

Clinical, radiological, surgical, and pathological determinants of olfactory groove schwannoma

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ABSTRACT

Background: Olfactory groove schwannomas (OGS) are rare anterior cranial fossa base tumors with only 41 cases reported in literature. Olfactory ensheathing cell schwannoma (OECs) has similar clinico-radiological features as OGS, but a different cell of origin. In recent years, there is growing interest in OECs as more cases are being reported. **Aims:** The objective was to study the clinico-radiological features of OGS and define the histological differentiation from OECs. **Materials and Methods:** We retrospectively analyzed clinical, radiological, surgical and histopathological picture of all cases of OGS managed in our institute. Immuno histochemical studies were performed in these tumors for differentiating from OECs. A comprehensive review of articles published until date describing the operative treatment was done. **Results:** All three cases had presented with seizures, two had anosmia and papilledema. Gross-total resection was achieved in all our patients. One patient expired in the postoperative period due to septicemia. Positive expression to newer immuno histochemical biomarker CD57 (Leu7), with negative staining to smooth muscle α -actin (SMA) was helpful in confirming the diagnosis of OGS and differentiating it from OECs in all our cases. **Conclusions:** OECs, though rare has to be differentiated from OGS using immuno histochemistry. Gross-total resection of OGS with preservation of olfactory function is often possible and curative. Although these tumors are commonly treated with microsurgical skull base approaches, an endoscopic endonasal approach can be considered in some cases, with repair using mucoperiosteal pedicled flap to prevent cerebrospinal fluid leak.

Key words: Leu7 (CD57), olfactory ensheathing cell schwannoma, olfactory groove schwannoma, olfactory tract, smooth muscle α -actin

INTRODUCTION

Nerve sheath tumors arising from the anterior cranial fossa (ACF) base are uncommon. They usually arise in relation to olfactory groove. Only 41 cases of olfactory groove schwannoma (OGS) have been found to be reported until date, the clinico-radiological features of which are summarized in two reviews.^[1,2] Most of these cases were misdiagnosed before surgery as olfactory groove meningiomas, especially those cases presenting without anosmia. Yasuda *et al.* in 2006 described a new entity called olfactory ensheathing cell schwannoma

(OECs) that has similar clinico-radiological features as OGS, but a different cell of origin.^[3] Recently, there is growing interest in this tumor as more cases are being reported.^[4-9] These cells share similar morphological and immunohistochemical features with Schwann cells. Hence, we cannot differentiate OGS from OECs by using routine histopathological methods. Newer immunohistochemical markers can help in differentiating these two tumors. Classically, OECs do not express CD57 (Leu7), though schwannomas have a positive expression.^[3-9] However, 20% of schwannomas can be negative for CD57 (Leu7). Two new biomarkers, smooth muscle α -actin (SMA) and calponin (actin binding contractile proteins in smooth muscle) have been identified to be expressed by olfactory ensheathing cells (OECs).^[10] Hence, we suggest that immuno histochemical studies with these biomarkers should be performed before confirming the diagnosis of OGS. We reviewed the clinical, radiological, surgical, and histopathological findings of all cases of OGS managed

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in our institute. The immunohistochemical methods to confirm schwannoma in this location has been discussed.

CLINICAL DATA

The clinical and radiological details of 3 cases of OGS surgically managed in our Institute from 1998 to 2011 were reviewed from the medical records and the image archives. The histopathological slides were reviewed and immuno histochemical studies were done using the tissue blocks.

Case 1

A 22-year-old gentleman presented with history of generalized tonic-clonic seizures of 8 years, headache and blurring of vision for 3 months. On examination, he had bilateral anosmia and bilateral papilledema. Cranial imaging [Table 1] revealed a well-defined, lobulated, midline ACF mass lesion with a homogenously enhancing solid component inferiorly and nonenhancing cystic components postero-superiorly [Figure 1]. The diagnoses considered included meningioma, esthesioneuroblastoma, and fungal granuloma. At surgery, the tumor was extra-axial, well encapsulated, soft, yellowish, hypo vascular, and attached to the cribriform plate. A large cyst was found posterior to the lesion. Computed tomography (CT) scan done postoperatively confirmed total resection.

