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Calcification and Ossification in Craniopharyngioma; Four Cases Report, and Literature Review

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Abstract

Intracranial calcifications are common findings in brain tumor neurosurgical practice. However, brain stones, as well as cerebral calculi, are rarely come upon. Here, we report four cases of craniopharyngioma displaying extensive ossification: Histologically, 3 of them with bone trabeculae, mature bone formation and giant osteoclasts, the fourth one presenting ossification nodules and dystrophic calcifications, with an osseous, fine multilobulated capsule. Furthermore, the remaining two CPs portray a cleft cholesterol granuloma, with a dense and solid stellate reticulum. These tumors expressed osteoponin, osteoconectin, EGFR, BFGR, vimentin, cytokeratin 7/8/18, EMA, focal cells expressed p53 and Ki-67li < 5%, and were negative to E-Cadherin, GFAP, chromogranin and synaptophysin. So, we suggested a differentiation of multipotential mesenchymal cells or epithelial mesenchymal transition or senescence phenotype understanding its biogenesis and pathogenesis. Calcification of adamantinomatous craniopharyngioma (ACP) is some important mechanism involving complications from surgical therapy.

Introduction

Craniopharyngiomas (CPs) arise in the sellar region, it is a rare type of brain tumor resulting from embryonic tissue of pituitary gland. They often involve the third ventricle, optic nerve, and pituitary gland [1]. Histologically, they are classified as benign, however, as many brain tumors, treatment can be difficult, and these tumors carry significant morbidities, which are related to both the tumor recurrence and treatment [1]. Two distinct types are recognized: Adamantinomatous craniopharyngioma (AdaCP), resembling to ameloblastoma, which is the most common type of odontogenic tumors (OTs), and are characterized by activating CTNNB1 mutations [2]. AdaCP and papillary craniopharyngioma (PaCP) characterize distinct

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tumor subtypes that carry commonly limited gene alterations [1,2], added replicated in variances in gene expression [3], and they are characterized by BRAFv600E mutations [3]. Transcription factors mandatory for ameloblast differentiation (BCL11B, MSX2) are shared by AdaCP, implying a common cellular origin [2,3].

Rarely, calcified sellar tumors have been described as Pituitary Adenomas (PA). The prevalence of calcification in PA has been determined to be 0.2–0.8% radiologically and 5.4–25% on light microscopy [4]. A total of 21 English-language articles published from 1961 to 2015 documented cases of calcified lesions in the sellar region; counting, chondroid chordoma, chondroma, craniopharyngioma, odontome, osteoma, pituitary adenoma, pituitary stone, Rathke cleft cyst, retinoblastoma, schwannoma, and xanthogranuloma, cerebral and aneurysm [4] etc. In AdaCP, calcifications are visible on neuroimaging and are helpful in diagnosis. On the other hand, PaCP rarely calcifies [1]. On gross aspect, CPs are cystic or partially cystic with solid areas [1]. On light microscopy, cysts are lined by stratified squamous epithelium. Keratin pearls and dystrophic calcifications may also be seen [1]. The cysts are usually filled with a yellow, viscous, and oily fluid, termed Oil Machinery Fluid (OMF), which is rich in cholesterol crystals [5].

Ossification is extremely rare and has been considered as a degenerative change [6]. Calcifications in CP might be a common event, though, identifying extended calcifications is infrequent, and it is even more uncommon to find large cerebral calculi [6].

The aim of this work was to reported six rare craniopharyngioma cases with extended calcified to display the experience in our institution; a clinical, histological, immunohistochemical approaches and electron structure analysis.

Clinical cases

We studied 4 cases of craniopharyngioma with extensive calcifications and bone metaplasia, and we excluded all those tumors showing isolated calcification foci or tumors which calcification extent was smaller than 10%. In **table 1**, clinical characteristics of the cases are observed. 3 were cases of biopsies, and the other one corresponded to an autopsy. Case 1 corresponded to a pituitary stone. All the cases presented recurrences. Three of them presented a tumor at the time of death, and all received complementary treatments with chemotherapy and radiotherapy. Four of these patients were obese. All presented endocrine disturbances and case 4 presented hypogonadotrophism. Two cases presented persistent diabetes insipidus. The figures represent the characteristic images of each one of the cases studied.

