Challenging Management of Plexiform Schwannoma and Plexiform Neurofibroma

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Challenging management of plexiform schwannoma and plexiform neurofibroma

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ABSTRACT

Plexiform variants of neurofibromas and schwannomas are rare and typically arise in superficial soft tissues in the head and neck region. The treatment of these tumors is challenging and no generally accepted guidelines exist for their optimal management. The purpose of this study was to review the management and long-term prognosis of head and neck plexiform neurofibromas and schwannomas at 2 tertiary- care academic hospitals in Finland over a 31-year period. The pathology files were searched for plexiform neurofibromas and schwannomas between the years 1990- 2020. The case notes were reviewed for full management details. Two plexiform schwannomas and 6 plexiform neurofibromas were identified. Five of the 6 plexiform neurofibromas were managed operatively. All patients with a surgically managed plexiform neurofibroma underwent multiple operations. Sclerotherapy abolished 1 patient's cutaneous plexiform neurofibromas. The management of plexiform neurofibromas and plexiform schwannomas remains challenging. Sclerotherapy may offer a promising management option for cutaneous plexiform neurofibromas.

INTRODUCTION

World Health Organization (WHO) 2020 classification lists all mesenchymal tumors together as tumors of soft tissue and bone (1). Among these, the entity of peripheral nerve sheath tumor (PNST) includes neurofibromas and schwannomas. Like 90-95% of PNSTs, they are benign in origin (2), but their symptoms are highly variable depending on the site of the lesion. Different variants of neurofibromas and schwannomas are listed in Supplemental Table 1. A plexiform schwannoma (PS) typically originates in superficial soft tissues showing partiality for the head and neck region (3) (Supplemental Table 2). A plexiform neurofibroma (PN) occurs in subcutaneous or deep peripheral nerves and, like neurofibromas in general, is seen in patients with neurofibromatosis type 1 (NF1) (1). Up to twenty percent of PNs may undergo transformation into malignant peripheral sheath tumor (MPNST) (4). This highlights the importance of correct diagnosis of these tumors.

Due to the rarity of these tumors, only scarce data exist in the literature concerning the radiological features of a plexiform PNST, and especially of a PS. More information is

available on non-plexiform nerve sheath tumors. On computed tomogram (CT) scans, PNSTs tend to show relatively low attenuation (5-25 Hounce field units) (5) and well- defined margins. The latter may be absent in plexiform tumors, which are characterized by multinodular or diffusely infiltrative growth pattern. The signal intensity of a PNST on magnetic resonance imaging (MRI) is often non-specific (iso- or hypointense relative to muscle on T1, and iso- or hypointense relative to fat on T2) and heterogenous (6). Enhancement can be variable; it is usually heterogenous in larger tumors, and more evident on MRI than on CT. The characteristic target sign (central hypointensity on T2) is only evident in about half of the cases and is reported more frequently in association with neurofibromas (7). The most useful signs that are suggestive of neurogenic tumor origin are proximity to major nerves, nerve entering or exiting the tumor (tail sign), and a surrounding fat rim (split fat sign) (5, 7, 8), but these signs may become obscured in plexiform variants.

Information about the management of a PS/PN is equally scarce in the literature. While surgery remains the main treatment option for these tumors, complete removal of PS/PN can be unachievable due to involvement of multiple nerve fascicles and substantial vascularity. While PNs possess a 20% recurrence rate (9), PSs may recur if incompletely excised (1).

The purpose of this study was to assess the management of a head and neck PS/PN and its success at 2 tertiary academic teaching hospitals over 3 decades. Practical suggestions are given for improved management of both tumor types.

MATERIAL AND METHODS

The pathology files of the 2 tertiary-care academic centres were searched for plexiform schwannomas and neurofibromas over a 31-year period (1990-2020). Two plexiform schwannomas and 6 plexiform neurofibromas were identified. Medical charts were reviewed for patient and tumor characteristics including operative and radiological details.

RESULTS

Case reports

Case 1.

A previously fit and well 48-year-old male was referred to the ENT Department with a 10-year history of an asymptomatic swelling in the left tonsillar area. There had been no subjective growth in the area. On examination an egg-shaped swelling was seen behind the left anterior tonsillar pillar. MRI scan showed multiple tumor nodules up to 6 cm in greatest diameter, extending from the retropharyngeal space into the cervical soft tissues along the cervical plexus (Fig. 1a, b). A histopathological analysis of a surgical biopsy of one of the tumors was consistent with schwannoma. A control MRI 2 months after the biopsy showed no increase in the tumor size. A multidisciplinary tumor board recommended removal of the most prominent part of the largest tumor because of the over 50% narrowing it caused in the oropharynx. An encapsulated oro- and parapharyngeal tumor nodule with a diameter of 6 cm (Fig. 1c) was removed through an intraoral approach without intraoperative complications. The final histopathological diagnosis remained as schwannoma. After an overnight in-patient stay, the patient was discharged symptom-free. At the 1-month follow-up appointment, Horner's syndrome and First bite syndrome were diagnosed as post-operative complications. These symptoms disappeared over the following 8 months. The patient was first followed up 6-monthly and then annually with biennially MRI scans. The latest MRI showed no new growth in the multinodular schwannoma residual along the cervical plexus. The patient was discharged after a 6-year uneventful follow-up.

Case 2.

