnosis. Cases were classified according to the WHO nomenclature[26] as papilloma (PP) and carcinoma (CA). We further divided the carcinomas into well [WCA] or poorly differentiated [PCA], similarly to what was done by others[21,27]. Five cases of normal fetal choroid plexus (NFCP) (between 16 and 40 gestational weeks) were also studied to compare their immunohistochemical pattern with those of tumors.

New sections were cut for immunohistochemical studies, placed on silanized slides, dewaxed and hydrated. Antigen retrieval was achieved by immersing slides in citrate buffer, pH 6.0, 10 mM, for 25 minutes in steamer (95° C). Sections were incubated with the primary antibodies at 4° C overnight (Table 1). Revelation of the reaction was made using the streptavidin-biotin-peroxidase complex (Dakopatts, Carpenteria, USA), stained with 3,3-diaminobenzidine, and counterstained with hematoxylin.

Table 1. Antibodies used in the present study.

Antibody to	Dilution
Cytokeratin, AE1/AE3	1:50
Cytokeratin, 35βH11	1:50
Cytokeratin, 34βE12	1:50
Epithelial membrane antigen (EMA)	1:80
Carcinoembrionic antigen polyclonal (CEA)	1:1000
Vimentin, V9	1:100
S100 protein	1:1000
Neurofilament	1:200
Synaptophysin	1:50
Neuron specific enolase, monoclonal (NSE)	1:100
Glial fibrillary acid protein (GFAP)	1:100
Transthyretin protein (TTR)	1:100
Desmin, D33	1:20
Smooth muscle actin, 1A4	1:25
Laminin	1:1000
P53 protein, DO7	1:100

Source of antibodies: Dakopatts, Carpenteria, USA.

Table 2. Immunodetection of proteins in choroid plexus tumors and fetal normal choroid plexus.

Markers	PP N=5	WCA N=2	PCA N=6	Fetal choroid plexus n=5
AE1/AE3	5	2	6	4
35βH11	5	0	0	0
34βE12	0	0	0	0
EMA	2	0	4	2
CEA	1	0	2	0
Vimentin	5	1	6	5
S100	4	2	6	5
NF	0	0	0	1
SNF	5	2	1	4
NSE	5	2	6	4
GFAP	5	0	5	5
TTR	5	2	5	5
Desmin	4	0	0	3
1A4	2	0	4	2
Laminin	4	2	0	5
P53	0	0	0	0

PP, choroid plexus papilloma; WCA, well differentiated carcinoma; PCA, poorly differentiated carcinoma. Markers: see Table 1.

