January 2017

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NEUROLOGY INDIA
Publication of the Neurological Society of India

NI FEATURE: PATHOLOGICAL PANORAMA - ORIGINAL ARTICLE
Year : 2017 | **Volume** : 65 | **Issue** : 3 | **Page** : 570--576

Papillary craniopharyngioma: A clinicopathologic study of a rare entity from a major tertiary care center in Pakistan

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Abstract

Background: Papillary craniopharyngioma (PCP) are uncommon variants of craniopharyngiomas (CP), which are benign epithelial neoplasms of the sellar and suprasellar region. Histologically, PCPs are typically composed of well-differentiated stratified squamous epithelium; however, focal variations are not uncommon. A distinction from other lesions of the region, despite being difficult to achieve due to the overlapping radiological and clinical features, is important for adequate treatment to be administered. **Objective:** Our aim was to study the clinical and histological features of PCP with emphasis on features that are helpful in its distinction from other lesions that are similar in appearance. **Materials and Methods:** We reviewed 13 cases of PCP diagnosed in our institution between January 2010 and December 2015. **Results:** The mean age at presentation was 30.76 years. Two of the patients belonged to the pediatric age group. Male-to-female ratio was 2.25:1. Suprasellar location (either alone or in combination with sellar region) was the most common tumor site. Microscopically, all of the cases showed stratified squamous epithelium with frequent pseudopapillae formation. Focal adamantinomatous epithelium and columnar epithelium with variable cilia and goblet cells were seen in 4 (30.7%) cases. Brain invasion was observed in 3 (23%) cases. Four patients died of their disease; 2 of the 7 patients with an available follow up, developed recurrences; and, 5 experienced severe postoperative morbidity. **Conclusion:** Majority of the PCPs exhibited typical features with minor variations. Knowledge of the variations in histologic features helps in reaching the correct diagnosis. These tumors can behave aggressively with a high recurrence rate and decreased overall survival.

How to cite this article:
Tariq MU, Din NU, Ahmad Z, Memon W. Papillary craniopharyngioma: A clinicopathologic study of a rare entity from a major tertiary care center in Pakistan.Neurol India 2017;65:570-576

How to cite this URL:
Tariq MU, Din NU, Ahmad Z, Memon W. Papillary craniopharyngioma: A clinicopathologic study of a rare entity from a major tertiary care center in Pakistan. Neurol India [serial online] 2017 [cited 2018 Jul 13];65:570-576
Available from: http://www.neurologyindia.com/text.asp?2017/65/3/570/205934

Full Text

Craniopharyngiomas (CPs) are benign nonglial tumors which predominantly involve the sellar and suprasellar regions. They are more common in the pediatric age group where they account for 5.6–15% of all central nervous system (CNS) neoplasms. Overall, they comprise 1.2–4.6% of CNS neoplasms.[1],[2] They arise from the epithelial remnants of the craniopharyngeal duct or the epithelial cells of adenohypophysis.[3] These solid and cystic tumors compress the surrounding brain structures, and patients present with headache, loss of vision, endocrinal abnormalities, and personality changes.[4] Two histological variants of CP have been described, namely the 'adamantinomatous craniopharyngioma (ACP)' and the 'papillary craniopharyngioma (PCP).' In addition to their distinct histological features, PCPs also differ from ACPs on the basis of their lesser frequency, later age of presentation, their circumscription, and gross appearance of their cyst contents.[3],[5] Microscopically, PCPs are composed of solid nests of stratified squamous epithelium with

pseudopapillae formation. In contrast to the ACPs, they lack ameloblastic/adamantinomatous epithelium with basal palisading and stellate reticulum, nodules of wet keratin, frequent calcification, and invasion into the adjacent brain tissue [Table 1]. Cystic and solid lesions of the sellar and suprasellar region such as Rathke's cleft cyst (RCC), epidermoid cyst (EC), arachnoid cyst (AC), and xanthogranuloma (XG) are included in the differential diagnosis of PCPs.[3],[6] Presence of unusual morphological features may pose a diagnostic challenge in small biopsy specimens. The clinical course is usually benign and associated with recurrences. Surgical excision followed by radiotherapy are the most common treatment modalities used in these patients.[7]{Table 1}

Our aim was to study the clinical and histological features of PCP with emphasis on features that are helpful in its distinction from other lesions of this region which are similar in histologic appearance.