A 76-year-old man presented to the ENT Department with a past medical history (PMH) of NF1, high blood pressure and hypercholesterolaemia. Plastic surgeons had removed many of his head and neck neurofibromas over the previous 10 years mainly from the right trigeminal nerve area. His presenting complaint was pain in the right external auditory canal (EAC). On examination a soft neurofibroma was seen obstructing the anteriosuperior part of the right EAC whereas smaller neurofibromas were seen in the posterior and inferior part of the canal. Additional neurofibromas were seen in the patient's right cheek as well as sublingually. All neurofibromas were painful on palpation. An MRI scan showed multiple small (up to 1.5 cm)

tumor nodules along the course of the right facial nerve fibres in the EAC, parotid and sublingual gland, around the auricle, in the temporal and infratemporal region, and right anterior tongue (Fig. 2). Altogether 5 ear canal neurofibromas were removed through an endaural incision. At the post-operative appointment, the patient complained of worsened hearing in the right ear. Pure tone audiogram (PTA) showed conductive hearing loss at 50 dB with a Carhart's notch. Stapedotomy was performed 8 months after the removal of the ear canal neurofibromas. Intraoperatively, neurofibromas were seen to cause stapes fixation. The post-operative period was uneventful, and the patient continues to be reviewed annually.

Case 3.

A 48-year-old man with a PMH of NF1 was referred to the ENT Department with recurrent otitis externa and painful cutaneous neurofibromas in the right cheek, parotid gland, ear, and chin. Two cutaneous neurofibromas had been removed from the patient's retroauricular region 10 years prior to presentation. On examination cutaneous neurofibromas were seen in the aforementioned regions. An MRI scan showed multiple small (up to 1.5 cm) tumor nodules in the right periauricular region, right parotid gland, and lateral retropharyngeal space (Fig. 3) consistent with PN. An operative removal of the ear canal and retroauricular area PNs was undertaken without immediate or short- term complications. The patient was followed up altogether 10 years before being discharged from the ENT clinic.

Case 4.

A 34-year-old woman with known NF1 was referred to the ENT Department from a regional hospital for further management. Over previous years, numerous neurofibromas had been operatively removed from her EACs. In another tertiary ENT center, sclerotherapy with etoxisclerol (60 mg to 4 different areas, twice) had been performed to treat cutaneous neurofibromas in her face and neck with near complete and permanent shrinkage of the tumors. The reason for referral was an extensive neurofibroma in the right retrobulbar space to which the patient desired sclerotherapy.

An MRI scan showed extensive, multiple neurofibromatous growths in the base of the skull, face, neck, and in the right orbit. The largest tumor was seen in the intraconal space in the inferior part of the orbit, which compressed the intraocular muscles and the optic nerve (Fig. 4). The right eye was exophthalmic (exophthalmometer readings 29- 126-19). The eye

movements were conjugated and symmetric without restrictions. The patient reported diplopia on left and upward gazes. The swinging flashlight reflex was normal. The pupils reacted to light normally and the Ishihara colour charts readings were accurate. After a discussion with the patient, addressing risks of the procedure, sclerotherapy was planned for the retrobulbar growth.

An ultrasound-guided sclerotherapy was given to the right retrobulbar tumor with a 2 ml of etoxisclerol and 3 ml of air -mix. The patient recovered from anesthesia with immediate vision loss: dilated, reactive pupil, and increased exophthalmos of the treated eye. Intravenous (iv) cortisone was administered, and the patient taken to an orbital CT scan. CT showed emphysema in the orbital and periorbital tumor nodules. On ophthalmologic examination, the pre-treatment status had returned. MRI showed

no decrease in tumor size 1 week and 4 months after sclerotherapy. Because of ongoing ophthalmodynia and exophthalmos, the orbital tumor was partially surgically removed using subciliary approach without perioperative complications 5 months after sclerotherapy. There was a marked reduction in the right eye's exophthalmos post- operatively. Seven months post-treatment, minor decrease in the size of the anterior part of the orbital tumor was seen on the MRI scan (Fig. 5). The patient's current symptoms include sensation of compression and pain in her neck for which neck dissection is being planned.

Case 5.

A 41-year-old woman was initially referred to the Department of Neurology in the 1990s with pain around her right ear. In 2002, patient was referred to the ENT Department with right-sided neck swelling and right otalgia. A tumorous right submandibular gland was discovered and later removed with a histological finding of schwannoma. A further operation was thereafter performed through a mid-neck incision in which a tumor surrounding the lingual nerve was removed. The tumor was consistent with neurofibroma. A year later, 2 neurofibromas were operatively removed from the floor of her mouth using mid-neck approach. Ten months later, 5 further neurofibromas were removed from the same area. In the following 16 years, 7 further operations were performed to control neurofibroma growths in the floor of the patient's mouth. In year 2017's follow-up, the sensation on the patient's right side of tongue was reduced while the function of the tongue remained normal. The histological samples revealed PN behind the necklace-like, pearly tumors. The Department of

Genetics failed to identify neurofibromatosis as the cause of the recurrent neurofibroma growths. The patient continues to be followed up in the ENT Department annually. Her current symptoms include difficulty speaking due to residual neurofibroma growths in the floor of the mouth. Eating and swallowing have been unaffected throughout. Fig. 5 shows multiple small (up to 1 cm) tumor nodules in the floor of the mouth and in the right masticator space.

Case 6.

A 2-year-old boy with known NF1 was referred to the ENT Department with a 6-month history of diffuse cheek swelling. An MRI scan showed a diffusely infiltrative enhancing lesion in the temporal and infratemporal masticator space, buccal fat pad, and lateral part of the orbit. There were no abnormalities in the brain. Radiologically the facial swelling was consistent with an extensive PN (Fig. 6), which was confirmed by a biopsy taken under general anaesthesia. On examination the patient had facial asymmetry corresponding to the radiological findings; the ENT and head and neck status was otherwise normal. An ophthalmologic exam revealed Lisch nodules in the patient's eye without other abnormal findings. The patient has been followed up annually for the past 15 years. Control MRI scans, taken at 1–2-year intervals, have revealed slow growth particularly around the zygomatic arch. Intracranially, hamartomatous lesions were detected in the basal ganglion and the base of skull in 2010; these have not subsequently grown.

Case 7.

