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Familial chordoma: A case report and review of the literature

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Abstract. Familial skull base chordoma is a rare tumor derived from the remnants of the embryonic notochord. The present study describes the clinical presentation of 4 cases of skull base chordomas in a family. A 15-year-old female received staged surgeries and was pathologically confirmed with a diagnosis of skull base chordoma. Among the patient's family, 2 members had previously undergone surgery and were pathologically confirmed with chordomas; 1 family member had also received radiation therapy. Furthermore, the patient's cousin, an 18-year-old male, was confirmed to have this condition by epipharyngoscopy. All confirmed cases within the family remained alive with the condition. A literature review of familial chordoma was undertaken and 8 chordoma pedigrees were found. Familial chordoma was rare, with an estimated rate of 0.4% in all chordomas. The skull base was the predominant location for familial chordoma. Compared with sporadic chordoma, familial chordomas were diagnosed at a younger age. The brachyury gene was strongly associated with familial chordomas, however, the exact pathogenesis and genetics mechanisms remains unclear.

Introduction

Chordomas are rare tumors that are believed to be derived from the remnants of the embryonic notochord. They are usually apparent along the axial side of the body, predominantly in the skull base and sacral regions (1). The mean age at diagnosis is between 40 and 60 years, with a marginally younger mean age for cases at the skull base (2). The tumor often presents with cranial nerve dysfunction, and slow-growing but infiltrative characteristics. In addition, the surrounding bones and neurovascular structures are involved (3). The current approach of radical surgery plus adjuvant radiotherapy has improved the outcome, however, the majority of patients develop tumor recurrence and treatment complications, resulting in a median survival period of 6.29 years, with 5-, 10- and 20-year rates of 67.6, 39.9 and 13.1%, respectively (2,4,5).

The incidence of the tumor is ~0.08/100,000 individuals (1-5) and little is known about its etiology. As the majority of cases reported in the literature are sporadic, familial chordoma cases with >3 patients identified within 1 family, involving >2 generations have been reported only 8 times in the literature (Table I) (6-13). The present study reports the case of a patient with familial skull base chordoma and the details of 3 other pathologically confirmed cases within the family, with a review of the literature.

Case report

History and physical examination. In November 2011, a 15-year-old female with no other medical history presented to the Department of Neurosurgery at Beijing Tiantan Hospital (Beijing, China) with snoring and apnea that had persisted for ~4 years, along with a headache that had been present for ~6 months, which had been aggravated by symptoms of nausea and vomiting for ~1 month. The patient had no history of surgery or communicable diseases. On clinical examination, the patient exhibited hoarseness. Eye movement was normal and there were no signs of facial paralysis or dysaudia. No symptoms of deglutition dysfunction were present. The patient exhibited good strength in the limbs and the results of Romberg testing were negative. The magnetic resonance imaging (MRI) and computed tomography scans showed a bony invasive mass of the skull base area, involving the nasal regions and clivus. The scans further revealed that the lesion was compressing the brain stem from the left side (Fig. 1A-C).

Surgery and post-operative course. A staged surgery was suggested, and a far lateral approach was performed with a gross resection of the intracranial mass, under electrophysiological surveillance. The post-operative period was uneventful, with the exception of aggravation of the hoarseness and sixth nerve palsy. The symptoms improved 6 months later and MRI showed a good resection of the intracranial lesions (Fig. 1D-F). The patient then received the second surgery for the mass of the nasal region using a subtotal resection (Fig. 1G-I). Following the staged surgery, the patient exhibited no symptoms of cerebrospinal fluid leakage, and the main