Histological features for each case are seen in **Table 2**. A fibrous stroma, with proliferation of fibroblasts, and inflammatory cells were observed, also giant osteoblastic cells. Three cases showed changes characteristic of osseous metaplasia, two of which presented stone formation at the sellar region in the case of the autopsy and the surgical sample in case 4. The formation of pituitary stone refers to the replacement of tumor tissue by the presence of dense hyalinized stroma with the presence of bone spicules. In case 1, we observed calcification foci in the adjacent brain tissue. In case 3, an intense granulomatous, xanthomatous reaction of foreign body type with cholesterol crystals is observed. The other cases did not present it. This was the only case that did not present osseous metaplasia **(Figure 1)**.

By immunohistochemistry results are seen in **Table 3**. All tumors were positive for E- and N-cadherin, in cases of sellar stones, this decreases in intensity inside the cellular areas. All cases were positive for osteoconectin and osteoponin both in bone metaplasia changes and in osteoclast-like multinucleated giant cells. In case 3, showing only dystrophic calcifications without bone formation, the giant cells were of the foreign body type with cholesterol crystals and negative for post-connective and osteoponin. The mib-1 index (Ki-67) was low in all cases. βFGF, EGFR, SMA and HIF 1α were densely positive in areas with proliferation of elongated and perivascular cells.

The MVD-li was high in all cases. The presence of OMF that we observed as yellowish crystals, were observed in all cases, where the inflammatory response was more intense and where we suggest rupture of the cystic lesions. Considering that the completely calcified lesions and the formation of the stones could be directly related to a longer survival time and a longer evolution of the patients.

By electron microscopy, in the semi fine sections stained with toluidine blue, we observed that the epithelial cells show signs of necrosis with variable vacuolation **(Figure 5a)**, excreting the OMF, forming dense deposits in different forms and aspects that are found both in the cytoplasm as in loose form that forms in association with the OMF **(Figure 5b)**. In the stroma, micro crystal deposits are also seen, in the sections evaluated by EM **(Figure 5c)**, we observed areas of wet keratin, there is a greater deposition of crystals and dense fibrillary structures **(Figure 5d)**. Irregular intermediates that surround the cells with the presence of small crystals **(Figure 5e)**. The crystals or calcifications begin as sparse and independent entities that become confluent **(Figure 5f)** and grow following an amorphous pattern **(Figure 5g)**, until forming large acellular masses in the middle of the OMF.

Table 1: Showed the clinical data of the cases studied.

Clinical data	Case 1	Case 2	Case 3	Case 4
Age	25y	34y	37y	36y
Gender	Male	female	male	male
Time of start	12mo	11mo	9mo	9mo
Age at 1 surgery	15y	30y	30y	33y
Visual disturbance	Yes	yes	yes	yes
Hormonal disturbances	Yes	no	yes	No
Patient weight	67 kg	80kg	72kg	90kg
Radiotherapy	Yes	yes	yes	non
Quiotherapy	Yes	non	non	non
Number of recurrences	4	5	3	2
Clinical embarrassment	Yes	yes	yes	yes
Clinical improvement	Non	non	non	non
Follow up	10y	4y	7y	3y
Death	Non	yes	non	yes

Table 1: Histological features of the last histological analysis.

