Primary intracranial ectopic craniopharyngioma in a patient with probable Gardner’s syndrome

Case report

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The authors describe a patient with an adamantinomatous craniopharyngioma (CPG) arising in the cerebellopontine angle (CPA), who also had probable Gardner’s syndrome. This 31-year-old man presented with headache and dizziness. Brain CT and MRI showed a 5 × 4–cm lesion with multiple small calcifications in the left CPA. The patient underwent suboccipital craniotomy with tumor removal. Histopathological findings indicated an adamantinomatous CPG. This patient also showed characteristics of Gardner’s syndrome. Although this syndrome is associated with intracranial neoplasms, it is unclear whether patients with both Gardner’s syndrome and CPG are part of the heterogeneity of Gardner’s syndrome.

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KEY WORDS • craniopharyngioma • cerebellopontine angle • adenomatous polyposis coli • Gardner’s syndrome • oncology

CRANIOPHARYNGIOMAS (CPGs) typically develop in the infundibulohypophyseal axis and frequently occupy the sella and/or suprasellar cistern. Ectopic CPGs have been very rarely reported in the pharynx, sphenoid bone, pineal region, and cerebellopontine angle (CPA). 1 A CPG occurring primarily in the CPA is rare. 1,3,7,10,12,17,20,21 Only 3 cases of CPG in the CPA have been associated with Gardner’s syndrome. 1,3,12 However, it is unclear whether genetic abnormalities in individuals with familial adenomatous polyposis (FAP) are associated with CPG. 1 In this paper, we describe a case of adamantinomatous CPG in the CPA. The patient in this case was also found to have probable Gardner’s syndrome. We discuss the pathogenesis of CPG in this patient, focusing on the adenomatous polyposis coli (APC) gene, and review the pertinent literature.

Abbreviations used in this paper: APC = adenomatous polyposis coli; CPA = cerebellopontine angle; CPG = craniopharyngioma; FAP = familial adenomatous polyposis; GSK-3β = glycogen synthase kinase–3β.

Case Report

History and Examination. A 31-year-old man presented with headache and dizziness. Brain CT showed a 5 × 4–cm, slightly high-density lesion with multiple small calcifications in the left CPA. Mild thin peripheral enhancement around the tumor appeared on the brain CT scan (Fig. 1), and no definite tumor staining was found on cerebral angiograms. Both T1- and T2-weighted MRI revealed heterogeneous hyper- and hypointense lesions with irregular enhancement on the tumor wall (Fig. 2). The preoperative diagnosis was hemorrhagic schwannoma. The patient had an 80-year-old grandmother who had no CNS tumors or intestinal polyposis. He did not have any medical information for his parents because he had been separated from them since birth. His younger brother refused to undergo any gene study or colonoscopy.

Operation. The patient underwent suboccipital craniotomy with tumor removal. Intraoperatively, the tumor had soft tissue with a thick wall and no vascularity. The tumor capsule adhered densely to adjacent critical neuro-
vascular structures, especially the lower cranial nerves, rendering the tumor difficult to resect completely.

**Postoperative Course.** Postoperatively, the patient showed no abnormal neurological findings except for dizziness. Postsurgical brain MRI showed a small remnant tumor along the lower cranial nerves (Fig. 3). Histopathological findings indicated an adamantinomatous CPG (Fig. 4).

**Workup for Gardner’s Syndrome.** We reviewed case reports describing instances of primary ectopic CPG. We identified multiple osteomas in the patient’s skull on brain CT (Fig. 5). We suspected Gardner’s syndrome given the multiple osteomas. We performed colonoscopy and gastroduodenoscopy for diagnosing FAP. Colonoscopy demonstrated multiple polyps but fewer than 100 (Fig. 6). Biopsy of 1 rectal polyp identified villotubular adenoma with high-grade atypia associated with intraepithelial adenocarcinoma. Gastroduodenoscopy showed more than 100 polyps (Fig. 7). Biopsy of 1 stomach polyp demonstrated fundic gland polyposis. Computed tomography scanning of the patient’s jaw revealed dental anomalies, and a panoramic view demonstrated 1 osteoma located in the right mandibular angle (Fig. 8). Abdominal CT scanning demonstrated bilateral adrenal adenomas (Fig. 9). Congenital hypertrophy of the retinal pigment epithelium was not found on fundoscopy or retinal CT scans. No abnormal skin lesion was identified.