Materials and Methods

We retrieved 13 cases of PCP from the surgical pathology database of the Section of Histopathology, Aga Khan University Hospital, reported between January 2010 and December 2015 through "Integrated Laboratory Management System" software. As this was a retrospective study and did not involve actual identification of patients, approval from the hospital ethical committee was not required. The clinical information regarding age, sex, location, presenting complaints, and tumor size were obtained from the pathology reports. Hematoxylin and eosin-stained microscopic glass slides were reviewed by two pathologists (MU and NU), and were analyzed for various histologic features including the type and configuration of epithelium, presence of columnar cells, cilia, goblet cells, calcification, and invasion into adjacent brain tissue. The inclusion criteria were the presence of well-differentiated stratified squamous epithelium as the predominant type of epithelium and absence of wet keratin nodules.

The patients were contacted using their telephone numbers provided at the time of specimen submission. Verbal consent was obtained via telephonic conversation, and follow-up information was obtained either from the patients' attendants or from the patients themselves.

Results

The patients' age at presentation ranged from 3 to 62 years with the mean age being 30.76 years ± 14.94 years, and the median age being 30 years. Two (15.3%) patients in our study belonged to the pediatric age group. Nine (69.2%) patients were males, 4 (30.8%) were females, and the male:female ratio was 2.25:1. The presenting complaints in almost all of the patients were headache and visual disturbances. The suprasellar region was the most common site of tumor involvement, followed by the involvement of sella [Figure 1] and [Figure 2]. Four tumors involved the suprasellar region alone, 3 tumors involved the sellar region alone, 4 involved both the suprasellar and sellar regions, and a single case involved the third ventricle. The tumor site was not mentioned in one case. All the specimens were received piecemeal and the extent of tumor removal (total versus subtotal resection) was not mentioned. The maximum size of tumor tissue measured was 4.5 cm, with the mean tumor size being 2.6 ± 1.1 cm.{Figure 1}{Figure 2}

Microscopically, all the cases showed a well-differentiated stratified squamous epithelium comprising at least 95% of the epithelial component. The arrangement of this epithelial component was in the form of either solid nests with pseudopapillae formation or as lining of the cystic spaces. Keratinization was also observed in a few cases in the form of individual cell keratinization and keratin pearl formation [Figure 3]a,[Figure 3]b,[Figure 3]c,[Figure 3]d. The pseudopapillae had loose fibrovascular stroma and the epithelium had stellate reticulum and basal palisading [Figure 4]a,[Figure 4]b,[Figure 4]c,[Figure 4]d. Few of the cases showed focal areas (<5%) of columnar epithelium, which was variably ciliated and contained goblet cells [Figure 5]a,[Figure 5]b,[Figure 5]c,[Figure 5]d. Calcification was observed in the stroma of 2 cases [Figure 6]a. Neutrophilic abscesses within the epithelium were seen in 3 (23%) cases, and 1 of these cases showed microcysts within the epithelium, which were filled with acute inflammatory cells [Figure 6]b. The lumina of the cases with cystic configuration did not show any material as the cysts had already ruptured except for a single case in which the lumen was filled with mixed inflammatory cells. Microscopic evidence of invasion into the adjacent brain tissue was observed in 3 cases and it was associated with xanthomatous reaction in 2 cases [Figure 6]c and [Figure 6]d; [Table 2].{Figure 3}{Figure 4}{Figure 5}{Figure 6}{Table 2}

Follow up information was available for 7 patients, and the follow up duration ranged from 2 to 33 months. Majority of these patients had postoperative morbidity in the form of endocrinal dysfunction, seizures, uncontrolled hypertension, and overall deterioration of the general condition. Postoperative scans showed surgical changes of cerebrospinal fluid collection at the operative cavity [Figure 7]. Five patients had additional radiotherapy. Two of 7 patients with an available follow up developed recurrence and 4 died of the disease [Table 3].{Figure 7}{Table 3}

Discussion

CPs are the most common tumors of the suprasellar region.[7],[8] The mean incidence calculated from various studies is 1.44 (1.33–1.56) per million person year for the childhood population and 1.34 (1.24–1.46) per million person per year for the overall population. The highest incidence was reported in the Danish population.[9] ACP is 9 times more common than PCP.[10] Apart from occurring in a small proportion of pediatric population, PCPs usually occurs in adults, with a peak incidence between 50 and 75 years of age with the mean age being 44.7 years.[5],[11] Only 2% PCPs are seen in the pediatric age group.[2] The age range and the mean age of patients in our study was less than that observed in literature. Two of our patients were less than 20 years of age. CPs generally affects both the sexes equally.[1],[2] In our study, males were twice more commonly affected than females.