Histological features	Case 1	Case 2	Case 3	Case 4
Classical AdaCPs	non	non	non	non
External epithelium	+	++	++	+
Reticulum stellate	+	++	++	+
Fibrous or sarcomatous Appearance	+++	++	++	++
Dystrophic calcification	+++	++	+++	++
Ghost cells	non	non	non	non
Wet keratins	++	++	+	+
Rosenthal fibers	non	+	+	+
OMF	non	+	+	++
Gliosis	non	+	+	++
Osteoclast cells like	non	++	++	+
Inflammation	non	+	+	+
Cleft cholesterol	Non	+	+	++
Granulomas formation	Non	+	+	++
Brain invasion	Non	+	+	++
Necrosis foci	non	non	non	+
Hemorrhage	non	non	non	++
Basal cells	Non	Non	+	non
Osseous metaplasia	+	++	+++	++
Chondroid metaplasia	non	+	+	non
Erythropoiesis	non	non	non	++
Cellular atypia	non	non	+	non
Mitosis features	non	non	non	non
Pleomorphism	non	+	+	non

Table 3: Immunohistochemistry results.

Primary antibodies used	Case 1	Case 2	Case 3	Case 4
Cytokeratin's 7	+	++	++	++
B-caterin	+	++	++	++
E-cadherin	+	++	++	++
N-cadherin	+	++	++	++
B-FGF	+	++	++	++
PDGF	+	++	++	++
Osteochondrin	+++	+++	+++	++
Osteoconectin	++	++	++	++
calretinin	+	++	++	++
CD68	non	+	+	++
Il6	non	++	++	++
GFAP	non	+	+	++

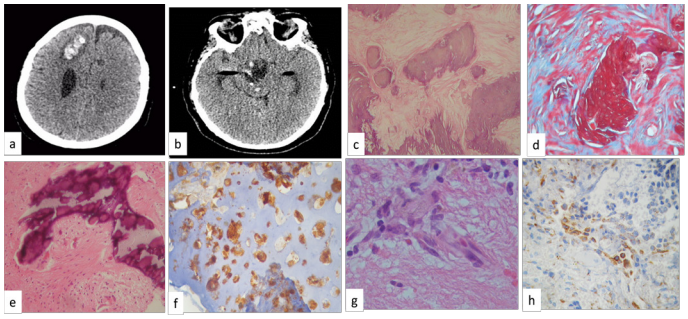

Figure 1: Sagittal TAC in **(a)** showed a calcified structure in cerebral lobes and in **(b)** selar region showed a calcified tumor. Histologically tumor showed extended calcified tumor in **(c)**, Masson stain shoed intense blue stain (x400), **(d)** close up of the calcified areas, in **(e)** those areas were strong positive reaction to osteoponin and in **(f)** observed few epithelioid cells of external epithelium and those cells were loss of E-cadherin immunoexpresion (original magnification x400). Was diagnosis as pituitary stone.

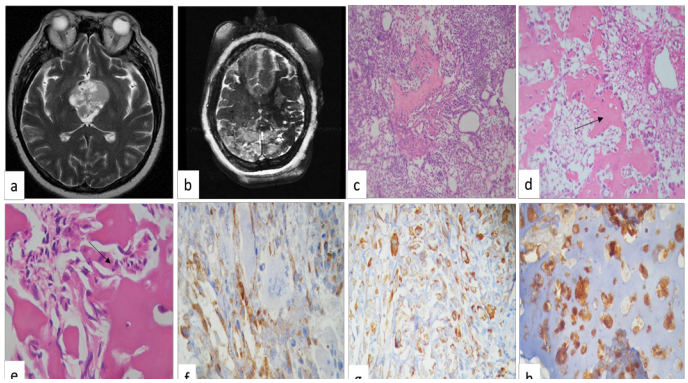

Figure 2: case 2. **(a)** and **(b)** MRI showed and hyperintense cystic lesion with extension into the sellar, suprasellar. **(c)** Histologically, the tumor in all cases was composed of dystrophic calcification by stromal cells surrounded by amorphous structures in **(d)**. and in **(e)** a close up of bone trabeculae and giant osteoblast-like cells layer were observed. **(f)** Showed osteoid stroma with basaloid proliferation cells and giant osteoblast-like cells. Inflammatory reaction with clef of cholesterol and giant osteoblast-like cells **(g)**, and in the hyalinized stroma some pleomorphic cells were observed positive to osteoponin expression in (h)(x400).