**Gene Study.** The germline status of the APC gene on chromosome 5q22, which is mutated in individuals with FAP, was identified in peripheral blood leukocyte DNA. The APC gene was analyzed via polymerase chain reaction and direct sequencing of the entire exon and intron region of the APC gene using an ABI genetic analyzer (3500xL, Life Technologies). A truncating frameshift mutation in the APC gene was detected in the 16th exon (c.4541_4547delCATTTATinsTTTCC coded according to the reference sequence at http://www.ncbi.nlm.nih.gov/nuccore/NM_000038). This resulted in a frameshift change with proline-1514 as the first affected amino acid, replacing it with a leucine and creating a new reading frame ending in a stop at the position of the 18th codon.
Follow-Up. We recommended radiosurgery for the residual CPG and total removal of the colon and rectum with preservation of the anus, but the patient refused further treatment because of economic and medical insurance problems. He showed no additional neurological deficit after 3 months.

Discussion

Familial Adenomatous Polyposis and Gardner’s Syndrome

Familial adenomatous polyposis is an autosomal dominant disorder resulting from a mutation of the APC tumor suppressor gene residing at position 21–22 on the long arm of chromosome 5. Different families with FAP can have different mutations of the APC gene, but all mutations are in stop codons and result in truncation of the APC protein. It is clinically diagnosed in individuals with more than 100 colorectal adenomatous polyps or in those with fewer than 100 polyps and a first-degree relative with FAP.

In our patient, we identified an APC gene mutation, more than 100 gastroduodenal polyps, and fewer than 100 colorectal polyps. We think that he may have had FAP; however, we could not identify a family history for FAP, and the patient had fewer than 100 colorectal polyps. Therefore, we could not confirm FAP, although we think that he will develop more than 100 polyps in the colon, which would confirm FAP.

Fig. 4. Photomicrographs showing tumor tissue with features consistent with the diagnosis of adamantinomatous CPG. Upper: Wet keratin formation. Lower: Strands or cords of multistratified squamous epithelia with peripheral basal palisading of nuclei. H&E, original magnification ×40 (upper) and ×100 (lower).

Fig. 5. Three-dimensional volume-rendering image of the skull demonstrating multiple osteomas (arrows).

Fig. 6. Colonoscopy revealing numerous polyps.
Gardner’s syndrome is a variant of FAP with the same mutation of the \textit{APC} gene.\textsuperscript{16} It is an autosomal dominant form of polyposis characterized by the presence of multiple polyps in the colon together with tumors outside the colon. Gardner’s syndrome is associated with characteristic multiple craniofacial osteomas, dental anomalies, skin and soft-tissue tumors, and congenital hypertrophy of the retinal pigment epithelium.\textsuperscript{3} Other common extracolonic manifestations of Gardner’s syndrome include osteomas of the long bone, fibromas, leiomyomas, lipomas, mesenteric desmoid tumors, periamputary and duodenal carcinomas, hepatoblastomas, benign and malignant biliary and adrenal neoplasms, and papillary carcinomas of the thyroid. In our patient, we identified dental anomalies, multiple skull osteomas, 1 osteoma of the mandible, and bilateral adrenal adenomas. Although he did not satisfy the strict criteria for FAP, we think that he may have had Gardner’s syndrome.