A 45-year-old woman with PMH of juvenile glaucoma (since the age of 8) and NF1 was referred to the ENT Department for further management in 2002. She had suffered from exophthalmos since her early teens and consequently lost sight in her right eye. The details of her complex operative treatment can be studied in Supplemental Table 3. The exophthalmos had recently increased and, on an MR scan, small tumor nodules were seen intra- and extraconally in the right orbit, mostly along the lateral orbital wall. On examination several subcutaneous tumors were seen in the right side of the patient's diffusely hypertrophic face. The right eye was exophthalmic and the right nasal pyramid prominent. The facial nerve was functioning normally. The epiglottis was "omega shaped", the right tonsillar pillar was projecting down, and the right buccal mucous membrane was hypertrophic. Fronto-orbital craniotomy using coronal incision was performed with macroscopically complete removal of

the orbital tumor and the plexiform buccal tumors underneath the zygomatic arch. Six years later (VIII/08), the patient was seen in the Department of Neurosurgery with symptoms including severe pain in the trigeminal nerve area (V3) for which gabapentin had been prescribed. On MRI, a multinodular, residual tumor was seen in the right orbit, extending to the cavernous and sphenoid sinuses as well as to the pterygopalatine fossa and the internal carotid artery (Fig. 7a, b).

The patient underwent 5 further operations for removal of residual PNs (Fig. 7c). In the latest operation the estimated blood loss was 1700 ml. An MRI has been performed before every operation. The patient continues to be reviewed by the ENT Department annually and currently receives treatment for trigeminal neuralgia with gabapentin, paracetamol and codeine.

Case 8.

A 3-year-old boy with PMH of bilateral epiretinal membranes was referred to pediatric surgeons with a 3-month history of a diffuse, non-mobile, non-tender swelling over the parietal aspect of his head. An MRI scan showed 2 adjacent 2-3 mm subcutaneous swellings on top of an intact skull. A subsequent MRI, done to further investigate epiretinal membranes, showed contrast enhancement indicative of bilateral vestibular schwannomas. Both parietal swellings were operatively removed. The histology was initially consistent with incompletely excised PNs. Because of the challenging histology, the pathological specimen was re-examined by a neuropathologist and a head and neck pathologist with the resulting change in diagnosis from PN to PS. The patient was later diagnosed with neurofibromatosis type 2 (NF2) and underwent left vitrectomy and epiretinal membrane excision. The latest MRI scan showed contrast enhancement in bilateral vestibular and right facial nerve areas as well as a small 1-2 mm parietal PN. The patient continues to be reviewed biannually by pediatric neurologists.

DISCUSSION

This study reviews the management of 8 head and neck PS/PNs at 2 tertiary-care academic hospitals over a 31-year period. The centres cover a referral area with 2.9 million inhabitants in Southern Finland, which corresponds to more than half the country's total population. This series reflects the occurrence rather than the incidence of these rare entities in the studied population.

PSs and PNs are rare, largely benign PNSTs that often occur in the head and neck region. While surgical management continues to be their mainstay treatment option, resection of these tumors can be limited by the tumors' infiltrating nature and high risk of postoperative morbidity. Several approaches have been used in the treatment of these tumors with no clear guidelines on surgical techniques.

PS was first described in 1978 by Harkin et al (10). This rare variant of schwannoma is characterized by macroscopic and/or microscopic plexiform pattern of intraneural tumor growth with multinodularity. PS differs from the non-plexiform schwannoma by not having a well-formed capsule and thick-walled vessels (1). While PS carries no malignant potential, it may recur if resected intracapsularly (3, 11).

In both PNs and PSs, the structural tumor content resembles a "bag of worms"; soft areas taking turns with firm nodular areas. PNs can be vascular, involve multiple nerve fascicles and become large enough to cause significant deformity (12) as well as pain and functional changes. The risk for progression and/or recurrence is higher in the head and neck region, if the patient is young, and if the surgical resection has been incomplete (8, 13). Because PNs lack a well-defined capsule and consist of a mesh of interwoven spindle cells, collagen fibers and axons that diffusely infiltrate the involved nerve (1), surgical separation from normal tissue may be difficult.

A recent study reports the incidence of NF1 as 1:2000 (14). Approximately 10% of patients with NF1 develop MPNSTs mostly arising from PN (15, 16). MPNSTs are highly aggressive sarcomas that have high local recurrence rates, metastasize early and are often resistant to therapeutic intervention. If complete resection of MPNST is not possible or if metastases are present, the outcome from MPNST is grim. While surgery remains the only effective therapy

for MPNSTs (17), novel biological agents may open new treatment avenues for this notorious sarcoma (18). Selumetinib, a mitogen- activated protein kinase (MAPK) kinase (MEK) inhibitor has already shown durable tumor shrinkage and clinical benefit in children with NF1 and inoperable PNs in a phase 2 trial and has recently been approved for their treatment in the USA (19, 20). Cabozantinib, a multireceptor tyrosine kinase inhibitor, is another promising agent for treatment of symptomatic, inoperable PNs related to NF1 in paediatric and adolescent patients in a phase 2 study (NCT02101736). An ongoing study (NCT03433183) assesses the combination of selumetinib and mTOR inhibitor sirolimus in the treatment of metastatic or unresectable MPNST that are sporadic or associated with NF1.

Because of the malignant potential of PNs and because PSs and PNs share similar clinical, radiological and histopathological features, discrimination between the 2 entities is both challenging and important. Having 2 or more of the following MRI signs: peripheral enhancement, perilesional oedema, intratumoral cystic lesions, and a diameter of 5 cm in the largest tumor nodule is reported to have 61% sensitivity and 90% specificity for MPNST (21). Fluorodeoxyglucose (FDG)-positron emission tomography (PET) can be used to rule out malignant transformation in NF1 with symptomatic lesions with a negative predictive value of 100%, and to target biopsy (22).