Histopathology [Figure 2] revealed a lobulated, partially circumscribed tumor with characteristic biphasic pattern having compact Antoni A and loose Antoni B zones with verocay bodies and xanthomatous change [Figure 2a and b]. No nerve root origin could be discerned in the material submitted. Immunohistochemistry revealed strong diffuse positivity in tumor cells for S-100 protein (nuclear and cytoplasmic) [Figure 2c]. The tumor cells were also diffusely positive for Vimentin (2D). Epithelial membrane antigen (EMA) was negative excluding meningotheial origin [Figure 2e]. However, glial fibrillary acidic protein (GFAP) was positive in this case [Figure 2f]. Desmin was negative in

tumor cells [Figure 2e]. Immunostaining for Leu7 (CD57) also revealed patchy labeling of tumor cells [Figure 2g]. MIB-1 labeling index was low [Figure 2h]. SMA was negative in the tumor though positive in vascular smooth muscle [Figure 3] excluding OECS. The radiological, surgical and histopathological findings were consistent with a schwannoma arising from the olfactory groove. Patient succumbed to sepsis and expired on third postoperative day. Blood culture and postmortem lumbar cerebrospinal fluid (CSF) grew *Klebsiella*, which was multidrug resistant.

Case 2

A 20 years female, 3 months postpartum presented with one episode of generalized tonic-clonic movements followed by unresponsiveness. She complained of nonspecific intermittent headache for 1½ years. On examination, she had bilateral anosmia and papilledema with no evidence of other focal neurological deficits. There were no frontal lobe signs. Cranial imaging [Table 1] revealed a large heterodense lesion with specks of calcification located in the frontal region [Figure 4]. A diagnosis of olfactory groove meningioma was made. Per operatively, the lesion was extra-axial, well-encapsulated, soft, yellowish and highly vascular, attached to olfactory groove without obvious attachment to olfactory tract, which was preserved.

Histopathology revealed large lobules of tumor that were highly vascular punctuated with large dilated ectatic thick walled vessels embedded in a fibrous stroma. Tumor was paucicellular with islands of spindled cells distributed in clusters with wavy nuclei forming verocay bodies in addition to perivascular foci of calcification/ossification. Immuno-histochemistry revealed diffuse S-100 protein expression in tumor cells (nuclear and cytoplasmic), Vimentin was diffusely positive, Leu7 (CD57) labeled tumor cells in foci and GFAP was negative [Figure 2f]. EMA was negative (entrapped meningotheial cells positive), CD34, SMA and desmin were negative in tumor cells, though positive in vessels. MIB-1 was very low (<0.5%). The radiological, surgical,

Table 1: Radiological features of index cases compared with those previously reported^[1,2]

Features	Case 1 (Figure 1)	Case 2 (Figure 4)	Case 3	Previously reported cases in literature ^[1,2] (n=41) (%)
Aspect	Solid, large peri-tumoral cysts	Solid	Solid	Solid 25 (60.9), cystic 11 (26.8)
Enhancement	Intense heterogeneous enhancement of solid areas	Intense heterogeneous enhancement of solid areas	Well	Heterogeneous 22 (53.6), homogeneous 14 (34)
Bone erosion	Present	Present	Unknown	Present 17 (41)
Calcification	No	Yes	No	Seen 6 (14.6)
Microbleeds on Gradient/SWI* images	Yes	Yes	NA	NA
DWI**	Restricted	Restricted	NA	NA
Solid	Facilitated	Facilitated		
Cystic				

*SWI – Susceptibility weighted imaging; **DWI – Diffusion-weighted imaging; NA – Not available