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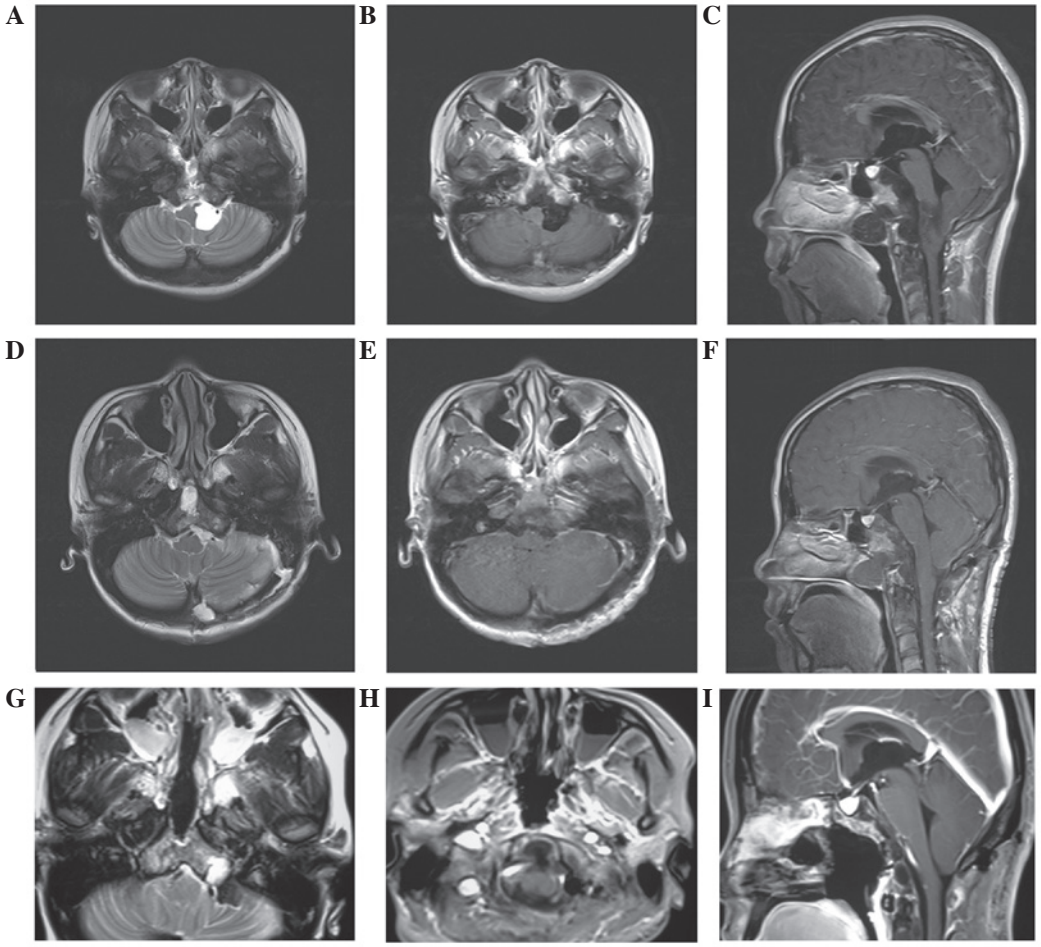

Figure 1. Magnetic resonance imaging (MRI) of the skull base chordoma using T2-weighted axial MRI, and enhanced axial and sagittal MRI. (A-C) Skull base chordoma involving the nasal regions and clivus, revealing the lesion compressing the brain stem from the left side. (D-F) MRI after the first surgery showing the total resection of the intracranial region. (G-I) MRI after the staged surgery showing a subtotal resection.

