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Case Report

Surgical management of primary Ewing's sarcoma of the petroclival bone extend into the sphenoid sinus: A case report and review of literatures

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ABSTRACT

Background: Ewing's sarcoma (ES) is a malignancy that arises from bones or soft tissue, characterized by primitive small and round blue cells. Primary ES typically occurs in the long bones, vertebrae, or pelvis, and is extremely rare in the skull base.

Case Description: A 14-year-old girl presented with posterior cervical pain and dysfunction of multiple cranial nerves (CNs). Radiological investigation revealed a solid mass of the petroclival bone extending into the sphenoid sinus. The patient underwent endoscopic transsphenoidal surgery for diagnosis of the pathology, and partial resection was safely achieved. Histopathological, genetic, and radiological examinations confirmed the diagnosis of primary ES. Subsequently, the patient underwent adjuvant chemotherapy and radiotherapy following which the clinical symptoms resolved. Complete response was achieved after multimodal treatment. Twenty months after treatment, the patient remains in remission without recurrence or metastatic disease. Primary ES of the petroclival bone has been reported in only three cases in the literature. As seen in the present case, dysfunction of multiple CNs is the most common manifestation of petroclival ES. Diagnosis should be confirmed by histopathological and genetic examinations considering the nonspecific clinical symptoms and radiological features.

Conclusion: Multimodal treatment, including surgery, chemotherapy, and radiotherapy, can result in favorable outcomes. Clinicians should consider safe resection during surgical management to prevent complications that can delay postoperative multimodal treatment.

Keywords: Endoscopic transsphenoidal surgery, Ewing's sarcoma, Garcin syndrome, Petroclival, Sinonasal, Skull base

INTRODUCTION

Ewing's sarcoma (ES) is a malignancy that arises from bones or soft tissue, characterized by primitive small and round blue cells.[9] ES is relatively uncommon, accounting for 6%–8% of primary bone tumors, however, is the second most commonly encountered primary bone and soft-tissue cancer in children and adolescents.[4] This tumor is of neuroectodermal origin, arising from primitive neural crest cells.[2] Skeletal lesions of primary ES commonly occur in the diaphysis of long bones (47%) and pelvis (29%), followed by the ribs and vertebrae (12%), whereas extraskeletal

lesions occur in the soft tissue of the lower extremities, paravertebral tissue, chest wall, and retroperitoneum.[1,5] Primary ES of the cranium is extremely rare, accounting for 1% of the total cases. Only three cases of primary ES of the petroclival bone have been reported; therefore, the etiology is not well known.[1,7,8] Here, we report a rare case of primary ES of the petroclival bone extending into the sphenoid sinus that was successfully treated by endoscopic transsphenoidal surgery, adjuvant chemotherapy, and radiation, and discuss the clinical features and surgical management.

CASE REPORT

A 14-year-old girl who presented with the left posterior cervical pain and dysphasia was diagnosed with polyneuropathy due to reactive herpes virus infection by otolaryngologists. She was treated with antiviral drugs and adrenal corticosteroids; however, the symptoms worsened rapidly. Moreover, the patient developed hoarseness of voice due to vocal cord palsy 2 weeks after the initial manifestations. Additional investigations were performed considering the uncommon clinical course, and a skull base tumor was identified. The patient was referred to our department a month after the initial manifestations. Physical examination revealed left anterior and posterior cervical pain and multiple left cranial nerve (CN) palsies (glossopharyngeal, vagus, and accessory nerves). Serological examination did not reveal any obvious abnormalities. Computed tomography (CT) revealed enlargement of the left petroclival synchondrosis with osteoclastic changes and a soft-tissue mass within the adjacent sphenoid sinus [Figure 1]. Magnetic resonance imaging (MRI) revealed a heterogeneously enhanced en plaque lesion involving the left jugular foramen and hypoglossal canal, extending into the left sigmoid sinus [Figure 2a and b]. Whole spinal MRI and body positron emission tomography CT did not reveal any abnormal findings. Granulomatous diseases, such as Langerhans cell histiocytosis, metastatic tumor, and primary malignant bone tumor, were considered in the preoperative differential diagnosis based on the radiological findings.