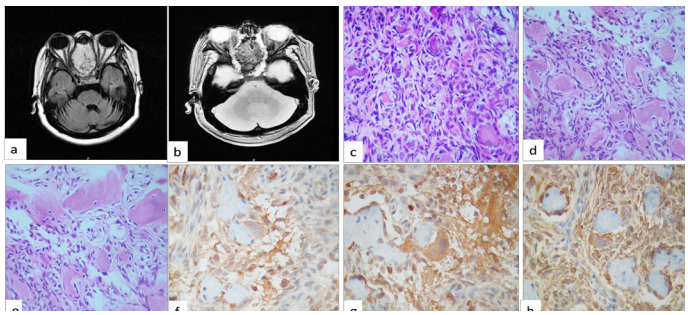

Figure 3: Case 3. **(a)** and **(b)** showed the sagittal MRI that showed and extended selar tumor Histologically tumor was formed by stromal or RE cells mixed between osseous spicule with a sarcomatous appearance in **(c)** and **(d)** and **(e)**. Immunohistochemistry was positive to osteoponin **(f)**, and osteoconectin in **(g)**, in **(d)**. E-cadherin strong immunoexpression (IHQ stains x400).

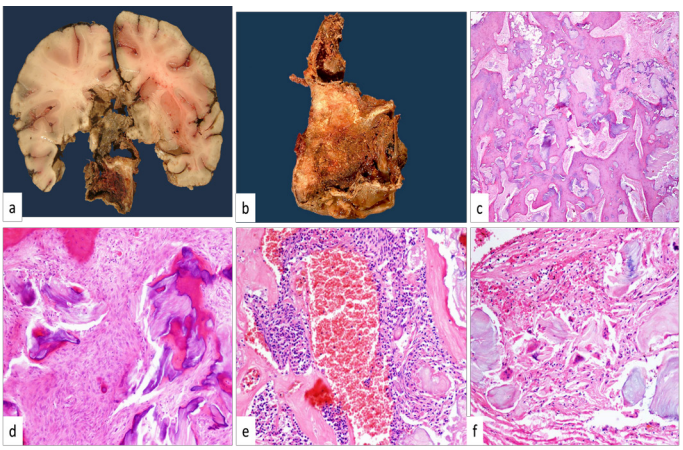

Figure 4: Case 4. Was autopsied **(a)** showed a coronal curt of the encephalon that observed an extended necrosis area and calcified selar tumor. **(b)** A close up of the calcified selar tumor with osseus appearance. **(c)** Histological features showed calcified in **(c)** and mixed with stromal fibroses appearance (H&Ex200), **(d)** with erythropoiesis formation in **(e)** and giant cells cleft cholesterol formation in **(f)** (H&Ex400).