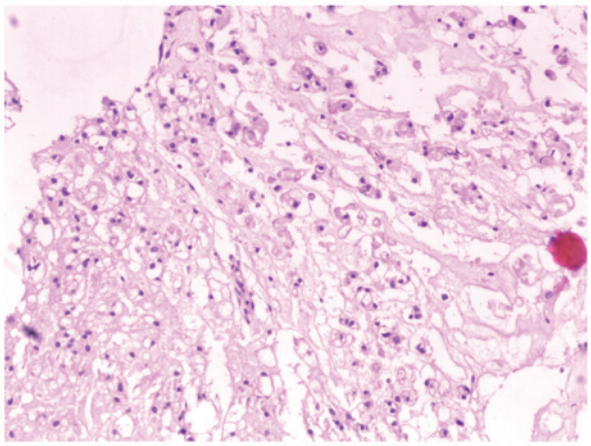

Figure 2. Pathology of the tumor (hematoxylin and eosin staining; magnification, x400). The tumor was composed of cords and strands of intermediate-sized tumor cells, showing typical bubble-like cells with a bolus distribution.

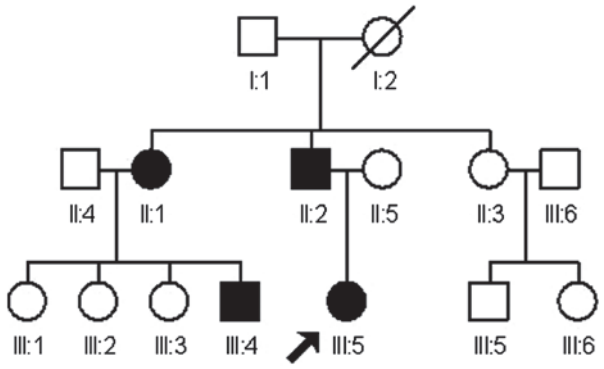

Figure 3. Family tree with the original study patient indicated by an arrow.

symptoms of snoring and apnea had almost disappeared. The patient received radiation therapy (γ-knife, 28 Gy, one time) 1 year after the first surgery, prior to returning back to school with no marked symptoms. At the 4-year follow-up, the patient exhibited no signs of recurrence, as confirmed by MRI.

Pathological findings. The tissue appeared reddish in color upon gross inspection. Under the light microscope, the tumor was composed of cords and strands of intermediate-sized tumor cells, showing typical bubble-like cells with a bolus distribution. The bubble-like cells were intermediate in size and round in shape, with abundant cytoplasm. The nuclei were surrounded by cytoplasm containing vacuoles (Fig. 2).

Family history. The patient had a strong familial history of chordoma. At 6 months prior to presentation, the patient's

Table I. Familial chordomas reported in the literature.

ID	Date (ref)	Number of patients	Locations	Male:female	Age range, years	Mean age, years
1	1958 (13)	2	Sacral	1:1	52	52
2	1964[a] (12)	2	Nasopharynx	/	/	/
3	1975 (9)	3	Nasopharynx, clivus	1:2	3-51	25
4	1998 (11)	4	Skull base, sacral	2:2	20-44	32
5	1999 (7)	2	Clivus	1:1	8-12	10
6	2001 (8)	10	Skull base, sacral	/	/	/
7[b]	2006 (18)	8	Skull base	1:3	/	/
8[b]	2006 (18)	3	Clivus	1:2	3-55	30
9	Present case	4	Clivus, nasopharynx	2:2	14-47	31

[a]Indirect essay quote; [b]these two cases are distantly related. /, no details reported.

father (II:2) presented with a clivus chordoma at the age of 44 and underwent removal via an endoscopic endonasal approach, followed by radiation therapy. The patient's paternal aunt (II:1) had presented with a clivus chordoma at the age of 47, which was also treated with endoscopic endonasal therapy and confirmed to be a chordoma pathologically. Furthermore, the son of this paternal aunt, an 18-year-old male (III:4) who also presented with symptoms of snoring, underwent an epipharyngoscopy and was confirmed with chordoma of the nasal region. Finally, the patient's paternal grandmother (I:2) had succumbed from an unknown cause during the fourth decade of life, with the symptoms of a chronic headache and deglutition disability. Among the remaining paternal family members, 3 members of a second aunt's family (II:3, III:5, III:6) suffered from snoring, but did not receive any examination. According to these clinical findings, a family pedigree was achieved (Fig. 3).