Due to the rapid progression of clinical symptoms, the patient underwent endoscopic transsphenoidal surgery for diagnosis of the pathology. Intraoperatively, the tumor was found to extend into the sphenoid sinus and underlie the edematous mucosa of the sinus [Figure 3a]. The tumor was soft and relatively hypovascular, and was resected in sections [Figure 3b]. The majority of the tumor was smoothly detached from the adjacent mucosa; however, it was partially adherent to the clival region, which was presumed to be a consecutive lesion with a petroclival component [Figure 3c]. No obvious cerebrospinal fluid (CSF) leakage was observed.

Histopathological examination revealed a lesion composed of round cells with clear cytoplasm and uniformly round nuclei

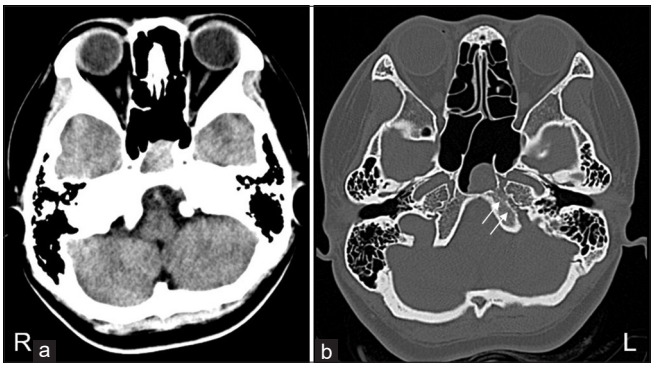

Figure 1: Preoperative computed tomography (CT) findings. Initial CT image on admission showing tumor in the sphenoid sinus (a) and destructive changes in the left petroclival synchondrosis (arrow) (b).

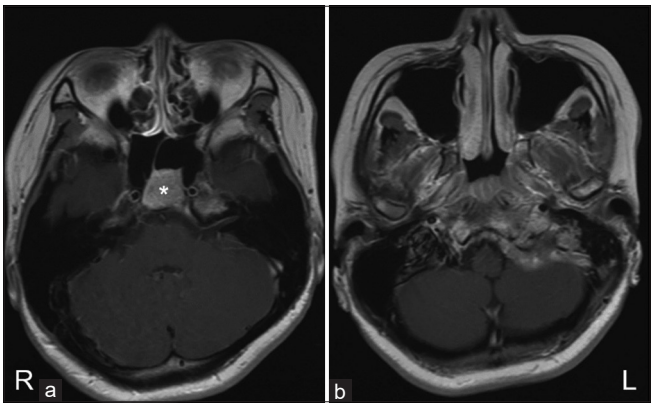

Figure 2: Preoperative magnetic resonance imaging findings. Contrast-enhanced T1-weighted image showed the sphenoid sinus lesion with homogenous enhancement (*) (a). The tumor involved several skull base structures and extend into posterior fossa (b).

[Figure 4a]. The tumor cells were immunohistochemically positive for CD99 [Figure 4b]. Although interphase fluorescence *in situ* hybridization (FISH) did not reveal translocation of the Ewing sarcoma breakpoint region 1 (*EWSR1)* gene (22q12), *EWSR1*-friend leukemia virus integration site 1 (*FLI1)* gene fusion was screened by quantitative real-time polymerase chain reaction (RT-PCR). The findings confirmed the diagnosis of primary petroclival ES.

Subsequently, the patient underwent adjuvant multidrug chemotherapy and radiotherapy. Five cycles of adjuvant chemotherapy using vincristine (2 mg/m^2), doxorubicin (37.5 mg/m2), and cyclophosphamide (1200 mg/m^2), alternating with etoposide (100 mg/m^2) and ifosfamide (1800 mg/m^2) combined with G-CSF, were performed every 2–3 weeks along with intensity-modulated radiation therapy (60 Gy/30 fractions). In addition, two cycles of chemotherapy using vincristine and cyclophosphamide, alternating with etoposide and ifosfamide, were performed at 2-week intervals. The patient experienced