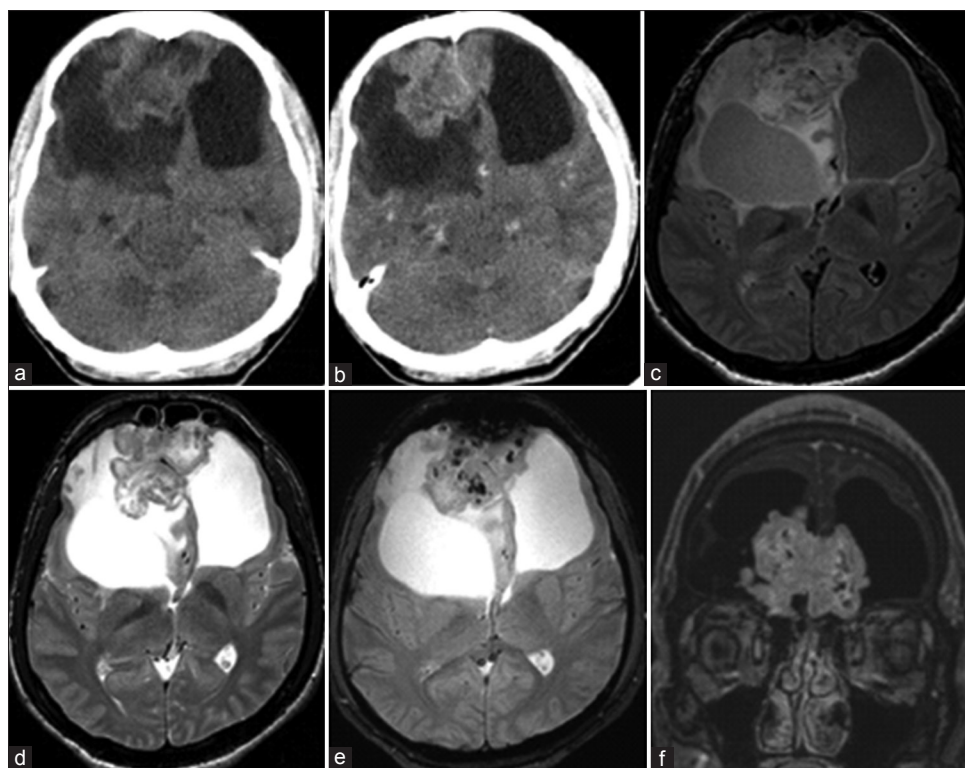


Figure 1: (a and b) Preoperative plain and postcontrast computed tomography (CT) images. (c-f) represents preoperative fluid attenuation inversion recovery, T2-weighted imaging, gradient and postcontrast images, respectively. Images are showing solid and cystic lesion in the anterior cranial fossa with enhancement of the solid component. Cystic part are compressing and splaying the anterior horn of the lateral ventricles. No calcifications are seen on the CT imaging. T2*-weighted gradient-echo image show multiple foci of hypo intensities suggestive of micro-bleed. Paranasal sinuses are free from the tumor (preoperative imaging: CT and magnetic resonance imaging of Case 1)

