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Adamantinomatous craniopharyngioma associated to odontogenic classification of the jaw as a prognostic factor

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RESUMEN

Antecedentes: el craniofaringioma es un tumor de crecimiento lento, epitelial con una recurrencia inpredecible. Desde el punto de vista morfológico, son similares a los tumores ameloblásticos/odontogénicos de la cavidad oral.

Obtejivo: establecer un factor pronóstico en la conducta biológica de estos tumores.

Material y método: estudiamos 100 craniofaringiomas de tipo adamantinomatosos y los reclasificamos de acuerdo con la clasificación propuesta por la OMS de los tumores de la cavidad. Además, se obtuvo un índice de proliferación nucleo celular (PCNA) por inmunohistoquímica.

Resultados: identificamos 58 quistes calcificantes odontogénicos, 18 se identificaron como tumores adenomatoides y 17 reticulares o plexiformes, 8 de tipo folicular y 2 de tipo basaloide. 54 pacientes fueron mujeres y 46 hombres. La edad de los pacientes varió de 15 a 86 años, con una media de 49.19 años. El índice de proliferación PCNA varió entre 13 y 43 (media de 29.49%; p =0.001). Para el quiste odondogénico fue de 24.60 ± 4.51, para el tipo folicular fue de 22.29 ± 8.69, para el tipo reticular, de 25.85 ± 9, para el tipo basaloide fue de 29.06 ± 9.59 y para el tipo adenomatoide fue de 19.00 ± 1.41 (p = 0.260). El tipo basaloide y el reticular tuvieron un mayor indice de proliferación, asimismo, estos tipos presentaron mayor tamaño, recurrencia, muerte y menos tiempo de seguimiento que los otros subtipos.

Conclusiones: cuando aplicamos la clasificaciones de los tumores de la cavidad oral en los craniofaringiomas encontramos que el tipo basaloide y el reticular tienen peor pronóstico que los otros tipos histológicos. Por tanto, reclasificarlos de acuerdo con la clasificación de los tumores de la cavidad oral puede ayudar a predecir un mal pronóstico.

Palabras clave: craniofaringioma de tipo adamantinomatoso, recurrencia, inmunohistoquímica, PCNA, clasificación de los tumores de la cavidad oral.

ABSTRACT

Background: Craniopharyngioma is a slow-growing epithelial tumor with an unpredictable tendency to recur. Morphologically craniopharyngiomas are similar to ameloblastomas of the oral cavity.

Objective: To establish a prognostic factor in the biological behavior of these tumors.

Material and method: We studied 100 adamantimomatous craniopharyngiomas reclassified as odontogenic tumors, according to WHO classification of the jaw. Clinical-pathological analysis and immunohistochemistry PCNA-LI correlation between the different histopathological types were performance to verify the reliability in predicting the clinical outcome.

Results: Odontogenic cyst calcification tumors accounted for 58; adenomatoid type, 18; reticular or phexiform type, 17; follicular, 8 and just 2 were basaloid type. 54 were male and 46 female. The age varied from 15 to 86 years (median 49.19 years). PCNA labeling index was 13-43 (mean 29.49%, p = 0.001). OCCT was 24.60 ± 4.51, follicular type was 22.29 ± 8.69, reticular was 25.85 ± 9, basaloid type was 29.06 ± 9.59 and adenomatoid type was 19.00 ± 1.41 (p = 0.260). The basaloid and the reticular type presented a higher proliferation index than OCCT and the adenomatoid ones. Also, they showed a bigger size, more recurrence, dead, and less follow-up time.

Conclusion: In summary, reclassifying craniopharyngiomas according to the odontogenic tumor of the jaw could be useful to predict the biological behavior of this tumor. Our data provide a translational basis for further clinical studies on the predictive histological value.

Key words: adamantinomatous craniopharyngioma, recurrence, immunohistochemistry, PCNA, ameloblastomas of the jaw classification.