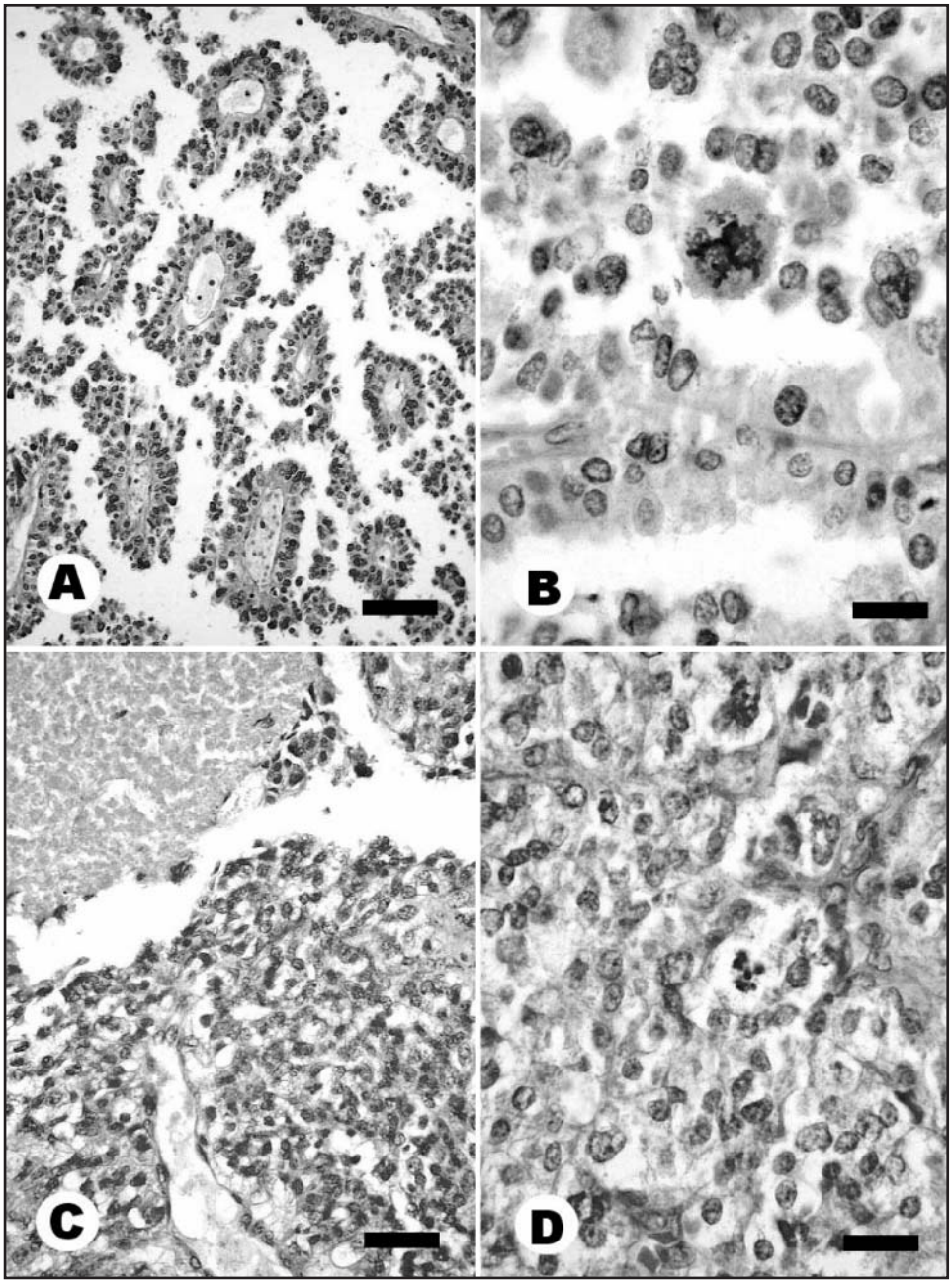

Fig 1. All sections stained with hematoxylin and eosin (HE). A and B) Well differentiated choroid plexus carcinoma: (A) cells arranged in single layer around capillaries forming papillary structures. (Bar 100 μm); (B) the lower half of the picture shows part of a papilla; in the upper half, cells are loose and an atypical mitotic figure is seen. (Bar 25 μm). C and D) Poorly differentiated choroid plexus carcinoma: (C) neoplastic cells forming solid sheets, with poorly defined cell limits; no papillary arrangement can be seen; in the upper left hand corner, area of coagulative necrosis. (Bar 50 μm); (D) detail, showing variation in nuclear size, nucleoli, and an atypical mitotic figure at center. (Bar 25 μm).

Cases were considered positive when at least 10% of the cells showed the characteristic brown staining, either in the nuclei, cytoplasm or membrane, according to each antibody pattern. The frequency of antigen immunodetection was studied comparatively in each tumor group and in normal fetal choroid plexus.

RESULTS

Between 1966 and 1999, 184 cases of CNS tumor were diagnosed in patients younger than 25 years. Thirteen (7%) corresponded to choroid plexus tumors: 5 PP and 8 CA (2 WCA and 6 PCA). Among the PP 3 patients were females and 2 males; age