Two separate theories have been presented for the development of variants of CP. According to these, the adamantinomatous variant develops as a result of neoplastic transformation of the ectopic embryonic epithelial remnants of the craniopharyngeal tract, which serves as a connection between the stomodeum and the Rathke's pouch, and therefore, resembles ameloblastic/odontogenic epithelium. The papillary variant develops as a result of squamous metaplasia of epithelial cells in the adenohypophysis and resembles the oropharyngeal mucosa.[2],[3],[6],[11]

Owing to their proposed origin from the craniopharyngeal duct, CPs, especially ACPs, can occur anywhere along its tract. Approximately 94–95% are either purely suprasellar or both supra- and intrasellar in location. The remaining 5–6% cases are purely intrasellar tumors. These tumors can occasionally extend into the anterior, middle, and posterior cranial fossae.[2] Rare cases with involvement of the nasopharynx, sphenoid bone, and cerebellopontine angle have also been reported.[12],[13] Papillary CPs are usually suprasellar in location and can be seen in the proximity of the third ventricle.[10] Eight (61.5%) cases in our study were suprasellar, 7 (53.8%) were sellar, and 1 case involved the third ventricle. Radiologically, majority of the PCPs are solid, but they can also be cystic.[3],[11] In contrast to ACPs, these tumors do not exhibit calcification. The most common presenting complaints due to their close proximity to the optic chiasma, hypothalamus, and pituitary gland are headache, loss of vision, and hormonal disturbances. Other less common symptoms include nausea, somnolence, focal neurological deficits such as hemiparesis, ataxia, hyperreflexia, and cranial nerve dysfunction. Most of the patients in our study had a history of headache and a loss of vision.[4]

Grossly, the cyst content of PCPs is clear-to-yellow colored viscous fluid whereas the cystic component of ACPs contains the “machinery oil-like fluid” rich in blood products, cholesterol clefts, and cytokeratin proteins.[1],[11] The mean tumor size of CPs reported in the literature is 3.5 cm.[2] The maximum tumor size in our patients was 4.5 cm and the mean size was 2.6 cm.

Microscopically, PCPs are composed of sheets of well-differentiated stratified squamous epithelium. The pseudopapillae are formed by the dehiscence of these sheets. These epithelia typically lack the basal palisading and central stellate reticulum seen in ACPs. Approximately, one-third of our cases focally exhibited these features. A careful search of the literature also reveals a few CP cases with both adamantinomatous and papillary type of epithelium.[11] Petito et al., reported mixed epithelium in as many as one-third cases of their cohort of CPs.[4] The term 'mixed CP' has been proposed for these tumors.[14] The degenerative changes within the epithelium lead to the formation of microcysts, which coalesce to form larger cysts. Although seen in both the variants, they are more common in the adamantinomatous variant than in the papillary variant.[4] The cyst formation was observed in 4 (30.7%) of our cases.

Rathke's cleft cysts (CCs) are asymptomatic non-neoplastic cystic lesions predominantly involving the sellar region and seldom involving the suprasellar region.[6] Rathke's CCs are lined by a simple columnar epithelium, which is focally ciliated and exhibit goblet cells in a few cases. In small biopsies with limited material, they have a closely resembling differential diagnosis with other lesions when they exhibit squamous metaplasia, which has been reported to occur in 12–39% of the cases.[3],[6] On the other hand, PCPs can show focal columnar and ciliated epithelium in up to 10% of the cases and goblet cells in up to 33% of the cases.[3],[11] We also observed these features in our cases. The diagnosis is made on the basis of the predominant type of epithelium (squamous vs. columnar) and the presence of the solid component, which favors a diagnosis of PCP. These findings support the theory of origin of PCP as a result of a metaplastic change.[2],[3],[6],[15] In order to distinguish between the two entities, Xin et al., conducted an immunohistochemical study. They concluded that RCCs stain positively for both cytokeratin 8 and cytokeratin 20 whereas CPs are negative for these cytokeratins.[16] However, the utility of these markers could not be established, as a study conducted later by Brain et al., reported contradictory results, i.e. a positive cytokeratin 8 expression in both the entities and a negative cytokeratin 20 expression in most of the RCCs.[6]