**Craniopharyngioma Development in Patients With FAP**

Whether the origin of the CPG in our patient was the result of a genetic predisposition or purely coincidental could not be elucidated. Despite the association suggested by 4 cases, including the present one, little direct evidence of a link between FAP and CPG has been found.\textsuperscript{12,16}

Two clinicopathological variants of CPG have been identified\textsuperscript{6,17,21} the adult papillary squamous type and the classic childhood adamantinomatous variant. Adaminomatous CPGs are the more commonly encountered subtype, and although seen predominantly in the pediatric population, they can present at any age. Histologically, they contain nodules of wet keratin, a palisading basal layer of cells, intense surrounding gliosis, and profuse Rosenthal fiber formation.\textsuperscript{8} All 3 CPGs previously associated with Gardner’s syndrome were of the adamantinomatous type.

The molecular pathogenesis of CPG has not been extensively investigated. The mutations of genes encoding \(\beta\)-catenin (\textit{CTNNB1} and \textit{APC}) are an exclusive characteristic of adamantinomatous CPG and may play a role in CPG initiation and growth.\textsuperscript{9,14,19} Mutations in \(\beta\)-catenin encoding genes and overexpression of \(\beta\)-catenin are considered to be characteristics of adamantinomatous CPGs. All mutations affect exon 3, which encodes degradation targeting box of \(\beta\)-catenin, consistent with an accumulation of nuclear \(\beta\)-catenin.\textsuperscript{4} In the absence of Wnt, the intracellular proteins axin, APC, and glycogen synthase kinase–3\(\beta\) (GSK-3\(\beta\)) form a stable complex, which functions to phosphorylate and degrade \(\beta\)-catenin. However, when Wnt is bound to the cell-surface receptor complex composed of fizzlelod and low-density lipoprotein receptor-related protein, the phosphorylation of \(\beta\)-catenin is prevented. The subsequent unphosphorylated form of \(\beta\)-catenin is protected from axin/APC/GSK-3\(\beta\)-mediated protease degradation and is therefore accumulated within the cytoplasm and nucleus.\textsuperscript{8} In adamantinomatous CPG, all genetic alterations targeted only the GSK-3\(\beta\) phosphorylation site of the \(\beta\)-catenin encoding gene.\textsuperscript{4} Therefore, mutation of \(\beta\)-catenin seems to play an important role in the etiology of an adamantinomatous CPG.\textsuperscript{19}

In contrast to Wnt/\(\beta\)-catenin–mediated tumorigenesis in other cancers, mutations in APC and axin have not been described in CPG.\textsuperscript{4} Interestingly, CPG cells with-
out mutations in the \textit{CTNNB1} gene can overexpress $\beta$-catenin,\textsuperscript{3} implying alternative mechanisms of $\beta$-catenin nuclear accumulation that may be relevant to tumor development.

Familial adenomatous polyposis results from mutations in the \textit{APC} gene, which encodes a negative regulator of the Wnt pathway. Patients with FAP can develop Wnt pathway–associated neoplasms such as desmoid tumors.\textsuperscript{15} Germline mutations affecting the \textit{APC} gene are the underlying cause of FAP, and somatic mutations in those regions of the \textit{APC} gene, known to compromise the ability of APC to interact with $\beta$-catenin, can be detected in the majority of sporadic colorectal cancers.\textsuperscript{16} Nuclear accumulation of $\beta$-catenin derives also from loss-of-function mutations of the \textit{APC} gene within a clustered region corresponding to the $\beta$-catenin/axin binding domain.\textsuperscript{4} The APC mutations almost always cause loss of the C-terminal functions of the APC protein—probably involved in microtubule binding, cell polarity, and chromosome segregation—and deletion of the serine-alanine-methionine-proline repeats that are important for binding to axin and formation of the $\beta$-catenin phosphorylation complex.\textsuperscript{18}

We think that the origin of adamantinomatous CPG in our patient may have been a phenotypic result of \textit{APC} gene mutation, and this occurrence is not coincidental. However, not all patients with FAP present with CPG. We think that the development of CPG depends on further somatic genetic events, each of which may be under different influences and selection pressures.

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