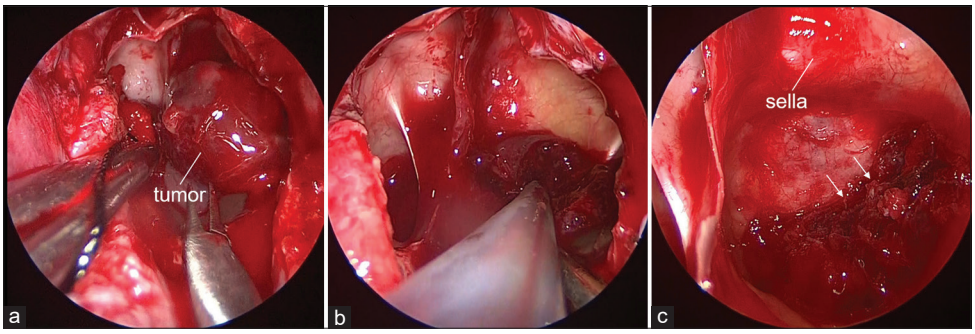

Figure 3: Intraoperative findings. The tumor exposed by the transsphenoidal approach underlying the edematous sphenoid sinus mucosa (a). The tumor was relatively fibrous and was resected using ultrasound aspirator (b). Residual tumor connected to the petroclival lesion through the destructive clivus (allows) (c).

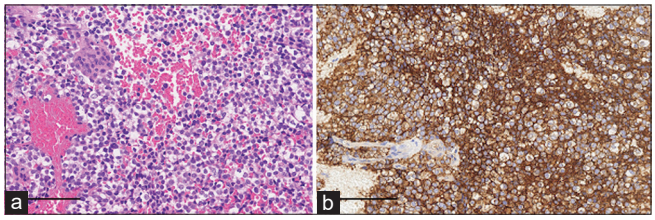

Figure 4: Hematoxylin-eosin staining of tumor cells and immune histochemical staining of CD99. HE staining showed proliferation of atypical round cells with hyperchromatic nuclei, containing some myotonic figures (a). Immunohistochemical staining showing CD99 expressions in the cell membrane (b).

anemia, neutropenic fever, and thrombocytopenia. Complete response was achieved 9 months after adjuvant chemotherapy. At the 22-month post-surgical follow-up, the patient had recovered well with no clinical or radiological evidence of recurrence or metastatic disease [Figure 5].

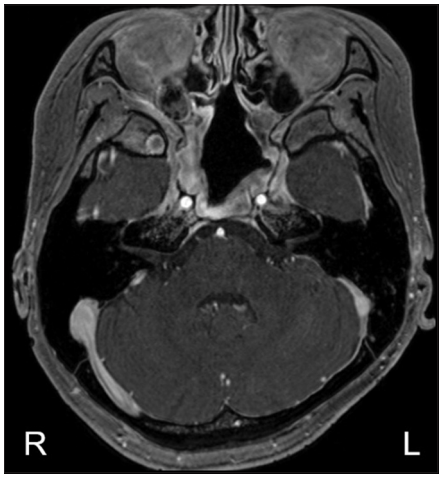

Figure 5: Postoperative magnetic resonance imaging findings (22 months after). Contrast-enhanced T1-weighted image showing that thickening of the sinus mucosa due to sinusitis, however, elimination of the petroclival tumor that had extended into the surrounding structures.

DISCUSSION

Primary ESs of skull base involvement are extremely rare, and to date, only three cases of primary ES of the petroclival bone have been reported [Table 1].[1,7,8] The four reported cases include two male and two female patients. Most of patients are younger with a median age of 23 years (14–72). CN palsy is common in cases of petroclival ES, with the majority of the patients presenting with multiple CN palsies (75%). Abducens nerve palsy was observed in three patients; trigeminal, glossopharyngeal, vagus, accessory, and hypoglossal nerve palsies in two patients, and oculomotor, trochlear, facial, and vestibular nerve palsies were observed in one patient. The tumor extended into the surrounding structures, such as the petrous and occipital bones (50%), sphenoid sinus (25%), and sellar and parasellar regions (25%). Extensive debulking was performed in one patient, and the other three patients underwent partial resection including biopsy. After surgery, radiotherapy and adjuvant chemotherapy were performed in all patients. CN palsy improved in three patients several months after the treatment. The majority of the patients demonstrated a good prognosis after multimodal treatment. Based on the findings of the reported cases, it may be considered that ES of the petroclival bone develops with primitive osteoclastic changes in the surrounding structures and is likely to cause several CN symptoms. Moreover, CN palsies developed within a short period in most of cases. This suggests that clinicians should consider surgery or biopsy for diagnosis before progression to multiple CN palsies.