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Craniofaringiomas (CPs) are the main tumors of the cellar region, and may be solid or cystic; they present a bimodal age distributions: 5 to 14 years and 65 to 74 years. The incidence of CPs is 2/100,000; diagnosis is based on characteristics EMRI TAC.[1-7]

CPs correspond to the two histological subtypes, adamantinomatous (ACP) and papillary craniopharyngiomas (PCP), according to WHO classification.[4] CPs are thought to arise from epithelial remnants of the craniopharyngeal duct or Rathke's pouch (adamantinomatous type) or from metaplasia of squamous epithelial cell rests that are remnants of the part of the stomadeum that contributed to the buccal mucosa (squamous papillary type).[6,8]

ACP histologically resembles some odontogenic tumors, as its name indicates, the histological resemblances between ACP and ameloblastoma, previously known as adamantinoma of the jaw, has long been especially well recognized.[3,5-8]

The most widely quoted classification of odontogenic tumors is that proposed in the WHO booklet published in 1992.[8] There is, however, a number of controversial issues that need to be addressed regarding the clinical-pathological subtypes, terminology, and diagnosis which all have direct bearings on therapeutic and/or prognostic implications.[3,5-8]

The aim of this study was to establish homology between the classification of brain CPs in association with the odontogenic tumors of the jaw, clinicopathological and PCNA labeling index correlation as a marker of biological behavior.

MATERIAL AND METHOD

Inclusion criteria

One hundred cases of ACPs were retrieved from the Department of Neuropathology archives of the National Institute of Neurology and Neurosurgery in Mexico City. Period comprised from 1998-2005. All patients underwent surgery. Clinical data included; age, gender, tumors size, tumor localization, recurrence, follow-up, and dead. The tumors that developed a recurrence are defined as the growth of the residual tumor with or without clinical symptoms. Clinical and histopathological findings observed and PCNA labeling index were correlated according WHO ameloblastic tumor of the Jaw classification.[8]

Histopathology

Specimens were obtained for craniotomy surgical biopsies, formalin-fixed paraffin-embedded tissue block were retrieved for all cases. They were stained with hematoxilin and eosin procedure, microscopic sections were examined from each case. Microscopically, the lesions were divided into five groups, according to WHO classification of odontogenic tumor of the jaw:[5,8] in odontogenic cyst calcification tumor (OCCT), follicular (F), adenomatoid (A), basaloid (B) and reticular (R) types.

Each specimen was further evaluated for the presence of necrosis, hemorrhage, inflammatory cells, ghost cell, wet keratin, atypia, pleomorphism, and mitoses, and on the other hand, calcifications. Brain invasion was defined as the presence of isolated remains of epithelial tumor cells surrounded by brain tissue.[9]

Three pathologists, without previous knowledge of the source of specimen, made the morphological analysis independently.

Immunohistochemistry

The fixation procedures were identical at both institutions providing the archival material. A 4 μm tissue was cut and mounted on treated slides (poly-L-lysine). Endogenous peroxidase activity was inhibited by incubation of the sections in 3% H_2O_2 in methanol, for 20 minutes. In brief, slides were deparaffinized in xylene and gradually rehydrated via graded ethanol. Antigen retrieval was done by boiling the slides in 0.01 m citrate buffer (pH 6.0) for 5 min using a pressure cooker. Slides were incubated with Protein Block reagent (Dako, Carpintery Ca) for 10 min at room temperature, followed by overnight incubation at 4°C with the primary antibodies. Each specimen was stained with the proliferating nuclear cell antigen (PCNA) antibody (DAKO Cytomation, Carpintery, Ca, dilution 1:100). Clone immunohistochemistry was performed using the Envision labeled polymer reagent (DAKO Cytomation, Carpintery, Ca).

The specificity of the immunostaining was verified by replacing the primary antibody with non-immunized serum. The control tissues were incubated with the corresponding preimmune sera, with the second antibody only. The sections were stained with 3,3'-diaminobenzidine as chromogen and counterstained with Harris hematoxilin.

The proliferating cell nuclear antigen (PCNA) labeling index (Li) was assessed by counting the percentage of posi-

tive /nuclear cells in five 40x fields. More than 200 cells from multiple 5 low microscopic fields were quantified.[10]

Statistical analysis

Statistical analyses were performed with SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Statistical differences between mean values of different types of adamantimomatous craniopharyngioma were evaluated using the unpaired t test, and those between mean values of more than five groups were evaluated using analysis of variance (ANOVA). PCNA-Li was scored by mean and standard derivation. Mann-Whitney and Kruskal-Wallis tests were used for comparison of PCNA-Li groups. Survival analyses were carried out by the Kaplan–Meier test with log rank test to compare differences in survival curves. Multivariate survival analysis was performed using the Cox regression model. Generally, P-values < 0.05 were considered to be significant.