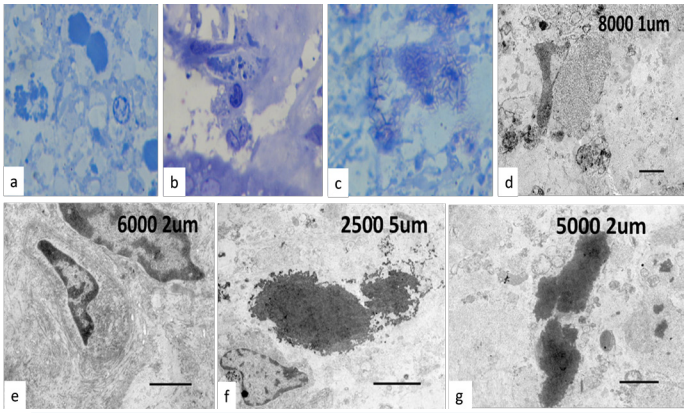

Figure 5: Case 5. Electron m Photomicroscopic photographsy. **(a)** Inof the semi-fine sections stained with toluidine blue. **(a)** WWe observed that the epithelial cells showing signs of necrosis with variable vacuolation leaving the OMF outwards; in **(ab)**, reaching dense deposits in with different forms and aspects that arewere found both in the cytoplasm and in loose form that forms in association with the OMF; in **(bc)**. In the stroma, micro crystal deposits are also observed **(5c)** (semifinal cuts with toluidine blue x100)., in the Transmission electron micrographs: **(d)** cuts by the ME we observe around the areas of wet keratin, a greater deposit of crystals and dense fibrillary structures around the areas of wet keratin were observed is observed (X5d) (8000; scale bar 1µum); **(e)**, formation of irregular intermediate filaments that surround the cells with the presence of small crystals **(5e)** (6000; scale bar 2uµm).; **(f)** The crystals or calcifications begining as micro-currents that become confluent (5f) (X2500; scale bar 5uµm) and grow in amorphous form **(5g)** (X5000; scale bar 2uµm).

Discussion

The molecular or pathological mechanisms that consequence in extenses calcifications of CP are unclear [1-3]. So, it is conferred that different types of calcification will exhibit a wide diversity in appearance, texture, form, radiologic findings, and clinical features, which is probably caused by the difference in the microcosmic composition [7]. Nonetheless, finding totally calcified tumors is a very rare condition [6].

Radiologically, cyst formation and calcifications in sellar masses are indicative of CPs [6-7], which are one of the most frequently calcified tumors of the brain. Differential diagnosis of intracranial hemorrhage vs calcification on conventional MRIs is often exciting [6]. While computed tomography (CT) confirms calcification, phase information obtained during susceptibility-weighted imaging can be useful Calcifications appeared hypo intense whereas hemorrhages were hyperintense on phase maps [7]. The relative proportions of calcium, phosphorus, and carbon influence the degree of calcification detected radiologically [7]. Samples with high calcium and phosphorus content and low carbon content have high degree of calcification. Calcified plaques constituted of hydroxyapatite crystals and some amorphous materials with different extents influences the degree of calcification [7].

Calcification and osseous metaplasia in AdaCP are a worrying situation for surgical intervention [8]. Difficulties caused by adhesion, invasion, extensive or erosion, skull base tumor attachment to the hypothalamus and thalamic injury [8], are factors which induce morbidity and mortality during surgical procedures [8,9].

Chronic hemorrhage, inflammation, granuloma formation, dystrophic calcifications bone metaplasia and cyst formations, pyloid gliosis have been described as degenerative changes in CPs [8], as well as, secondary changes which are due to the rupture of the cystic lesions and reorganization of the tissue after the exit of the OMF into the brain tissue [5], which might be modifying the cellular surrounding microenvironment [5, 9]. Furthermore, CPs are most frequently cystic tumors, the cyst contains the classical oil machinery fluid with shimmering cholesterol crystals [1]. However, little is known about this OMF compositions and adverse effects [5]. Hemoglobin fragments, α-1-antichymotrypsin, α-2-HS-glycoprotein or fetuin A, thymosins β4 and β10 Apolipoproteins A-I, A-II, C-I and J, vitamin D, ubiquitin, binding protein, α-1-acid glycoprotein, have been described in the cyst fluid content of CPs [10]. Furthermore, proteins and peptides involved in inflammation [11], mineralization processes [7, 8,11] and lipid transport have been identified, in agreement with the calcium flecks, cholesterol granules and bone residues characteristic of this fluid [5].

Also, matrix proteins are essential in the process of biomineralization and have been identified in CPs calcification [10]. Calretinin [11], bone morphogenetic protein-2 [12], pRunx2, Osterix [13], and Osteoponin (OPN) [14], bone-matrix glycoprotein, which binds strongly to hydroxyapatite and seems to form an integral part of the mineralized matrix, are probably important to the integrity of cell-matrix interactions [15]. Osseous metaplasia has been associated to the expression of osteophytes and osteochondrin, Calretinin, and the latter could induce stromal calcifications [11, 15]. The presence of osteogenic markers in craniopharyngioma cells could indicate differentiation into an osteoblast-like lineage, and the process of craniopharyngioma calcification resembles to that occurring in osteogenesis/odontogenesis [14]. OPN protein is probably synthesized and secreted by stellate reticulum-like cells and ameloblast-like cells [14]. Furthermore, osteoblastic differentiation in AdaCP has been convinced by bone morphogenetic protein-2 [13].