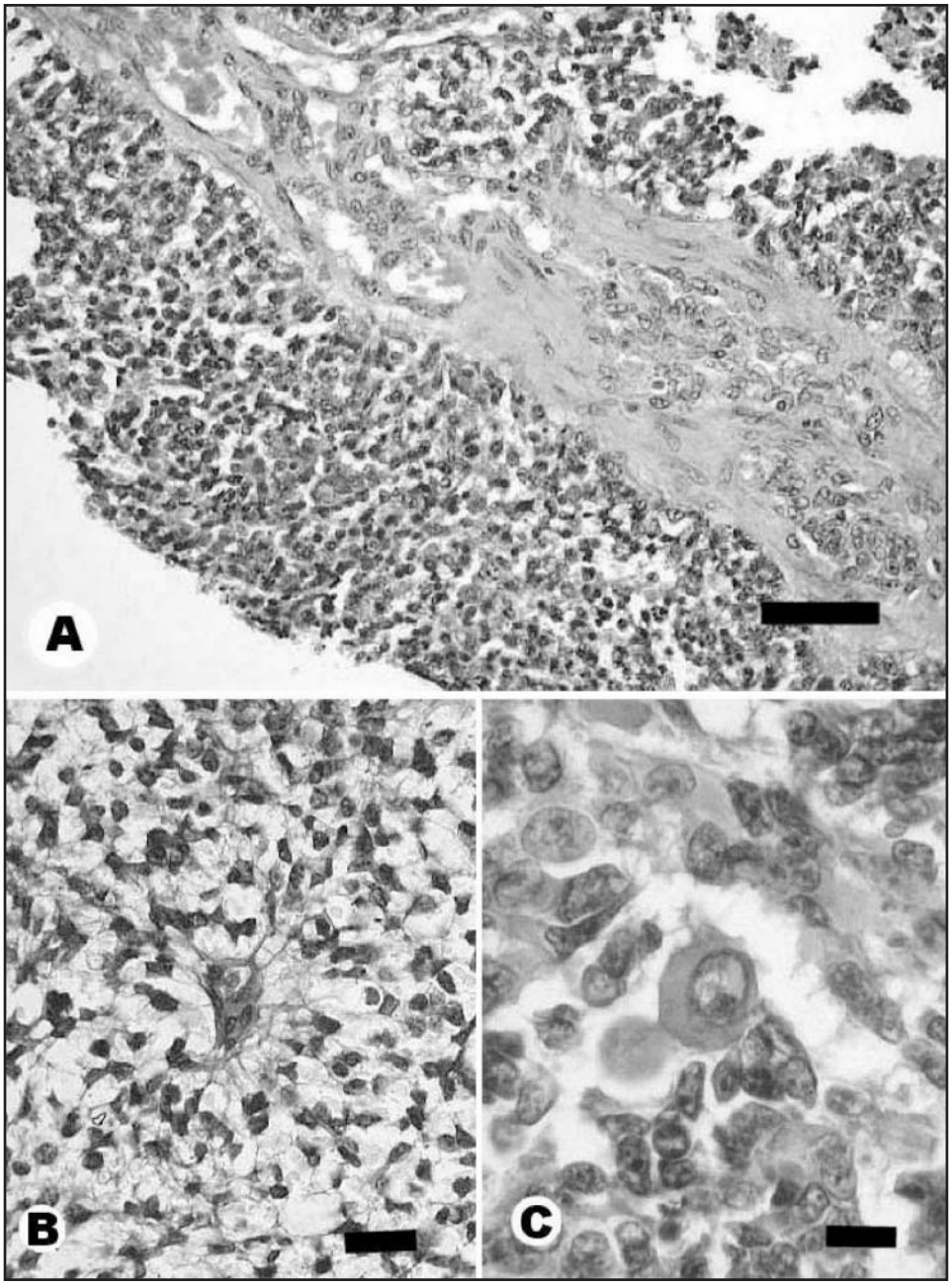

Fig 2. All sections stained with HE. Poorly differentiated choroid plexus carcinoma. (A) Area of vascular endothelial proliferation and thickening of a connective tissue septum. (Bar 100 μm). (B) Clear cell pattern. (Bar 50 μm). (C) Rhabdoid cell at center. (Bar 25 μm).

ranged between 1 month and 25 years, with median age of 1y 6mo. In 2 cases tumors were intraventricular without specification, one was in the posterior fossa / IV ventricle, another in the left lateral ventricle and in one case no information was available. Among the CA 6 patients were females and 2 males; age ranged between 5 months and 3 years, with median of 11 months. In one case tumor was intraventricular without specification, 5 were in the posterior fossa / IV ventricle and in 2 no information was available.

The cases of choroid plexus papillomas recalled the normal architecture of the choroid plexus: cuboidal or columnar epithelial cells formed a monolayer on papillary vascular connective tissue stroma. The nuclei were ovoid, with regular, well distributed chromatin and the luminal surface of the neoplastic epithelium was smooth and straight, as opposed to the hobnail appearance of normal choroid epithelium. The PP tended to have higher cellularity than normal choroid plexus, although no quantitation was attempted. Choroid plexus carci-