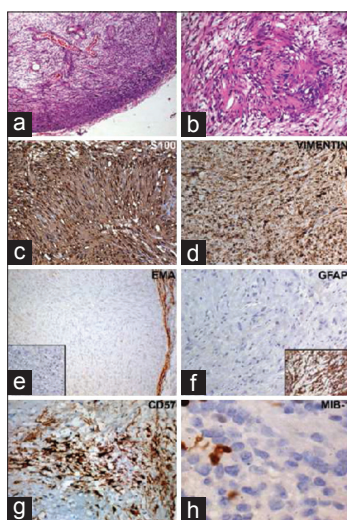


Figure 2: H and E, staining shows partially circumscribed tumor with compact fascicles of Schwann cells (a) and verocay bodies (b). Immunohistochemistry revealed strong diffuse positivity in tumor cells for S-100 protein (nuclear and cytoplasmic) (c) and Vimentin (d). Epithelial membrane antigen (EMA) (e) and glial fibrillary acidic protein (GFAP) (f) were negative in tumor cells, except in Case 1 with GFAP positivity (f, inset). Note preserved EMA reactivity in normal meninges (e). Desmin was negative in tumor cells (e, inset) (g and h) Immunostaining for Leu7 (CD57) also revealed patchy labeling of tumor cells (g). MIB-1 labeling index was low (h) (histopathology and immunohistochemical studies of Case 1) (a: H and E, \times Obj. 5, b: H and E, \times Obj. 20, c, d, f, g: Immunoperoxidase \times Obj. 20, e: Immunoperoxidase \times Obj. 10, e, f inset \times Obj. 20, h: MIB-1 \times Obj. 40)

and histopathological findings were consistent with a schwannoma arising from the olfactory groove. At 18 months follow-up, the patient is having no neurological deficits and has regained olfaction. Follow-up magnetic resonance imaging (MRI) showed no recurrence of the lesion [Figure 4f].

Case 3

A 45-year-old man presented with a history of intermittent headaches of 6 months duration and generalized tonic-clonic seizures in clusters 2 days prior to admission. Neurological examination revealed evidence of bilateral papilledema without any focal neurological deficit. Olfaction was intact bilaterally. Cranial CT scan revealed a midline isodense, enhancing, well-circumscribed, spherical extra-axial tumor in the right frontobasal region adjacent to the anterior falx. A diagnosis of olfactory groove meningioma was made. At surgery, the tumor was found attached to the olfactory groove on the right side, where the bone was scalloped. The olfactory bulbs or tract could not be identified. CT scan done after surgery had confirmed total excision of the lesion. He had transient CSF leak in the postoperative period, which subsided on conservative management.

Histopathology was characteristic of a schwannoma with biphasic compact and loose zones, Verocay bodies and hyalinized stroma. Immunohistochemistry revealed diffuse positivity for S-100, and Vimentin, focal positivity for Leu7 (CD57) but negative for GFAP, EMA and SMA. MIB-1 labeling was low (1%). Patient was asymptomatic on follow-up after 14 years, with preserved olfaction on the left side and no recurrence in CT scan.

Family history or cutaneous markers suggestive of

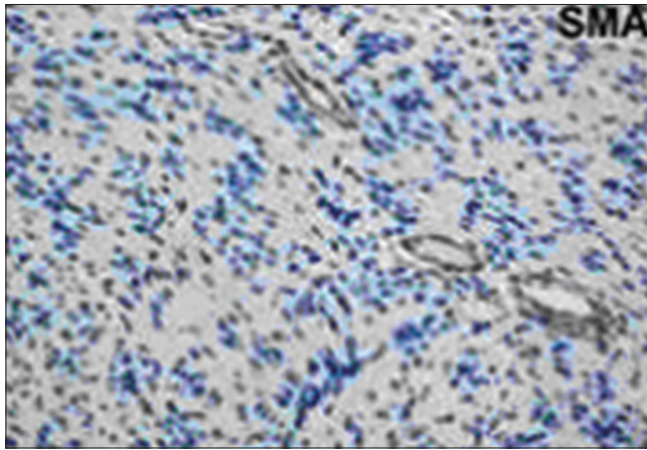


Figure 3: Immunostaining for smooth muscle actin was negative in tumor cells though positive in normal vascular smooth muscle (immunohistochemical study of Case 1)

Neurofibromatosis could not be identified in any of our patients.