Several studies in animal models have shown the activity of noggin, which inhibits osteogenesis by antagonizing bone morphogenetic proteins (BMPs) induced osteogenic differentiation of human bone marrow-derived mesenchymal stem cells [6]. Noggin suppression also reduced the expression levels of osteoblastic genes, osteopontin (OPN), osteocalcin (OC), ALP, Integrin-Binding Sialoprotein (IBSP), muscle segment ho-

meobox gene (MSX2), and runt-related transcription factor-2 (RUNX2) [16]. This mechanism could be directly proportional to the presence or absence of calcifications via autocrine or paracrine mechanisms [17]. It is an innovative mechanism has been shown for paracrine, non-cell autonomous tumor initiation in AdaCP, a benign nonetheless clinically aggressive tumor [1, 12-13], interesting cellular senescence in promoting tumorigenesis [13], facilitated by the β-catenin/WNT pathway [1], and stimulating neoplastic cell growth, helping the occurrence of Cancer Stem Cells (CSCs) and producing tumor cells-permissive microenvironments [2].

Ultrastructural, we observed that calcification is a process that can occur in different stages of maturation, and/or evolution, that is, it starts in the form of small dark crystals that are found in cells that present degenerative changes with the presence of intracytoplasmic vacuoles, presence of OMF [5]. Crystals that grow progressively in succession and we can observe them linearly as they would correspond in calcified wet keratin [5]. Extracellular vehicles (EVs) are a heterogeneous population involved in intercellular communication which might be related to tissues undergoing inflammation/repair, alterations present in the extracellular matrix [10,11,15].

We consider that the formation of calcifications, as well as stones, can be secondary to degenerative changes suffered by tumors in relation to treatments, surgeries, and specifically in CPs to the rupture of the cystic structures and to the exit of the OMF outside the tumor. Producing an intense inflammatory response [5]. Although these degenerative changes do not have the greatest importance from the histological point of view and even go unnoticed, they could be signs of self-control, of involution of the tumor itself.

We observed giant osteoclast-like cells in 5 cases that were positive for osteonectin, osteochondrin and βFGR, EVGF, HIF1α promote migration in vitro via the classic- and trans-signaling pathways by inducing epithelial-mesenchymal transition in ACP [5].

Inflammation suggests that IL-6 may promote migration in vitro via the classic- and trans-signaling pathways by inducing epithelial-mesenchymal transition in ACP [16].The presence of osteogenic markers (Runx2 and Osterix) in craniopharyngioma cells could induce differentiation into an osteoblast-like lineage, tended to be communicated in calcification-related epithelia, including the whorl-like array cells, external epithelia and around wet keratin formations and dystrophic calcification and the process CPs calcification [12,13].

Those cells forming cluster cells expressed high levels of several members of the FGF, TGFB and BMP, which signal to be activated by MAPK/ERK and inflammatory pathways in AdaCP [2]. They are often present at the invading edge and express growth factors that may participate in paracrine signaling to surrounding cells [13]. Wet keratin expressed in some proteins including enamel proteins (AMELX, AMBN, ENAM), keratins, and the glial tissue and GFAP expression even as variably expression enriched for immune genes, particularly MHC molecules and immune cells markers (including CD4, CD8, Il6 and CD68) [2,15]. It is another important factor for the beginning of the process of mineralization and calcification in CPs [8, 10, 12, 13].