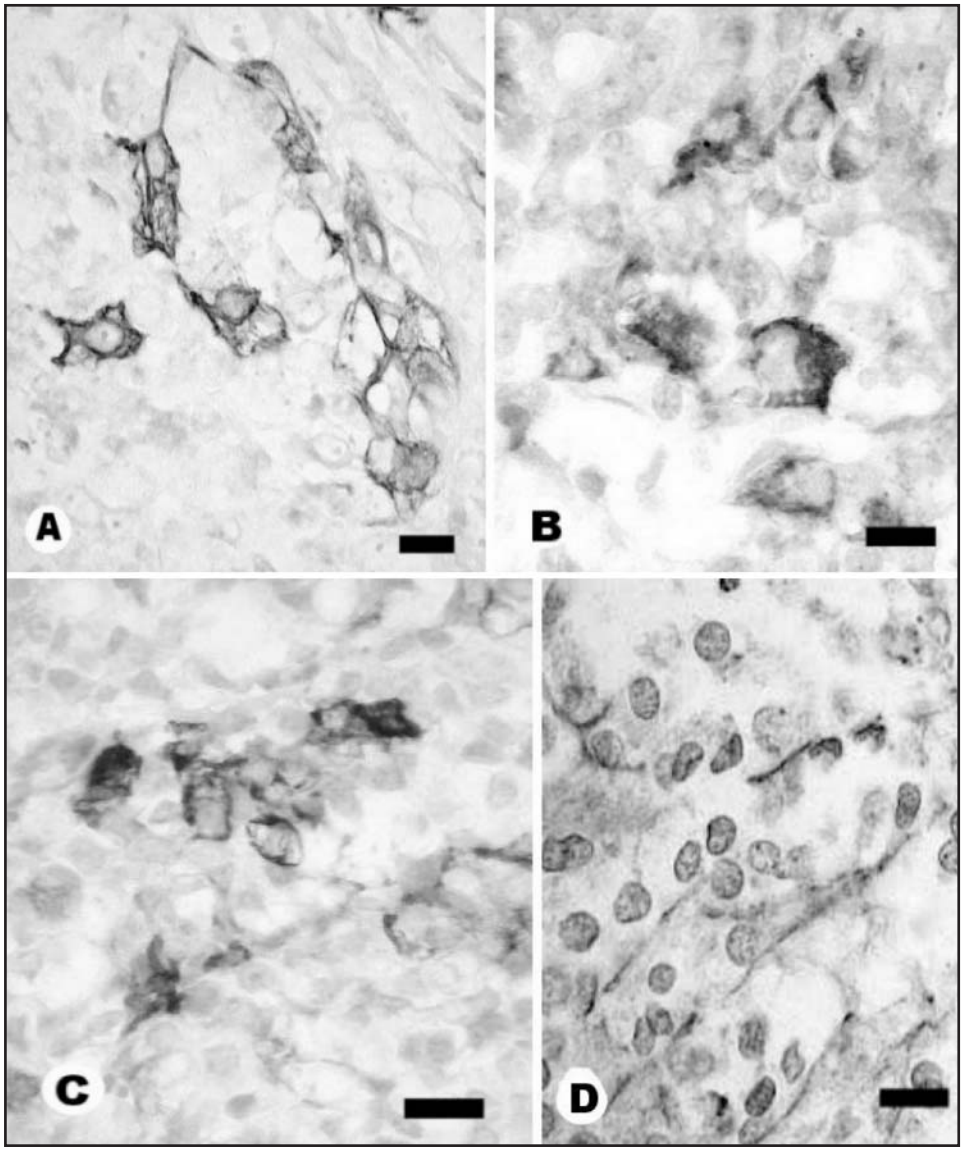

Fig 3. Positivity respectively for: (A) AE1/AE3, (B) GFAP, (C) 1A4 (all in poorly differentiated carcinomas) and (D) laminin (in well differentiated carcinoma). (Immunoperoxydase, bars 25 μm).

nomas were characterized by unequivocal malignant features, such as cytological atypia, necrosis, mitotic activity, brain invasion and/or loss of papillary architecture. Carcinomas were subclassified into well differentiated (WCA) and poorly differentiated (PCA) based on the predominance of papillary vs solid areas. There were 2 cases of WCA, with at least 50% of papillary areas and 6 PCA (Fig 1). Of these, only one showed a single focus of papillary structures. The other 5 consisted of solid tissue only.