DISCUSSION

Olfactory groove schwannoma was first reported by Sturm *et al.* in 1968.^[11] Since then individual case reports describing the features of OGS had appeared in literature. We reviewed two, recent meta-analysis of OGS.^[1,2] On combining these, we found that only 41 cases of OGS have been reported until date. The more common lesions originating from ACF base include meningioma, esthesioneuroblastoma, fungal granuloma, squamous cell carcinoma and adenocarcinoma (metastases).^[1,2] Olfactory nerve as an extension of central nervous system (CNS) lacks Schwann cells. So far, various theories have been put forward to explain the origin of OGS and include developmental and nondevelopmental hypothesis.^[12,13] The former suggest transformation of mesenchymal pial cell into ectodermal Schwann cells or migration of the neural crest cells within the substance of the CNS. The latter suggests that these schwannomas may arise from Schwann cells of adjacent normal structures like the perivascular nerve plexus, meningeal branches of the 5th cranial nerve and anterior ethmoidal nerve innervating the ACF and olfactory groove.^[12-14] OECS has similar morphological

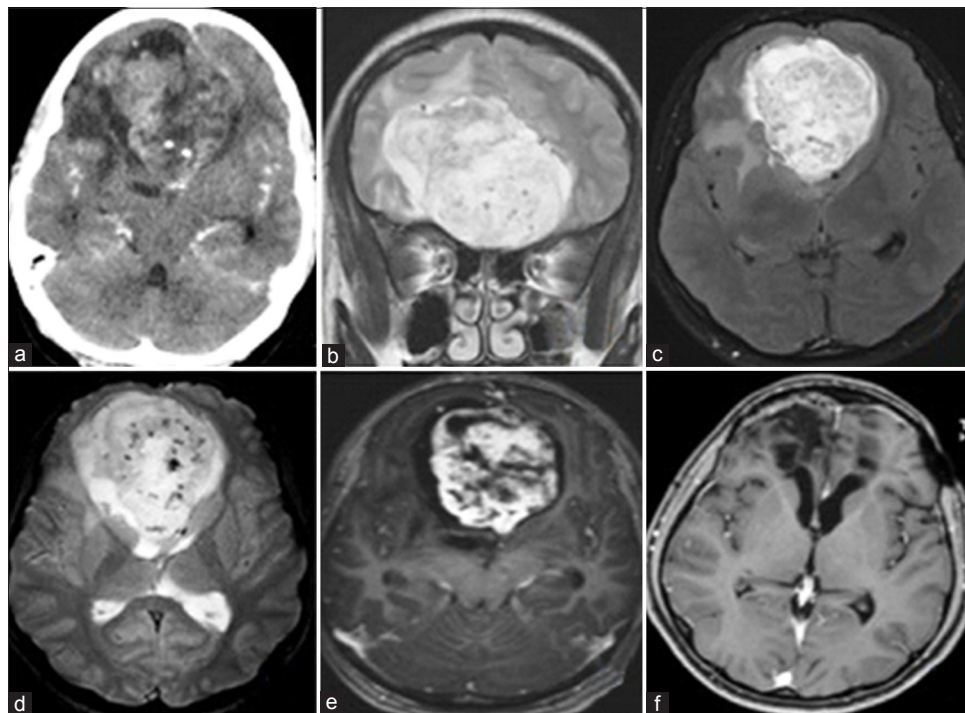


Figure 4: (a) Shows post-contrast computed tomography (CT) images. (b-f) Show T2-weighted imaging coronal, fluid attenuation inversion recovery, gradient, post contrast and 18 months post-contrast follow-up images, respectively. They show large lobulated mass lesion in the floor of anterior cranial fossa having both cystic and solid components. Heterogeneous postcontrast enhancement of the solid component noted. Two foci of calcifications are seen on CT scan. Multiple foci of micro-bleeds appearing hypointense on T2*-weighted gradient-echo image. Postoperative follow-up postcontrast image after 18 months show complete removal of the tumor with no recurrence in the anterior cranial fossa (preoperative CT, magnetic resonance imaging [MRI] and follow-up MRI of Case 2)

features of OGS.^[3] Embryologically, OECs derive from olfactory placodes, whereas Schwann cells originate from the neural crests.^[4]

We compared the clinical features of our patients with those reported previously^[1,2] [Table 2]. Two of our patients were of younger age compared to the previously reported cases. Headache and seizures were the most common symptoms in our cases also. Contrary to popular belief, many patients had normal olfaction preoperatively (39.5%). Both of our cases had intact olfaction on follow-up supporting the theory that the tumor may not be arising from the olfactory nerve. Olfactory groove was found to be the most common site of attachment of tumors in the reported cases. This was also observed in all our cases; however a normal olfactory tract was identified pre operatively and preserved in 1 case only.