In our cohort, there was initially only 1 case of PS; a slowly growing largely asymptomatic tumor, which was debulked with good effect. The residual tumor and the patient remained asymptomatic over annual reviews. After the pathological specimen of patient 8 was re-evaluated, the diagnosis of PN changed to that of PS. This highlights the challenge in distinguishing these occasionally overlapping histologies not only from other neural proliferations but also from one another (3, 23). While atypical histologies may demand re-evaluation by other experienced pathologists, it is also not rare for the diagnosis to specify as the diagnostic methods develop.

Berg et al noted a local recurrence in 1 out of 12 PS patients when the primary excision of PS was incomplete (3). Ijichi et al (24) recommend removing the tumor without nerve preservation for PS involving the carotid canal. If removing PS is straightforward and the patient is unlikely to suffer significant morbidity from the nerve sacrifice, removing the tumor with the nerve can be acceptable. Complete surgical removal of a head and neck PN/PS without causing significant morbidity may not be possible. Every case should therefore be evaluated individually without hard rules about optimal management.

The remaining 6 cases in this study represented PNs, 5 of which were NF1-associated. Case 4 in our study demonstrates an alternative option to treat PNs. Sclerotherapy had reduced this patient's cutaneous PNs successfully. An ultrasound-guided injection of

etoxisclerol-air mix to the patient's retrobulbar tumor induced transient loss of vision in the treated eye. While the vision returned, no decrease in tumor size was noted post-sclerotherapy. The tumor was later partially surgically removed to good effect. Schick et al report no recurrences after complete surgical resection of orbital schwannomas or neurofibromas (25). There are no reports about treatment of retrobulbar PN with sclerotherapy in the literature. Ali et al describe an unsuccessful attempt to manage a cutaneous neurofibroma with sclerotherapy (26). While we cannot recommend treatment of retrobulbar PNs with sclerotherapy, it may offer a viable treatment option for cutaneous plexiform or non-plexiform PNs. The benefits of these injections include avoidance of general anesthesia. Further studies are however needed to validate this alternative treatment option in the treatment of cutaneous plexiform or non-plexiform PNs.

PNs are not radiosensitive and - because of their slow-growing nature and the associated risk of treatment induced secondary malignant neoplasms (27) - are also not suitable for chemotherapy. Numerous biological agents, such as the aforementioned selumetinib, are being investigated in clinical trials and long-term measures of toxicity and the agents' effects on normal body function and development are being awaited (27). While biologic agents for PNs continue to evolve, the development of imaging techniques will further improve PS/PN diagnostics in the future. If operative treatment is considered, a risk-benefit assessment must be carefully carried out. Ball et al discuss the risks of observation vs. operative management of benign nerve sheath tumors (28). The risk of observation in PN includes the risk of malignant transformation. Those treated conservatively may experience progression of their symptoms and are at risk of having more complex surgery if operative treatment is eventually needed. Those who

undergo surgery may suffer from wound complications and nerve injury. While neuronavigators enable safe performance of more complex surgical approaches, complete removal of PNs may not possible because of the extent of the tumor and/or its anatomical location.

Managing pediatric PNs/PSs is particularly challenging. If safe surgical management of PN/PS is possible without causing damage to CNs or other vital structures, early removal should be carried out. In case the PN/PS cannot be removed completely, causing morbidity from damage to nerves or other vital structures should be avoided and subtotal extirpation carried out with ensuing long-term follow-up. If safe total or subtotal removal is not feasible, long-term clinical follow-up with regular imaging should be offered. With follow-up the possibility of PN's malignant transformation to MPNST should be remembered as in children both the length of follow-up and survival are likely to be long. In case of neurological or pressure symptoms from the PN/PS, it is paramount to choose the optimal time for surgery and only sacrifice CNs or other vital structures if the benefits outweigh the risks or sacrifices. The MEK inhibitor selumetinib has led to confirmed partial responses in 70% of patients while offering 84% progression-free survival over 3 years (19) and as such offers a novel way to treat NF1 patients' symptomatic, inoperable PNs. While biological agents continue to evolve and long-term data on their use is being gathered, the use of these agents may be limited by their availability, high cost, and on an individual level, toxicity.

In this study, cases 5 and 7 underwent up to 11 PN resections. Because of the anatomically challenging location of PNs in both cases, the tumours' complete removal was not possible. In case 5 the patient has experienced difficulty speaking because of the residual tumor growths but has been able to eat and drink normally. In case 7, the patient suffered damages to oculomotor and trigeminal nerves as a result of her multiple operations while PNs continue to remain in situ. In contrast, case 6 has received no active treatment to his PN. Because PNs have an unpredictable natural history, case 6 continues to be followed up annually.

Wise et al (29) advice debulking of massive PNs 1) to exclude malignancy in a rapidly growing but otherwise stable PN or where there is radiological evidence of necrosis within a mass; 2) if airway compromise exists (particularly if not relieved by tracheostomy alone); 3) to alleviate nerve compression symptoms, and/or 4) to improve cosmesis. Recurrence was seen within 3 years of initial surgery in most massive head and neck PNs while those that did not recur, were small and had undergone total resection (29). In the current study, surgery was offered for symptomatic or progressive lesions. Airway compromise, pain (especially if increasing), declining visual acuity, and mass effect secondary to tumor growth were the main operative indications.

Management of PSs and PNs remains challenging. Sclerotherapy may offer a treatment option for cutaneous PNs. Surgical treatment needs to be balanced with risks of surgery and of non-operative treatment. Centralization of the management of these rare and challenging tumors to experienced multidisciplinary Head and Neck centers is mandatory. It would also seem beneficial to develop consultation platforms between these teams to share and discuss cases and even to register the patient, tumor, treatment and outcome data for further analysis in larger series.

CONFLICT OF INTEREST

Declarations of interest: none.