Besides these characteristic findings, some noteworthy observations were found in our cases. Vascular endothelial proliferation was found in 3 of 6 PCA (Fig 2A). In the same 3 cases, stromal proliferation formed thick irregular septa (Fig 2A). Perivascular pseudorosettes were present in the 2 cases of WCA and in 5 out of 6 cases of PCA. Clear cells were a common finding (3/5 PP, 2/2 WCA and 5/6 PCA), mostly in focal areas (Fig 2B). In one case of PCA larger areas of clear cells were seen. These cells were a major finding in all examples of fetal choroid plexus examined. In every case, PAS reaction was negative in clear cells. Rhabdoid cells were found in 3 out of 6 PCA (Fig 2C). They were observed mostly in perivascular distribution and were characterized by clear vesicular nuclei, with single prominent nucleolus and abundant acidophilic cytoplasm devoid of the classical hyaline body usual in rhabdoid cells. These cells showed immunoreactivity for smooth muscle actin 1A4.

Immunohistochemical findings are summarized in Table 2 and shown in Figure 3, for AE1/AE3, GFAP, 1A4 and laminin.

DISCUSSION

Case selection was limited to ages from birth to 25 years because of the high incidence of choroid plexus tumors in the pediatric population with significant decrement after the second decade.

Some noteworthy points regarding frequency, histopathological features and immunohistochemistry of choroid plexus tumors in childhood arose from our study. Choroid plexus tumors account for 1.5 to 3.9% of CNS tumors in children, PP being at least four times more common than CA[1,2]. There is slight male predominance and the lateral ventricles are the most common site at this age. In the present series, the frequency of choroid plexus tumors was 7% (5 PP and 8 CA = 13 cases among 184 CNS tumors). The predominance of carcinomas as compared to papillomas does not reflect the incidence of the general population, since difficult cases from other institutions are often referred to our hospital. There was female predominance (9 F, 4 M). As regards tumor location, 3 cases were intraventricular without specification, 6 were situated in the posterior fossa / IV ventricle, one in the left lateral ventricle and in 3 no information was available.

While histological criteria for well differentiated choroid plexus tumors are clearly established[26,28] the diagnosis of poorly differentiated variants is not so well defined.

In our series, vascular endothelial proliferation and stromal desmoplasia forming thick irregular septa were present in 3/6 cases of PCA. This feature is frequently seen in astrocytic neoplasms, in which it is related to the degree of anaplasia and used as a criterion for histological grading. Endothelial proliferation is often found in high grade astrocytomas, in which the stimulus for proliferation is attributed to the production of angioproliferating factors by the neoplastic astrocytes themselves[29]. It is therefore possible that the findings of vascular proliferation and stromal desmoplasia in PCAs might hint at some sort of astrocytic differentiation of the choroid neoplastic cells. It should be recalled that the choroid plexus cell derives from a neuroepithelial common precursor cell, the so called oligopotential glio-ependymal precursor[10,11,17].

Perivascular pseudorosettes were seen only in WCA and PCA (2/2 WCA and 5/6 PCA) and may cause diagnostic difficulties with anaplastic ependymomas. While the perivascular pseudorosettes might be an indication of ependymal differentiation of the choroid neoplastic cells, it must also be kept in mind that ischemic necrosis of tumor cells at some distance from blood vessels might create a similar pattern.

Clear cells were common in all choroid plexus tumors, benign and malignant. As they are also very frequent in the fetal choroid plexus, they may suggest similarities between the neoplastic cells and immature related tissue.

Concerning the immunohistochemical profile, pancytokeratin AE1/AE3 was strongly positive in all tumor cases, even in the undifferentiated component of PCA, where reactivity was focal in 3 and diffuse in 3 cases. In contrast to the literature[8,9,14,18,19,21], low molecular weight cytokeratin (35βH11) was not expressed in any of 8 CA, but was present in all 5 PP. In 4/6 PCA, including one without rhabdoid-like features, there was reactivity for smooth muscle actin 1A4, which could be detected in 10 to 30% of the cells. Also, differently from some reports[19], laminin was not a helpful tool in the diagnosis of PCA, as it was not detected in any of the 6 cases. All 5 NFCP expressed GFAP, in contrast with previous reports[8-11,13]. Absence of expression of 35βH11 among all 5 cases of NFCP was similar to what was obtained in CA. On the other hand, all PP showed positivity.

The main histological and immunohistochemical criteria for classifying the undifferentiated tumors as choroid plexus CA were respectively the diffuse, solid growth pattern without a fibrillary background, the presence of a scant rim of cytoplasm in the small, round cells and strong reactivity for pancytokeratin AE1/AE3 in the undifferentiated component. Some PCA showed immunoreaction to 1A4, which could cause difficulties in differential diagnosis with the rare and controversial AT/RT, also present in the posterior fossa of young children (usually before one year of age)[22,23]. However, in PCA the pattern of positivity was distinct from that found in AT/RT in that it did not correlate exclusively with the rhabdoid-like cells but also with scattered undifferentiated epithelial and perivascular tapering cells. There was 1A4 positivity even in a case lacking the rhabdoid-like component.