Radiology

Computed tomography scan usually shows a well-circumscribed, lobulated ACF mass lesion with both solid and cystic areas and heterogeneous enhancement following contrast administration. Erosion of the crista galli is usually noted and was seen in two of our cases. Presence of calcification is rare in OGS and is usually suggestive of meningioma. One of our cases who had presented with postpartum seizures had specs of calcification on imaging. Hence a preoperative clinical diagnosis of meningioma was made. Radiologically, the absence of hyperostosis and presence of bone erosion on imaging are clues to suspect OGS.

Magnetic resonance imaging usually reveals a lobulated, heterogeneous, intensely enhancing extra-axial mass lesion in the floor of ACF. Focal high signal intensity on T1-weighted imaging seen in our case was suggestive of intratumoral hemorrhage. The T2*-weighted gradient-echo MRI/susceptibility weighted imaging (SWI) reveal multiple, small hypo intensities within the tumor due to micro-bleeds.^[15,16] On apparent diffusion coefficient mapping, increased diffusion in cystic areas and occasional restricted diffusion in the solid areas due to high cellularity are seen. In two of our cases, both solid

and cystic areas were present. T2*-weighted gradient-echo MRI images revealed micro-bleeds. On contrast enhanced images, dural tail was absent. These features helped in differentiating it from other ACF tumors such as meningioma, metastatic tumors, esthesioneuroblastoma and fungal granuloma. The adjacent para nasal sinuses were normal. Intranasal extension was seen in none of our patients. Follow-up imaging showed no recurrence in both the patients confirming that gross-total resection is usually curative.

Histopathology

All cases were reviewed with routine histopathology studies. They all had features diagnostic of schwannoma. Immunohistochemistry is essential to differentiate OGS from OECS, a recently described entity with only 7 cases on record.^[3-9] OECs are glial cells that ensheath the olfactory nerve axons. They share similar morphological and immunohistochemical features including S-100 positivity with Schwann cells. OECs tumor lacks Leu7 (CD57) expression, whereas Schwann cells are positive for Leu7.^[3-9]

Leu7 (CD57), also known as (human natural killer-1) is a carbohydrate epitope that contains a sulphoglucuronyl residue and is present in several adhesion molecules expressed in the CNS. It is expressed in up to 20% of lymphocytes (T lymphocytes or natural killer cells), epithelial, neural and chromaffin cells.^[17,18] Its expression is seen in large granular cell leukemia, small cell carcinoma, neural and carcinoid tumors. Antibodies to Leu-7 also recognise a component of myelin associated glycoprotein, hence reported as an important marker of Schwann cells and nerve sheath tumors.^[19] However, there are few immunohistochemical studies that have evaluated Leu7 (CD57) reactivity in cases of OGS,^[20-22] and 20% of tumors considered to be schwannomas are, in fact, Leu7 negative.^[23] Three conventional biomarkers for OEC are GFAP, p75 neurotrophin receptor, a marker for non myelinating Schwann cells and S-100, that it shares with Schwann cells. Recently, in addition these, two new biomarkers, SMA and calponin (actin binding contractile proteins in smooth muscle) have

Table 2: Clinical features of index cases compared with those previously reported^[1,2]