Senescent cells activate genetic programmers that irreversibly inhibit cellular proliferation, but also endow these cells with distinctive metabolic and signaling phenotypes, including cancer, the secretion of a vast array of pro-inflammatory cytokines, chemokines, and growth factors collectively known as the Senescence-Associated Secretory Phenotype (SASP) via autocrine/paracrine pathways can affect neighboring cells [17]. Which inducing senescence in neighboring cells and activating an immune response. The charge of novel functions of senescent cells on their microenvironment, and can be easily altered elsewhere the use of the open SASP-cancer development [17, 18].

Recently study showed that AdaCP calcification may be a result of osteogenic differentiation, which mimics the calcium deposition seen in osteogenesis and odontogenesis. The activation of Runx2 signaling due to Bmp2-induced osteogenic differentiation is a key factor in this process, HDAC3 reduces osteoblastic differentiation and calcification in Bmp2-treated ACP cells by suppressing Runx2 signaling pathways. HDAC3 expression has been increased in calcified AdaCP tissue, and inhibition of HDAC3 improved AdaCP cell calcification. Then, this procedure promotes Runx2 activation (osteoblastic differentiation) and calcium deposition in AdaCP [20].

Therefore, we consider that the so-called SASP can be figured out in different histological figures of CPs [17]. Perhaps, this is the mechanism of action between osseous metaplastic changes, extensive, mineralization, dystrophic calcification and / or stone formation in the histogenesis of CPs [8, 9]. As a mechanism of inhibition in cell proliferation, it might also be a mechanism of self-control [19]. We could suggest the existence of trans-signaling pathways by inducing epithelial-mesenchymal transition in AdaCP [15], or is it also a mechanism associated with SASP [17, 18], paracrine roles of cellular senescence in promoting tumorigenesis [17]. On the other hand, extracellular vesicle communication pathways are a machinery of regulated expulsion of bioactive molecules, a process that also facilitates cell-to-cell transfer of lipids, proteins, and nucleic acids transport. Biological effects of these processes have been implicated in several aspects of cancer-related pathology [18,19].

Ultrastructural features suggest a more efficient extracellular vesicle transport, location and relationship with different types of cells [21]. This could better explain the presence of paracrine secretion mechanisms in CPs [17]. Further studies are required to assess the role of EMVBs and SASP in these physio pathological conditions in dystrophic calcification in CPs [16-18].

Conclusions. Calcification of AdaCP frequently causes problems with tumor resection, leading to a high incidence of deadly complications and tumor recurrence. Identification of extensive calcifications in craniopharyngioma is not a common finding, we describe 4 cases of extensive calcification with stone formation, as with bone metaplasia, perhaps from the surgical point of view, this implies a greater challenge since these occur in diffuse form with adherence or attachment, and can be used to expect the surgical risk of hypothalamic injury and to plan the degree of removal therefore. When it is already formed and mature, surgery is easier because it can be removed completely. However, we do not know the mechanisms of stone formation. Necrosis, inflammation, rupture of cystic structures, dissemination of OMF, genetic and molecular studies, among other mechanisms are involved in the formation of calcifications in CPs. Mechanisms that could be directly involved in self-control vs. tumor involution. Favoring a better surgical resection and a better survival of the patient. However, it remains a surgical challenge.

Conflict of interest statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Disclosure

We have no conflict of interest to disclose.

Abbreviations

CPs: Craniopharyngiomas; AdaCP: adamantinomatous craniopharyngioma; OT: odontogenic tumors; paCP: papillary craniopharyngioma; OMF: Oil Machinery Fluid; CT: Calcified Tumors; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; SASP: Senescence-Associated Secretory Phenotype; OT: Odontogenic Tumors; GFAP: Glial Fibrillary Acidic Protein; DMV: Microvascular Density; BFGF: Beta Fibroblast Growth Factor; EVGFR: Endothelial Vascular Growth Factor Receptor; EGFR: Epithelial Growth Factor Receptor; SMA: Smooth Muscle Actin; HIF-1α: Hypoxic Inducible Factor 1α; EVs: Extracellular Vesicles; OIS: Oncogene-Induced Senescence; CSCs: Cancer Stem Cells.

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