RESULTS

Clinical findings pertaining to the one hundred patients were summarized in Table 1. This series included 54 male and 46 female adult patients, age from 15 to 86 years (median 49.19 year). Symptoms evolution time was between 3 and 48 months (mean 10.59 months) and the follow-up ranged from 12-56 months (mean, 32.31 months). 44 cases had a suprasellar location (22 cases were female and 22 were male). 25% cases had a parasellar location (14 were female and 11 were male) and finally, 31% cases had a mixed location (13 were female and 18 were male) [$p = 0.007$].

The cases were divided according to WHO classification of ameloblastoma of the jaw. 58 cases were odontogenic cyst, calcification tumor (Figure 1a), 18 cases were adenomatoid (Figure 1b), 17 cases were reticular o phexiform type (Figure 1c), 5 were follicular (Figure 2a), and 2 were basaloid (Figure 2b).

26 OCCT were located in suprasellar region, 14 were parasellar and 18 had a mixed location.

The tumor size was ranged from 23 to 49 mm (mean 35.74 ± 6.27 mm) with a mean time for recurrence was 34 months (mean 1.47 ± 47) [Table 1].

The suprasellar location tumor size ranged mean was 32.98 ± 1.02 mm, parasellar location was 36.88 1.01mm, and at mixed location was 38.10 ± 0.91 mm.

Recurrence observed in 33 cases. 17 cases were OCCT, 3 follicular, 3 reticular, 0 basaloid, and 7 were adenomatoid. And 11 cases death (Figure 3).

The follow-up varied from the different types, ranged from 12-56 months (mean, 32.31 mo. OCCT ranged mean time was 34.48 ± 11.23 mo, while basaloid was 21.60 ± 14.05 mo (Figure 4).

Histological findings for each group are shown in Table 2. Mitoses found in 18%, calcifications in 83%, wet keratins in 63%, hemorrhage in 27% ($p = 0.006$, ANOVA $p = 0.000$), necrosis 17% ($p = 0.000$, ANOVA $p = 0.000$). Rosenthal fibers in 65% ($p = 0.006$), 33% with inflammation, cholesterol in 10% and 51% presented brain invasion, and ghost cell in 27 cases.

The ranged mean of PCNA labeling index was 13-43 (mean 29.49%, $p = 0.001$). OCCT was 24.60 ± 4.51. Follicular type was 22.29 ± 8.69, reticular was 25.85 ± 9, basaloid type was 29.06 ± 9.59 and adenomatoid type was 19.00 ± 1.41 ($p = 0.260$). A comparison was made with the Kruskal-Wallis test and with the mean test, which showed significance between the different groups ($p = 0.011$) [Table 2, Figure 5].

DISCUSSION

CPs have been generally considered to arise from the remnants of Rathke's pouch or a misplaced enamel organ.[6-8] Tateyama H et al[8] tried to refine these hypotheses, by comparing the subtypes of craniopharyngioma with Rathke's cleft cyst, a known Rathke's pouch derivative, and with ameloblastoma, an enamel organ derivative.[8] The duct and pouch were derived from the stomadeum, which, amongst other things, forms teeth primordia. The theory of dysontogenic origin of cranopharyngiomas is supported by these findings. Metaplasia of cells of the adenohypophysis is not considered to be a likely cause of craniopharyngioma formation.[6-8]