Differential diagnosis between choroid plexus

PCA and AT/RT may be difficult. The main criteria favoring PCA were homogeneity of the histological picture, without heterologous elements often found in AT/RT, such as mesenchimal areas, epithelial differentiation into both squamous and glandular tissue. AT/RT are characterized by rhabdoid cells with globular intracytoplasmic bodies in 100% of cases, and a neuroectodermal (PNET) component evident in two thirds (predominant in 15-65%). In our cases, the undifferentiated component, although diffuse, was epithelial-like with scant cytoplasm. However, recent genetic studies have shown important similarities between choroid plexus carcinomas and AT/RT, both of which show inactivating mutations of the hSNF5/INI-1 gene in chromossome 22q11.2, considered an important step in the molecular pathogenesis of AT/RT. This points to a close relationship between these two entities[30].

Furness et al[19] detected laminin in subepithelial location and fragmented pattern in all choroid plexus CA; in contrast our PCAs did not show laminin, possibly due to the very undifferentiated state of the neoplastic cells without any reminiscence of papillary structures. On the other hand, PP (4/5) and all 5 NFCP showed strong, linear and continuous membrane reactivity for laminin. In both WCA laminin was found in a fragmented pattern.

The positivity to vimentin and S100 protein in almost all cases of PP, CA and NFCP is in agreement with other reports[9,10,14,21] that both are associated with tissues derived from the neuroectodermal plate.

Unlike some reports[11,14,19-21], in our cases there was no correlation between the degree of tumor anaplasia and immunodetection of CEA, TTR and EMA. TTR was positive in all tumors and in NFCP, except one PCA. EMA showed positivity in 2/5 PP, 4/6 PCA and 2/5 FCP, and CEA in 1/5 PP and 2/6 PCA.

As most reports in the literature[10,11,13,14,16-19,21,31], GFAP was strongly and widely expressed among all PP and 5/6 PCA, implying, as Rubinstein and Brucher[16] proposed that during neoplastic development choroid plexus epithelial cells express a feature which is the prerogative of glial and ependymal related cells. However in Rubinstein's and other authors' studies[8-11,13] of normal choroid plexus, there was no glial marker immunodetection, with rare exceptions[14]. Two explanations have been proposed: first, antigen retrieving techniques have been considerably improved compared to a decade ago when most of the reports were published; and second, most of the normal plexus studied were adult samples. In children choroid plexus cells may have greater propensity to divergent differentiation[17]. In summary, neoplastic choroid cells, either benign or malignant, and immature normal fetal choroid cells retain the genetic information of their parental neuroepithelial precursors which code for a glial phenotype in their progeny[16].

The p53 tumor suppressor protein was negative in all cases examined suggesting that, in contrast to astrocytomas, p53 mutation seems not to be important in the pathogenesis or progression of choroid plexus tumors. The actual role of the immunodetection of the p53 protein is still controversial, as other authors show high positivity of this protein mainly in choroid plexus carcinomas, although in variable intensities[32,33]. However, in a study including 10 choroid plexus tumors, Ohgaki et al[34] did not find mutations in exons 5-8 of the p53 gene, what is in accordance with our finding.

CONCLUSIONS

Pancytokeratin (AE1/AE3) was expressed in all choroid plexus PP, CA and 80% of NFCP.

Low molecular weight cytokeratin (35βH11) was expressed in all PP but not in CA or NFCP.

Expression of epithelial markers (AE1/AE3 and EMA) is important to define the epithelial nature of the tumor, particularly in undifferentiated areas.

An immunohistochemical panel of 16 antibodies is useful to help distinguish PCA from other anaplastic tumors, such as AT/RT.

Fetal choroid plexus demonstrates multipotentiality through coexpression of various markers: VIM, TTR, S-100, GFAP (100%), SNF, NSE, AE1/AE3 (80%), desmin (60%), EMA, 1A4 (40%) and NF (20%).

Laminin was not detected in PCA, but was useful for highlighting the basal lamina in PP and WCA.

Mutations of p53 gene do not appear important in pathogenesis and progression of choroid plexus tumors.

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