In cases of primary ES of the cranium, initial diagnosis can be difficult due to nonspecific clinical symptoms and radiological features. Therefore, the diagnosis should be confirmed by histopathological and genetic examinations. ES is characterized by primitive small round cells with high nuclear to cytoplasmic rate arranged in a sheet pattern.[10] Strong expression of the cell surface glycoprotein CD99 is also an important feature of ES.[2] In molecular genetic studies, ES is characterized by translocation of the *EWSR1* gene, which

Table 1: The summary of primary Ewing's sarcoma of the petroclival bone.

References	Age/ sex	Tumor extension	Clinical presentation	Diagnosis	Surgery	Radiation	Chemotherapy	Recurrence	Prognosis (follow-up)
Balasubramaniam, 2008	17/M	Petrous temporal bone occipital bone	Three-month history of headache, CN V–XII paresis, cerebellar signs, obstructive hydrocephalus	CD99+, vimentin (IHC)	Craniotomy (extensively debulking)	Done (40-50 Gy)	Iodophosphamide, ETP, VCR, DXR, CPA	-	The CN palsy improved tumor regression (12 months)
Thakar, 2012	29/M	Sellar and parasellar sphenoid sinus	Three weeks history of headache, vomiting, CN III–VI palsy	CD99+ (IHC)	eTSS	Done	VCR, DXR, CPA, actinomycin-D	NL	Death (3 weeks, multiple metastasis)
Schartz, 2020	68/F	Petrous apex cavernous sinus	Retro-orbital headache, diplopia, adenopathy, trismus, numbness, nasal congestion, recent epistaxis, CN VI palsy	Rearrangement of EWSR1 (FISH), EWSR1/FLI1 fusion (RT-PCR), CD99 + (IHC)	eTSS (biopsy), neck lymph node biopsy	Done	Dactinomycin/ CPA alternating with IFM/ETP	-	The CN palsy improved tumor regression (1 month)
Present case	14/F	Sphenoid sinus occipital bone	Two-month history of cervical pain, CN IX–XII paresis	EWSR1/FLI1 fusion (RT-PCR), CD99+ (IHC)	eTSS	Done (60 Gy)	VCR, DXR, CPA, alternating with ETP, IFM	-	The CN palsy improved maintain CR (22 months)

M: Male, F: Female, CN: Cranial nerve, CD: Cluster of differentiation, IHC: Immunohistochemistry, FISH: Fluorescence in situ hybridization, RT-PCR: Real-time polymerase chain reaction, eTSS: Endoscopic transsphenoidal surgery, ETP: Etoposide, VCR: Vincristine, DXR: Doxorubicin, CPA: Cyclophosphamide, IFM: Ifosfamide, NL: No listed, CR: Complete response

is located on chromosome 22q12. *EWSR1* is frequently fused with the *FLI1* gene, which is located on chromosome 11q24, in approximately 85% of the cases of ES.[2] A previous study described the sensitivity and specificity of the FISH assay as 91% and 100%, respectively, whereas RT-PCR had a sensitivity of 54% and a specificity of 85%. Moreover, RT-PCR was less sensitive in formalin-fixed paraffin-embedded tissues than in frozen tissue.[3] In the present case, translocation of the *EWSR1* gene (22q12) was not detected in the FISH assay; however, the *EWSR1-FLI1* gene fusion was detected in frozen tissue by RT-PCR. It is important to obtain both frozen and paraffin-embedded samples for accurate diagnosis and to consider molecular testing with multiple methods in addition to histopathological studies.

Regarding surgical management, previous reports have recommended that tumor resection should be as radical as possible.[1,6,7] However, radical tumor resection may be difficult in skull base lesions due to the inclusion of or proximity to critical structures. Among the current treatment protocols for primary ES, multimodal treatment including a combination of radiation therapy, chemotherapy, and surgery can result in a cure rate of ≥50%.[2] Moreover, adjuvant multimodal treatment may lead to recovery or improvement of CN palsy after several months.[1,7] Safe and minimally invasive surgery for diagnosis of the pathology and subsequent multimodal treatment without delay is a valuable strategy for patients with primary petroclival ES.

CONCLUSION

Primary ES of the petroclival bone is extremely rare and can commonly extend into the surrounding critical structures. Multimodal treatment can result in favorable outcomes, and

improvement in CN palsy can be observed several months after the treatment with regular follow-up. Therefore, to avoid delay in the induction of postoperative treatment, safe resection of the tumor without any complications rather than radical resection should be considered in cases of primary skull base ES associated with multiple CN palsies.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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