The histological resemblance between ACP and ameloblastoma of the jaw has long been especially well recognized.[11-13] These characteristics include ghost cell formation, a predominantly cystic morphology, and frequent calcification. Thus, ACP and COC have common histological features, embryonic origin and a common genetic alteration.[11] However, calcifying odontogenic cysts (COC) have also been found to closely resemble ACP.[5,11-13] ACP and OCCT share some histological char-
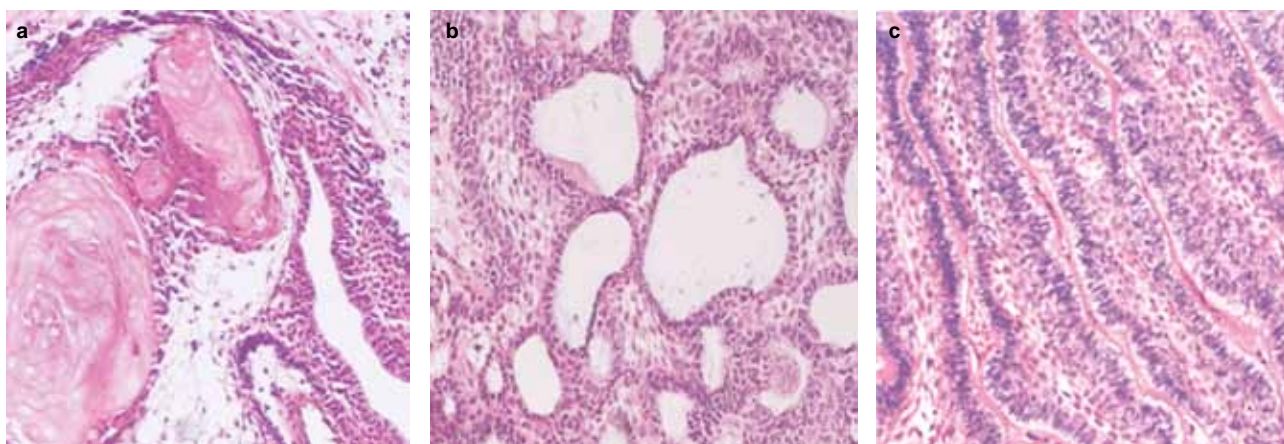
Figure 1. Histological features of the different subtypes of craniopharyngiomas. (**a**) OCCT type (H&Ex400). (**b**) Adenomatoid type (H&Ex400). (**c**) Reticular craniopharyngioma type (H&E x400). Figures of this paper are in color at the appendix 6 of this issue.
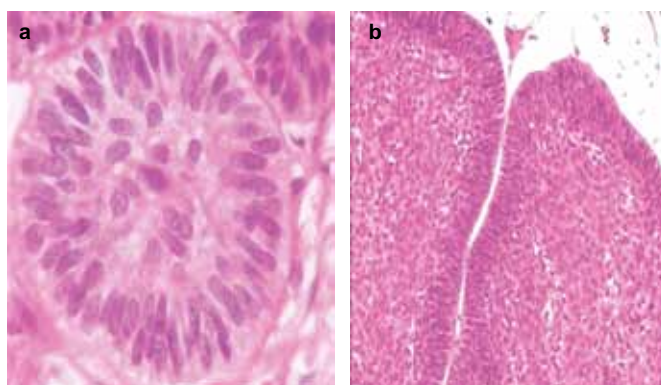

Figure 2. Histological features of the other different subtypes of craniopharyngiomas. (**a**) Follicular type. (**b**) Basaloid type (H&E x400).

Table 1. Characteristic of clinical data of 100 craniopharyngiomas

| Clinical findings	OCCT n = 58 (%)	Follicular n = 5 (%)	Reticular n = 17 (%)	Basaloid n = 2 (%)	Adenomatoid n = 18 (%)
Age/years	49.78±1.76	48.40±3.67	46.72±2.67	49.50±7.40	50±3.67
Gender					
Males	35 (35%)	1 (1%)	6 (6%)	1 (1%)	6 (6%)
Females	23 (23%)	4 (4%)	12 (12%)	1 (1%)	11 (11%)
Location					
Suprasellar	26 (26%)	9 (9%)	4 (4%)	1 (1%)	4 (4%)
Parasellar	14 (14%)	2 (2%)	0	1 (1%)	8 (8%)
Mixed	28 (28%)	7 (7%)	1 (1%)	0	5 (5%)
Tumor size/mm	36.84±.81	27.40±2.11	304.94±1.31	40.00±7.00	35.82±1.63
Evolution/months	9.89±.88	16.00±3.13	10.22±.78	12.00±00	11.65±1.04
Exeresis					
Total	35 (35%)	2 (2%)	8 (8%)	2 (2%)	10 (10%)
Subtotal	18 (18)	0	6 (6%)	0	7 (7%)
Partial	5 (18%)	0	4 (4%)	0	0
Recurrence	17 (17%)	3 (3%)	6 (6%)	0	7 (7%)
Death	5 (5%)	2 (2%)	0	2 (2%)	2 (2%)
Follow-up/months	34.48±11.23	34.0±15.86	32.11±12.17	21.60±14.05	28.06±10.07