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CAPTIONS TO ILLUSTRATIONS

Figure 1. Case 1. The axial MR image (a) shows the largest tumor nodule (asterisk) that caused symptoms and was removed operatively. Extension along the nerve root (arrowhead) is also visible, hinting at the neurogenic origin of the tumor. The other MR image (b) shows multiple smaller tumor nodules along the course of the cervical plexus. Operative specimen (c).

Figure 2. Case 2 with multiple small tumor nodules in the right parotid gland and sublingual space.

Figure 3. Case 3. Nodular tumor growth in the right parotid gland (left) and parapharyngeal space (right). The typical "target sign" – central T2 hypointensity within a hyperintense tumor – is clearly visible.

Figure 4. Case 4 pre-sclerotherapy MRI and 7 months post-sclerotherapy CT. Orbital tumor nodule that reacted to sclerotherapy is marked by an asterisk.

Figure 5. Case 5. Slight growth of the multinodular tumor component in the right tongue and floor of the mouth is mainly evident as a mass effect slightly compromising the airway. Left (earlier) and right MRI scans are taken with a 9-month time interval.

Figure 6. Case 6 MRI scans taken at the age of 2 (left) and 17 (right) years demonstrate the slow, mainly superficial growth of the left facial tumor.

Figure 7. Case 7. The axial MR image (a) shows the nodular intraorbital tumor growth along the right orbital wall. A luxated lens (asterisk) is visible in the heavily myopic right eye. The coronal MR image (b) shows the more extensive tumor growth in the right masticator space, extending into the foramen ovale. A smaller tumor nodule is visible in the right parotid gland. Intraoperative image (c) from year 2010's operation. Lateral craniotomy was performed through a coronal incision.