Clinical features	Case 1	Case 2	Case 3	Previously reported cases in literature ^[1,2] (n=41) (%)
Age (in years)	22	20	45	Mean 32.2±13.7
Gender	Male	Female	Male	Male:female=28:13:2.2:1
Main symptoms				
Head ache	Yes	Yes	Yes	22
Convulsions	Yes	Yes	Yes	17
Olfaction	Anosmia	Anosmia	Intact	Normal 17 (39.5), anosmia 24 (46)
Attachment	Olfactory groove	Olfactory groove	Olfactory groove	Olfactory groove 34, skull base 2, ethmoid sinus 1
Olfactory tract	Not seen	Not involved	Not seen	Not seen 13, involved 6, not involved 2, thinned 6

been identified to be expressed by these specialized cells both *in vitro* and *in vivo* and not by Schwann cells.^[10] SMA, is a differentiation marker of smooth muscle cells, constituting the microfilament system of the cytoskeleton of the smooth muscle, essential for contractility of these cells. It is abundantly expressed in vascular smooth muscle, intestinal muscularis mucosae and muscularis propria, as well as myofibroblasts, myoepithelial cells and pericytes that have contractile property.

All our cases had focal positivity for Leu7 (CD57). In Case 1, though diffuse GFAP positivity was seen in addition to S-100, the tumor cells failed to express SMA excluding the possibility of OECS tumor. Case 2 expressed only S-100 and was negative for GFAP and SMA confirming the diagnosis of OGS schwannoma. Case 3 revealed diffuse positivity for S-100 and vimentin, but were negative for GFAP, EMA and SMA. The variability in GFAP expression reflects different populations of olfactory glia – Schwann cell like and astrocyte like in the olfactory bulb. This study suggests negativity of SMA along with presence of Leu7 (CD57) expression can be used to confirm the diagnosis of OGS.

Surgical principles

Total surgical excision has to be done by careful extra arachnoidal dissection preserving the olfactory tracts. This is possible as the tumor is well-encapsulated and a plane of cleavage from olfactory tract is often seen. The tumor has to be decompressed intracapsularly before dissecting in the region of olfactory groove. Use of bipolar cautery at this region also has to be restricted to prevent damage to olfactory tract. This has prognostic significance as the patients often recover their olfactory function after surgery. Though routine ACF base repair is not advised, we have to be vigilant for CSF rhinorrhea during the postoperative period. Expanded endoscopic endonasal resection of an olfactory schwannoma has been described by Kanaan *et al.* in a pediatric patient as a strategy to minimize risk of brain retraction.^[20] In recent times, Ogino-Nishimura *et al.* has described endoscopic endonasal excision of OECS tumor in a similar way.^[8] Olfactory nerves were identified and preserved as CUSA assisted intra capsular decompression was done. Mucoperiosteal pedicle flap was used to close the defect, thereby emphasizing the need for proper ACF base repair in selected cases with bone destruction.

Prognosis

Olfactory groove schwannomas are benign lesions (MIB labeling was low in our cases - 0.5-1%), wherein surgical excision is the treatment of choice. Antiepileptic treatment has to be continued postoperatively for a longer duration as both our patients had recurrent seizures after

a long duration. These cases may have a propensity for seizure recurrence if antiepileptic is stopped early. On 14 years follow-up, our case had no recurrence confirming that total excision is often curative.

CONCLUSION

Olfactory groove schwannoma, though rare, should be considered in differential diagnosis of the ACF tumor presenting with seizures and anosmia. Radiologically, this can be differentiated from meningioma by the presence of bone erosion in the anterior cranial base and presence of micro-bleeds in SWI MRI, with absence of dural tail. Immunohistochemical studies using SMA along with Leu7 (CD57) have to be done in all cases before confirming the diagnosis of OGS. The variability in GFAP expression in OGS reflects Schwann cell like and astrocyte like populations of glia in the olfactory bulb. OGS are benign lesions where surgical excision with preservation of olfaction is the treatment of choice. Expanded endoscopic endonasal resection can be considered in selected cases, with careful repair of the defect using mucoperiosteal pedicled flap.

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