OCCT: odontogenic cystic calcifying tumors.
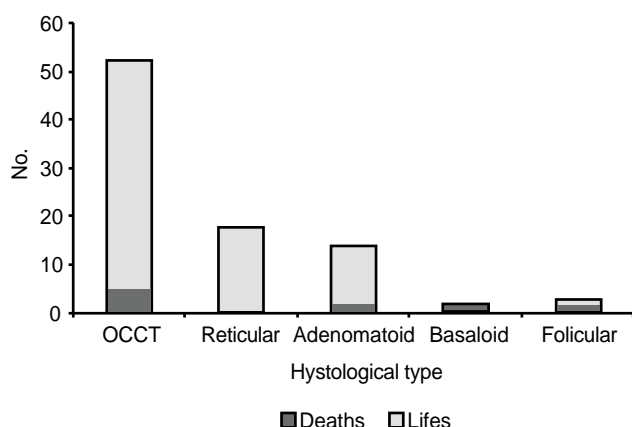
Figure 3. This histogram presents the relationship between living and death among the different histological types of craniopharyngioma included in this study. The proportion of deaths were 5 (8.6%) cases, 0 (0%) cases, 2 (11.8) cases 2 (100%), 2 (40%) cases, for each one of the histological types, respectively, finding a significant difference ($p = 0.001$).
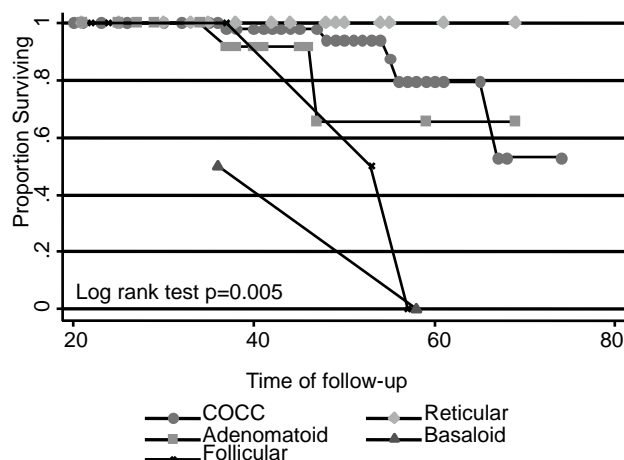
Figure 4. Kaplan-Meier survival analysis according the different types of craniopharyngiomas. The graph shows the evolution time in months among, where it was found that at least one of the histological types showed a different survival during the follow-up (Log rank test $p = 0.005$).

Table 2. Craniopharingioma and histological findings according to WHO classification of odontogenic tumors of the jaw

Histological findings	OCCT n = 58 (%)	Follicular n = 5 (%)	Reticular n = 17 (%)	Basaloid n = 2 (%)	Adenomatoid n = 18 (%)
Wet Keratin	41 (41%)	2 (2%)	8 (8%)	1 (1%)	9 (9%)
Ghost cells	13 (13%)	1 (1%)	6 (6%)	0	6 (6%)
Rosenthal fibers	39 (39%)	4 (4%)	12 (12%)	1 (1%)	9 (9%)
Calcification	55 (55%)	12 (12%)	3 (3%)	1 (1%)	12 (12%)
Inflammation	23 (23%)	2 (12%)	3 (3%)	1 (1%)	4 (4%)
Necrosis	4 (4%)	0	2 (2%)	1 (1%)	8 (8%)
Infiltration	27 (27%)	2 (2%)	5 (5%)	2 (2%)	10 (10%)
Hemorrhage	13 (13%)	2 (2%)	7 (7%)	1 (1%)	4 (4%)
Cholesterol	7 (7%)	0	0	0	3 (3%)
PCNA-LI	25.85±9.28	22.29±8.69	24.60±4.51	29.06±9.59	19.00±1.41

OCCT: odontogenic cystic calcifying tumors; PCNA-Li: proliferating cell nuclear antigen labeling index valuated by mean and Standard derivation.