Figure 1

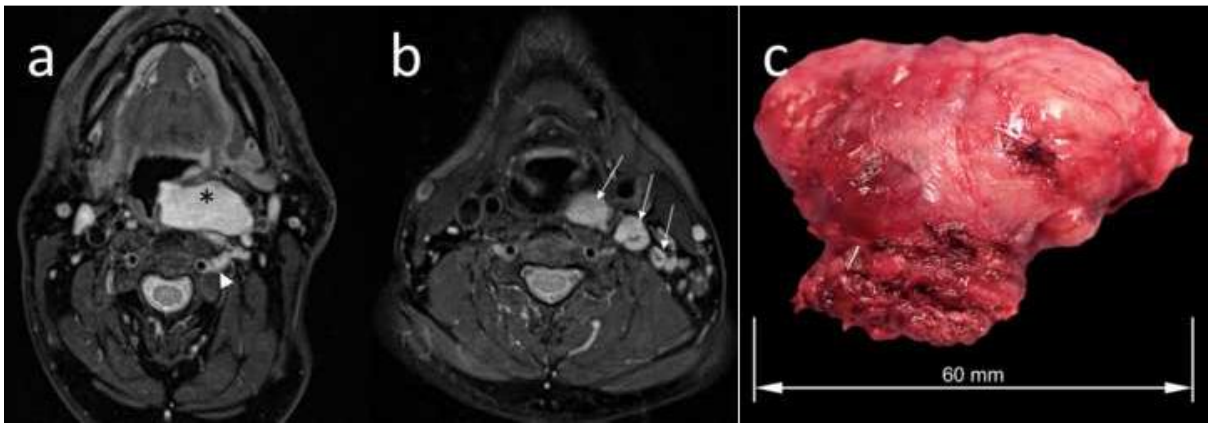


Figure 2

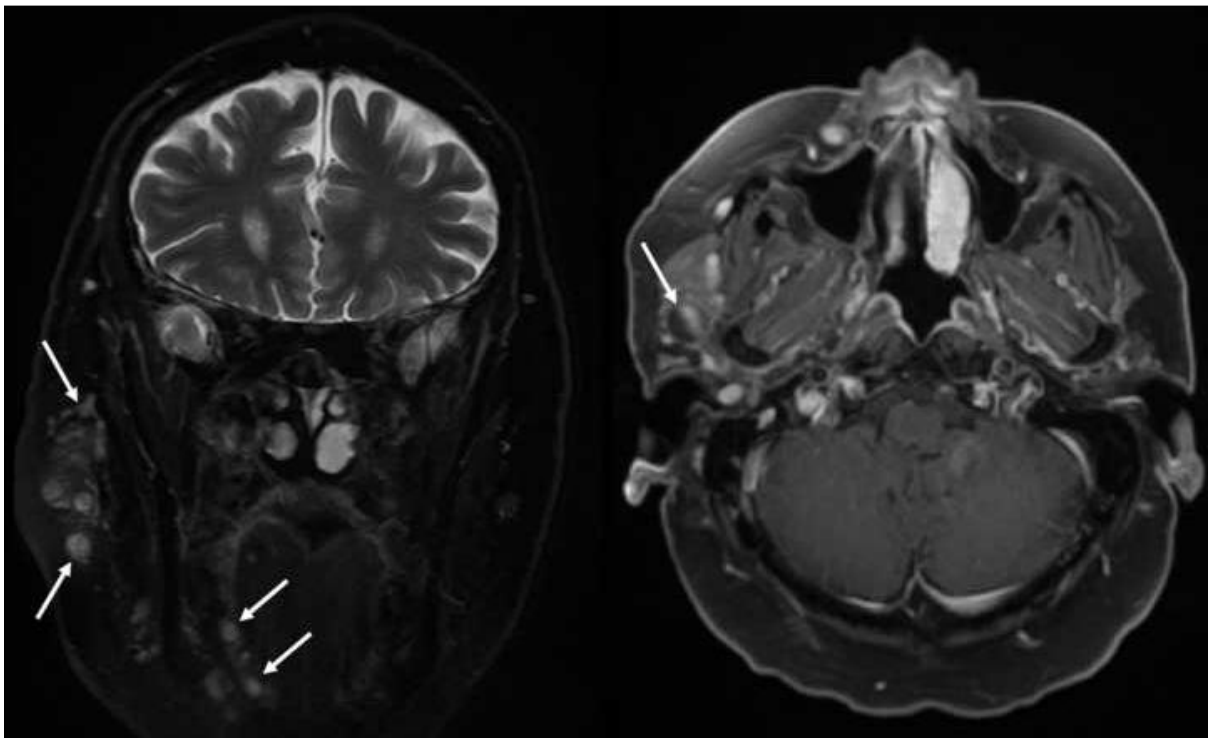


Figure 3

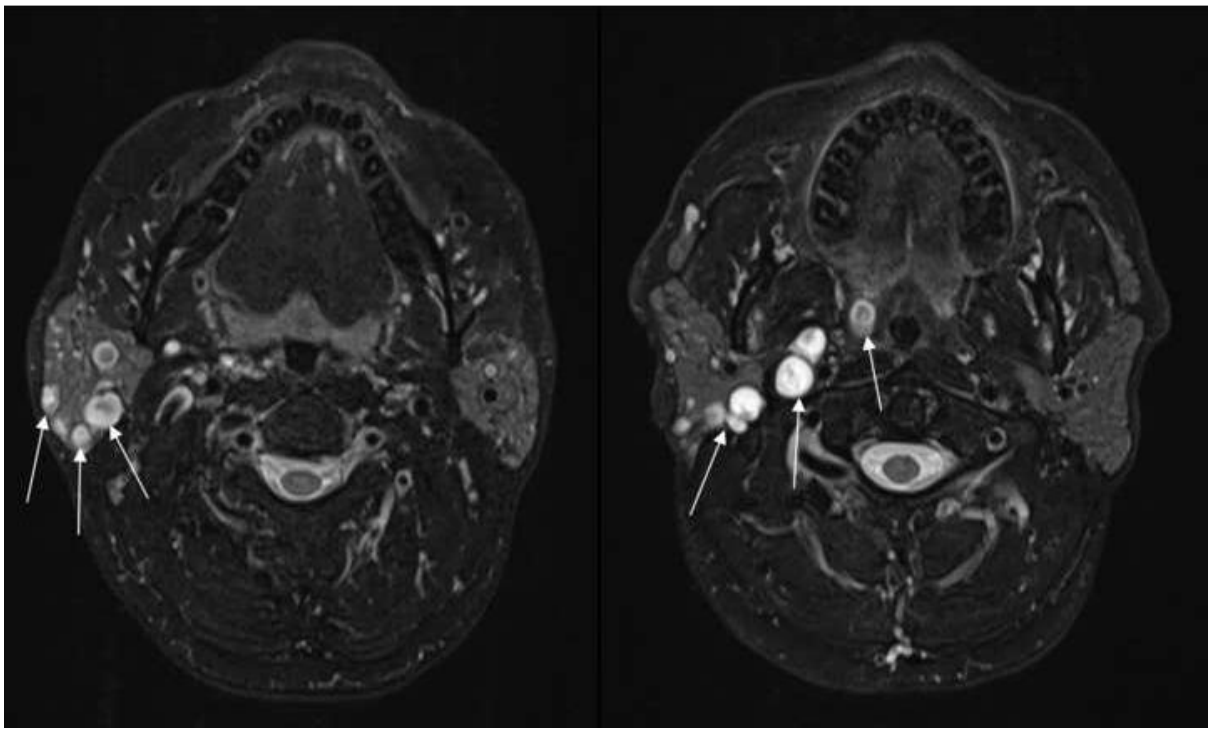


Figure 4

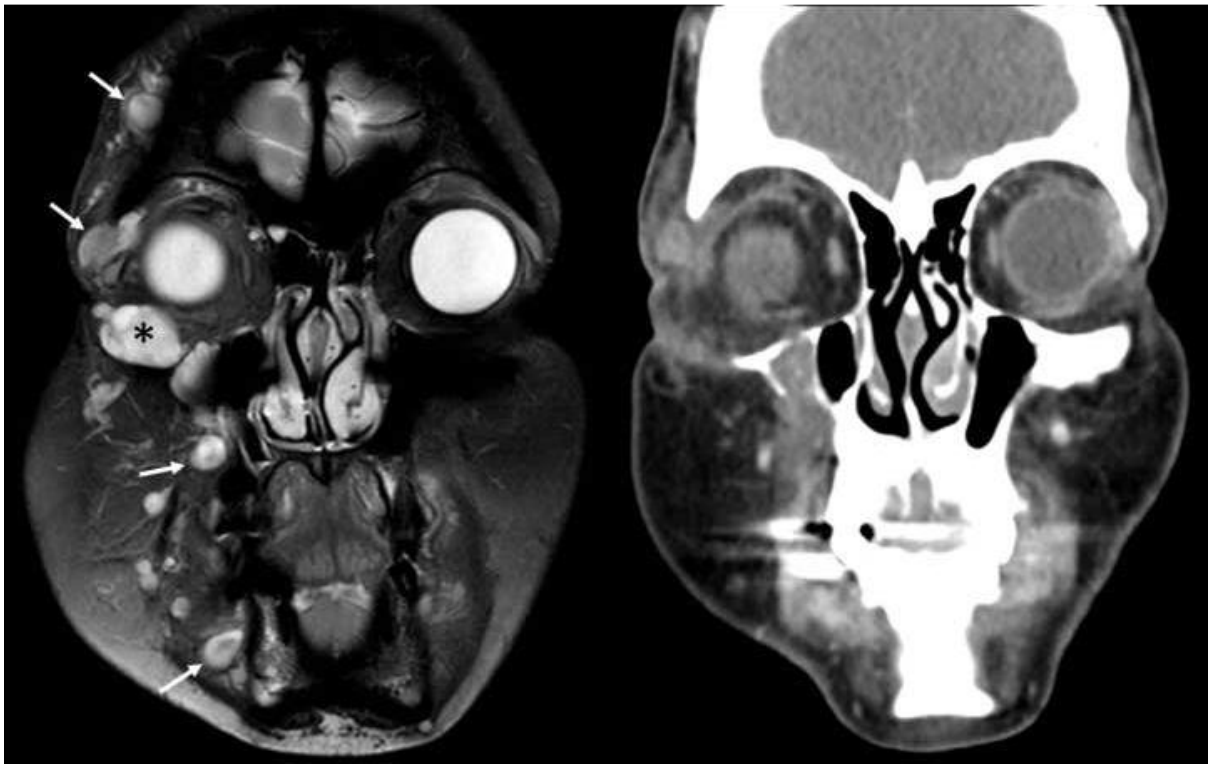


Figure 5

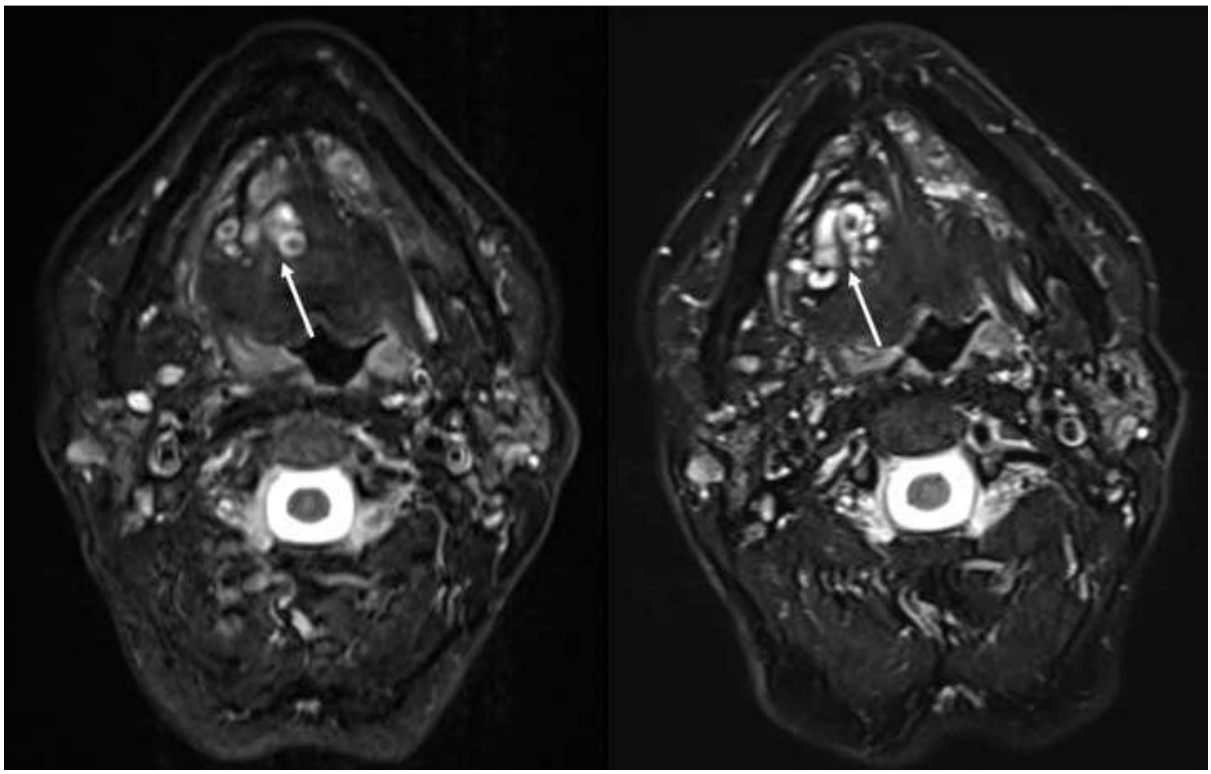


Figure 6

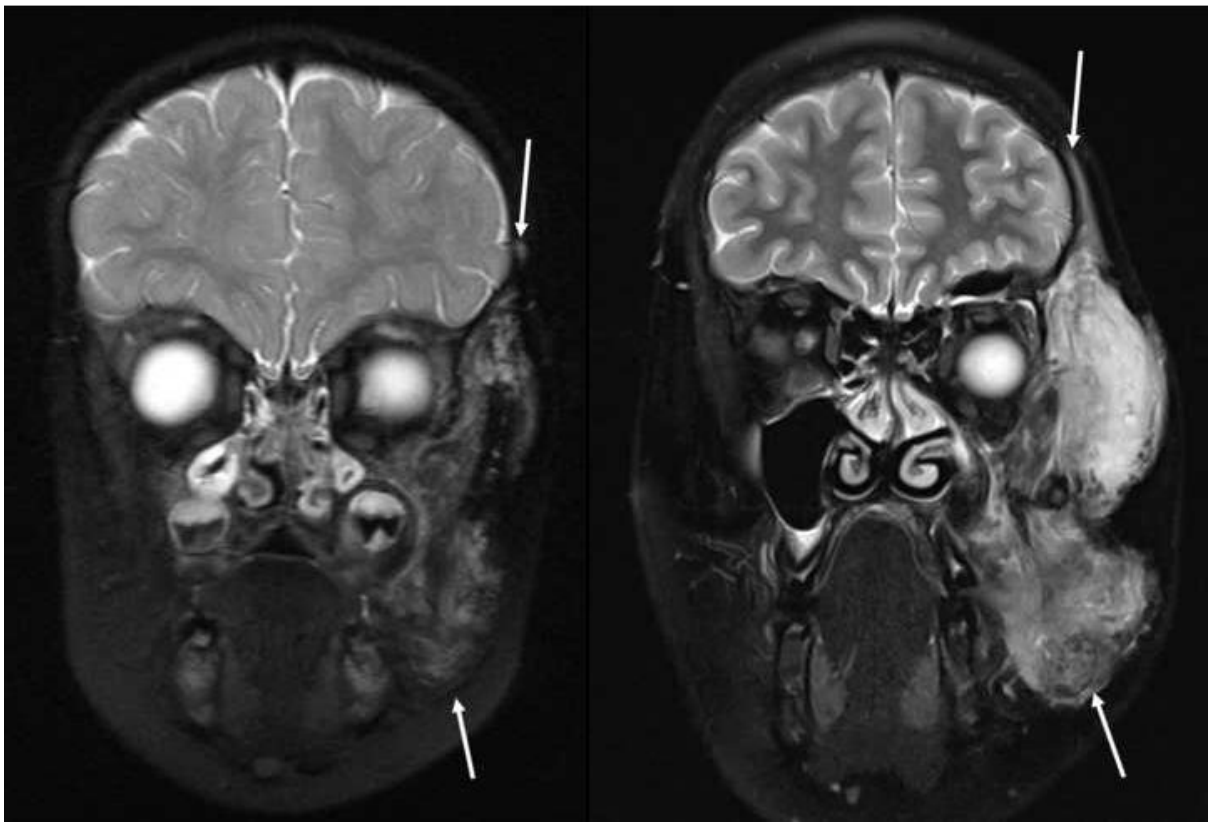
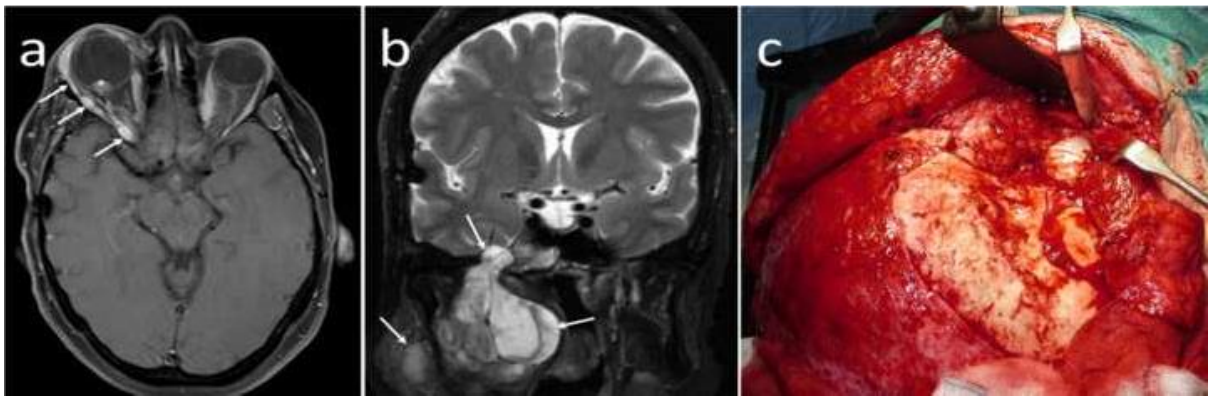


Figure 7



Supplemental Tables 1-3

SUPPLEMENTAL TABLES

Supplemental Table 1. Variants of schwannomas and neurofibromas (1).

Schwannoma variants	**Neurofibroma variants**
Conventional schwannoma	Localized cutaneous
Cellular schwannoma	Diffuse cutaneous
Plexiform schwannoma	Localized intraneural
Microcystic/reticular schwannoma	Plexiform intraneural
"Ancient" schwannoma	Massive diffuse soft tissue plexiform

Supplemental Table 2. Clinical features of plexiform schwannomas and plexiform neurofibromas (1). NF2 = neurofibromatosis type 2, NF1 = neurofibromatosis type 1.