Discussion

Familial chordomas are rare, and among the cases discussed in the literature, only 8 familial chordomas have been reported (Table I) (6-13). Between 1998 and 2011, ~256 patients with skull base chordomas have been treated in the 7th Ward, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University (Beijing, China) (2-3). Only one case presented with a familial history, so the estimated incidence of familial chordomas was 0.4% (1/256) in all the chordomas.

Chordoma is characterized as slow growing, often with recurrence, mostly within 8 years (2-4). Studies have indicated that a Hispanic ethnicity, a small tumor size, a high socioeconomic status and surgical intervention are factors that favor good survival, while adjuvant radiation therapy is a controversial factor (14-16). In the present case, the diagnosis of a chordoma was suspected at presentation and later confirmed pathologically. When considering the radical resection of the tumor, staged surgery plus adjuvant radiation (γ-knife) was recommended for the 15-year-old female patient, and the outcome was good at the time of follow-up. The results of the present case were similar to a case reported by Chau *et al* (17), in which a combined endoscopic endonasal and posterior cervical approach was used, together with proton radiotherapy, in an 18-year-old male with a clivus chordoma (17).

Reviewing the literature, a female predominance can be found in the familial chordomas, with a male to female ratio of 1:1.8, which is the same as the gender difference in the skull base chordomas (6-13,18,19). Familial chordomas were most likely to occur in the area of the skull base; among the 8 families identified, only two cases within 1 family were reported in the sacrococcygeal region in 1958 (19), while the other cases mainly occurred in the skull base area (6-13), including the present case. The familial chordomas may have exhibited an early onset of symptoms, which made the age of diagnosis much younger than that of the sporadic chordomas, with the mean age of 29 and 40 years, respectively. More children and adolescents were diagnosed in the familial chordomas (1,6-13,18,19). In the present study, there were 2 adolescents (aged 15 and 18 years), and 2 adults (aged 44 and 47 years), with a mean age of 31 years. The younger generation of the family were diagnosed earlier than the older generation, possibly due to earlier onset of symptoms as well as better access to healthcare as a result of the improved economy.

The majority of the studies concerning the genetic mechanism of chordomas were primarily concerned with sporadic chordomas. The cause of chordomas has been largely unknown, however, gene deletions and gains have been noticed in the majority of cases (20,21), and chromothripsis has become a great focus of attention in the research of chordomas (22). The same is true in familial chordoma. In 1998, Stepanek *et al* (11) first suggested the autosomal dominant inheritance pattern. Afterward, several studies using different methods analyzed the gene abnormities in familial chordomas, and the 1p36.31-1p36.13 and 7q33 regions were found to be associated. However, the studies failed to obtain a consensus (7,8,10,23). A promising chordoma-specific gene, known as brachyury, localized in 6q27, was proved to be a key point in chordoma research during cell line experiments (24-26). This gene was a member of T-box family, containing a brachyury transcription factor, with a critical role in notochord development (25). In 2009, Yang *et al* analyzed 8 familial chordomas using high-resolution array-based

comparative genomic hybridization and combined genetic linkage analyses, suggesting that the T/brachyury homolog was a major susceptibility gene for familial chordomas (6). A recent study confirmed that an allele at rs2305089 of the T gene, located in the exon area and resulting in a Gly177Asp alteration, was strongly associated with chordoma (27,28). However, the Gly177Asp single nucleotide polymorphism site was not associated with chordomas in the Han Chinese population studied (29).

In the current study, a family with 4 pathologically confirmed skull base chordomas was presented. In general, familial chordomas are predominantly located at the skull base and are diagnosed at a younger age compared with sporadic chordoma. The T/brachyury homolog gene may be a causative gene in familial and sporadic chordomas, however, the genetic mechanism for chordomas remains unclear. Further genetic studies and long term follow-up are required for elucidation.

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