acteristics that are not seen in ameloblastomas. As far as histopathological and immunohistochemical studies are concerned ACPs and ghost cell ameloblastoma of the jaw are homologous lesions.[11-13]

Although CPs have been examined in several microscopical studies to date, immunohistochemical analysis has not been sufficient. Amelogenin and enamelin are enamel proteins synthesized by ameloblasts.[14] These pro-

teins are secreted into the enamel extracellular matrix,[14,15] enamelysin (MMP-20),[16] integrin subunits,[17] LEF1,[18] etc., where they nucleate and regulate the growth of hydroxy-apatite crystals to form mineralized enamel.[15] Based on its histological resemblance to some odontogenic tumors Paulus et al[5] reclassified craniopharyngiomas according to the WHO classification of odontogenic tumors of the jaw and concluded that there were no apparent clinical
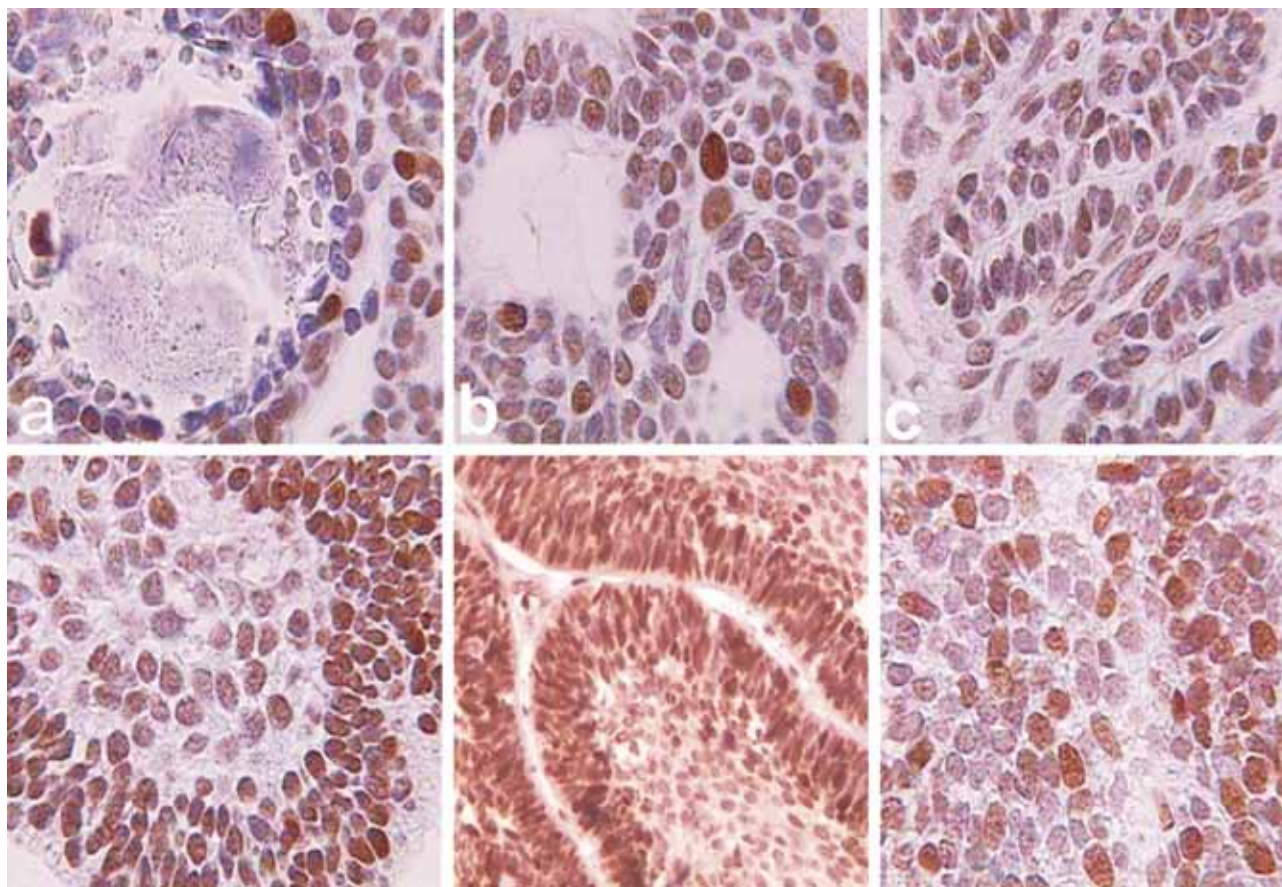
Figure 5. PCNA Immunohistochemistry. (**a**) OCCT type. (**b**) Adenomatoid type. (**c**) Reticular craniopharyngioma type. (**d**) Follicular type. (**e**) Positive cells in basaloid type and (**f**) showed positive cells in estrellate reticulum cells.