Epidermoid cyst (EC) is also one of the important differential diagnosis. The presence of keratohyaline granules and keratin flakes observed in EC are not seen in PCP. We did not observe keratohyaline granules and flaky keratin in any of our cases. However, individual cell keratinization and keratin pearl formation were identified.[4],[11] Arachnoid cysts (ACs) are rare cysts which are lined by a single layer of flattened arachnoid.[3]

Nodules of wet keratin are a characteristic feature of ACPs, which are not observed in PCPs. In some cases, the stromal hyalinization can resemble these wet keratin nodules. The cyst wall stroma is fibrovascular and contains scattered chronic inflammatory cells.[2],[11] Histiocytic reaction against spilled out cystic contents into the surrounding tissues is less frequently seen in PCPs. We also observed collections of foamy macrophages in 2 of our cases. XGs are uncommon lesions of sellar region, which are included in the differential diagnosis of CPs as they show a prominent xanthogranulomatous reaction. The epithelial component, if present, should be less than 10% to make a diagnosis of XG.[17] Calcification within the epithelium and the stroma is a common feature of ACPs but is rarely seen in PCPs.[1],[4],[11] Focal calcification was seen

in 2 of our cases. PCPs are characteristically circumscribed tumors and invasion of the adjacent brain tissue is less common than is seen in ACPs.[2] This phenomenon was more frequently seen in our patients as 3 (23%) cases demonstrated brain invasion.

CPs usually have a benign clinical course, and so far, only 37 cases of ectopic recurrences (attributed to surgical contamination) have been reported. Three of these cases were PCPs which involved the frontal lobe, the contralateral temporal lobe, and the lumbosacral spine.[18] Malignancy is also a rare phenomenon, and so far only 16 cases have been reported. Thirteen of these cases were recurrent and majority of the patients had received radiotherapy. Rests of the 3 cases were de novo malignant cases.[19]

The mean overall survival was reported to be 4.8 years in recent studies, with the 5-year survival being 88–94%, and the 10-year survival being 70–92%.[5],[7] A lack of calcification, negative cerebrospinal fluid examination, tumor size less than 3 cm, tumor diagnosis after 1995, and administration of radiotherapy, have been associated with an improved survival.[4] A recent study showed that aberrant membranous β-catenin expression is an independent factor for predicting the prognosis of CPs.[20] Jennifer et al., reported a high recurrence rate of 62%, which was exclusively observed in patients with subtotal resection.[3] Complete surgical resection of CPs is often a difficult task due to their location and relation to other vital brain structures, resulting in a recurrence rate of 32% within 3 years.[4] A number of surgical techniques have been developed over the last few decades for surgical excision of CPs, and the outcome has improved, with significant reduction in recurrence rates.[7]

Postoperative morbidity has been observed in these patients due to endocrinal, neurological, and ophthalmological dysfunction as well as personality changes. Adjuvant radiotherapy is also given to the patients in whom gross total resection is not achieved, and has been demonstrated to provide better control over disease progression.[2],[3],[5],[7] Unfortunately, we had a follow up information about only 7 of our patients, and out of these, 2 developed a recurrence (due to incomplete resection) and 4 died of the disease. Additional radiotherapy was not successful in achieving disease control by either improving disease-free survival or postoperative morbidity as 3 of 4 patients who died had also received radiotherapy and all had severe postoperative complications. A comparison of the clinicopathological features and follow up information of our study with a few other studies has been summarized in [Table 4].{Table 4}

Mutation in β-catenin (CTNNB 1) gene is observed in more than 70% cases of ACPs, which is manifested by nuclear translocation of the protein and can be demonstrated by immunohistochemical stains.[10],[21],[22],[23],[24] PCPs lack this mutation but demonstrate BRAF (V600E) mutation in 95% cases.[25] A single reported case of PCP treated with targeted therapy (vemurafenib) against this protein has shown a good control of tumor progression.[26]

Conclusion

Papillary CPs are rare neoplasms with distinct clinical and histological features. In our series, some findings were different from the published literature. These findings included a male predominance, a higher percentage of pediatric patients, a higher percentage of cases with co-existing adamantinomatous epithelium, aggressive behavior, and a poor outcome (mostly related to incomplete resection as a result of the complexity of surgery; and, proximity of the tumor to important brain structures). In depth knowledge of the histological features is necessary to avoid a misdiagnosis. Gross total resection should be attempted in every case, and strict follow up should be carried out to avoid postoperative morbidity and recurrence.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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