Tumor	**Epidemiology**	**Clinical features**	**Clinical associations**
Plexiform schwannoma	Both sexes, all races and ages affected. Peak incidence: 4^{th}-6^{th} decade in life. Paediatric cases often syndrome-associated.	> 90% of lesions solitary and sporadic Slowly growing Asymptomatic/symptomatic (depending on location)	NF2 schwannomatosis
Plexiform neurofibroma	Both sexes, all races and ages affected	multiple lesions possible (NF1) Asymptomatic/symptomatic (depending on location)	NF1

Supplemental Table 3. Operative management of case 7. N/a = not available, CNIII = oculomotor nerve, CNV = trigeminal nerve, V2 = maxillary nerve, V3 = mandibular nerve, TM tympanic membrane.

Year	Operative indication	Operation	Operative details	Post-operative morbidity/notable
1964	Juvenile glaucoma	n/a	n/a	n/a
1970s	Exophthalmos	Removal of an orbital neurofibroma	n/a	Right eye went blind pre- or post-operatively, recurrent otitis medias post-operatively (grommets to right TM)
2000	n/a	n/a	n/a	n/a
2002	Increase in exophthalmos	Fronto-orbital craniotomy	Macroscopically total removal of an orbital tumor and buccal tumors	CNIII damage, complete ptosis, right eye not functioning
2008	n/a	n/a	n/a	CNV damage, ptosis
2009	CNV_3 pain	Craniotomy	Removal of neurofibromas from the sphenoid sinus	CNV damage (V_2)
2010	Debulking of tumor	Lateral craniotomy	Removal of neurofibromas from the infratemporal fossa and lateral part of the cavernous sinus	n/a
2012	Debulking of tumor	Lateral craniotomy	Removal of neurofibromas from lateral part of the orbit; from the parapharyngeal space and from the infratemporal fossa	n/a
2012	Debulking of tumor	Lateral craniotomy	Removal of neurofibromas from the infratemporal fossa and from the parapharyngeal space. Mandibular (ramus) osteotomy.	Tumor had eroded most of the mandibular ramus