implications that would justify including the odontogenic variant in the classification of craniopharyngiomas given that the clinical presentation was the same.[14-18] However, recurrence and follow-up were no noted in Paulus et al study,[5] as well PCNA-Li.

There has been some controversy as to whether histological tumors subtypes have any prognosis importance or not.[1,5,11-13] Many researchers have tried with some success, to use a large set of biological markers to predict the clinical outcome of patients with craniopharyngiomas.[7,10,19]

CPs clinical predictors of poor prognosis include large tumor size, recurrence, severe hydrocephalea and hypopituitarism.[19] Controversially, total resection, as well as subtotal excision, followed by radiotherapy, is less likely to be associated with tumor recurrence.[3,10,19] However, despite radical excision, recurrence rates of 5-57% have been reported in most series of craniopharyngiomas.[3,10] The mean follow-up period was reported as 18.53 months (range 1-120 months) and peri-operative mortality in 7.4%.[3,10] The author reported recurrence in 33%, and in according this reclassification of CPs according with WHO classification of odontogenic tumors of the jaw, observed that OCCT showed more recurrence than the other type. Further, the follow-up varied from the different types, ranged from 12-56 months (mean, 32.31 mo). OCCT ranged mean time was 34.48 ± 11.23 mo, while basaloid type was 21.60 ± 14.05 mo.

Determination of proteins in the control of proliferation in normal cells helps to have a better understanding of cellular transformation and proliferation mechanisms,[20] Measurement of proliferative activity is important in determining the tumor grade, recurrence span and malignancy.[10,19-24] Primary craniopharyngiomas showed a mean

PCNA-LI of 1.7% (range 0.3-2%) to PCNA *vs* 4.1% (range 0.3-8%) in recurrences.[19] The MIB-1 Labelling Index has been seen in 22.1% of primary tumors, while 27.5% recurrences, 31.3% adult non-recurrent tumors, and 4.1% has been seen in the pediatric tumor.[19,20]

Sandra et al[24] have been studying the proliferating activities of ameloblastomas of the jaw, regarding the cytological pattern of the outer layer cells, the basal cell type had significantly higher PCNA and Ki-67 labeling indices than the cuboidal cell type. The solid type had significantly higher PCNA and Ki-67 labeling indices than the cystic and the mixed type. The labeling index of the younger patient was found to be the lowest, the middle age one was in the middle and the older patient was the highest.[24] These results indicated that the proliferating activities of ameloblastomas are quite variable, and the evaluations of Ki-67 and PCNA seem to be good indicators to assess the proliferating activity of each type of ameloblastomas.[21-15] Results suggest that cell proliferation of ameloblastoma was different depending on histological variation of the tumor. Further, the proliferative potential was higher in the plexiform o reticular ameloblastoma than that in the follicular type.[25]

Therefore, in our study PCNA-Li was found to be the lowest in OCCT, and was the highest basaloid type. Reclassifying them can be very useful in order to predict the biological behavior of craniopharyngiomas. We considered the basaloid tumor an aggressive tumor, but unfortunately, it is a very rare type and we only presented two cases.

Basaloid type emerged as a factor of potential value in this regard. Increased expression of PCNA-Li was more prevalent in high-grade and recurrence. These results indicate that basaloid type a characteristic of aggressive craniopharyngioma that progress, leading to decreased survival time.

We conclude that the classification of odontogenic tumors was useful at detecting those tumors in which mortality and recurrence were significantly more frequent (100% mortality for the basaloid type, 60% recurrence for the follicular type and 40% mortality for the same subtype). It is necessary to increase the size of the sample, so that the results observed acquire more validation, and in that way we can count with a more specific classification of craniopharyngiomas, based on embryologic principles and with useful clinical applications.

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