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Juvenile angiofibroma

MICHAEL GLEESON

SEARCH STRATEGY

The data in this chapter are supported by a PubMed search of publications focussing on the genetics, pathology and management of juvenile angiofibroma.

INTRODUCTION

Recognized since ancient times by Hippocrates, juvenile angiofibroma is an uncommon, benign and extremely vascular tumour that arises in the tissues within the sphenopalatine foramen. Rarely, it is found at other sites in the nasal cavity and paranasal sinuses.[1] Juvenile angiofibroma accounts for less than 0.5 percent of all head and neck tumours. It develops almost exclusively in adolescent males, though there are reports of this tumour being found in children, the elderly, young and even pregnant women. As it grows, the tumour extends into the nasopharynx, paranasal sinuses, pterygopalatine and infratemporal fossa. Larger tumours can involve the orbit and cavernous sinus. Juvenile angiofibromas are locally invasive, though a few have been reported to behave in a more malignant fashion. The vascular nature of juvenile angiofibroma has posed a significant problem for those charged with its management. In recent years, with the advent of endoscopic techniques, the surgical approach to this tumour has changed. This chapter aims to summarize current knowledge and management.

PATHOGENESIS

Juvenile angiofibromas present as well-defined, lobulated tumours that are covered by nasopharyngeal mucosa. The tumour consists of proliferating, irregular vascular channels within a fibrous stroma. Tumour blood vessels typically lack smooth muscle and elastic fibres, this feature contributing to its reputation for sustained bleeding. The stromal compartment is made up of plump cells that can be spindle or stellate in shape and give rise to varying amounts of collagen. It is this that makes some tumours very hard or firm, while others may be relatively soft.

As this tumour is almost exclusively found in adolescent boys, there has always been much speculation and indirect evidence that sex-hormone receptors play some part in its development. Recent immunocytochemical techniques have been used to show that androgen receptors are present in at least 75 percent of tumours, these receptors being present in both the vascular and stromal elements. A much smaller proportion of tumours also have some progesterone receptors. In contast, oestrogen receptors have not been demonstrated.[2] Other factors also play their

part in the development of this tumour. The angiogenic growth factor (vascular endothelial growth factor (VEGF)) has been found localized on both endothelial and stromal cells, perhaps indicating that both cell types play a role in tumour development.[3] Vessel density and both the expression and localization of VEGF correlate with the proliferative marker Ki67.[4] However, neither the proliferative index nor VEGF expression seem to bear any relation whatsoever to the stage of the tumour at the time of presentation; in other words, its degree of aggressiveness. Overexpression of insulin-like growth factor II (IGFII) has also been found in a large number of juvenile angiofibromas. The IGFII gene is situated on the short arm of chromosome 11 and at that site is the target of genomic imprinting, expressing the paternal allele only. It is thought that overexpression of IGFII might be associated with a tendency to recurrence and poorer prognosis.[5]

Juvenile angiofibromas have also been reported to develop 25 times more frequently in patients with familial adenomatous polyposis, a condition that is associated with mutations of the adenomatous polyposis coli (APC) gene. As a result, it has been suggested that germline mutations in the APC gene on chromosome 5q might also be involved in the pathogenesis of sporadic juvenile angiofibromas. This gene regulates the beta-catenin pathway which influences cell to cell adhesion. Mutations of beta-catenin have been found in sporadic and recurrent juvenile angiofibromas.[6] Localization of beta-catenin only to the nuclei of stromal cells has been interpreted by some to suggest that the stromal cells have a critical role in the development of these neoplasms.

PRESENTATION

Recurrent severe epistaxes accompanied by progressive nasal obstruction are the classical symptoms of juvenile angiofibromas at the time of presentation. These tumours do not grow fast and so many months or even years may pass before it occurs to the patient or their parents that there is anything seriously amiss. In most, there is a delay of at least six or seven months between the onset of symptoms and presentation. By that time, it is usual for the youth to have other signs and symptoms of tumour growth and extension. These may include swelling of the cheek, trismus, hearing loss secondary to Eustachian tube obstruction, anosmia and a nasal intonation or plummy quality to the voice. More extensive tumour growth with invasion of the orbit and cavernous sinus may cause proptosis, diplopia, visual loss, facial pain and headache.

Anterior rhinoscopy is likely to confirm the presence of abundant mucopurulent secretions in the nasal cavity that usually obscure the tumour from vision, though a few patients have tumour prolapsing from the anterior nares. The soft palate is often displaced inferiorly by the bulk of the tumour which can be seen clearly as a pink or reddish mass that fills the nasopharynx.

ASSESSMENT

In the past, the exact nature of these tumours was suggested by the plain lateral skull radiographic appearance that would show anterior bowing of the posterior wall of the maxillary sinus (**Figure 187.1**). Nowadays, the diagnosis is based on the CT and MR appearances that are sometimes confirmed by angiography. A trans-nasal biopsy is not necessary and can provoke brisk haemorrhage. The exact extent or stage of the tumour can only be determined by a combination of CT and MR imaging and this is vital when planning the surgical resection (**Figures 187.2** and **187.3**). Several staging systems have been proposed but that of Fisch is the most robust and practical (**Table 187.1**).[7] It defines clearly which tumours can be resected by endonasal techniques and those that would be better tackled by more open or infratemporal fossa/neurosurgical approaches. The Radkowski staging system appeals to those involved with the management of smaller tumours as there are more subdivisions but, in reality, this adds little to its utility (**Table 187.2**).[8] Diagnostic angiography is undertaken to evaluate the

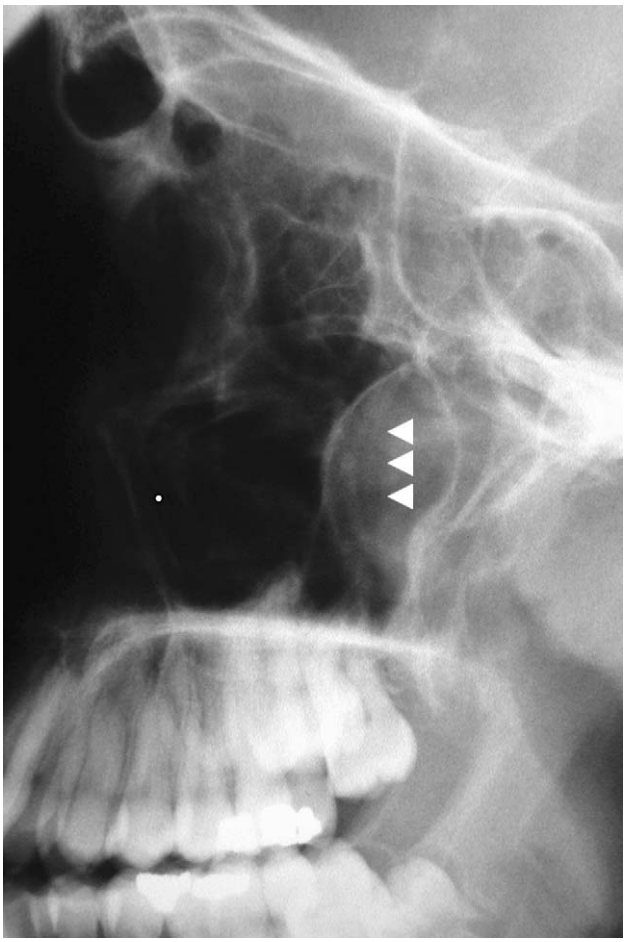

Figure 187.1 Typical plain radiographic appearance of an angiofibroma. The posterior wall of the maxillary sinus has been bowed anteriorly (arrowed).

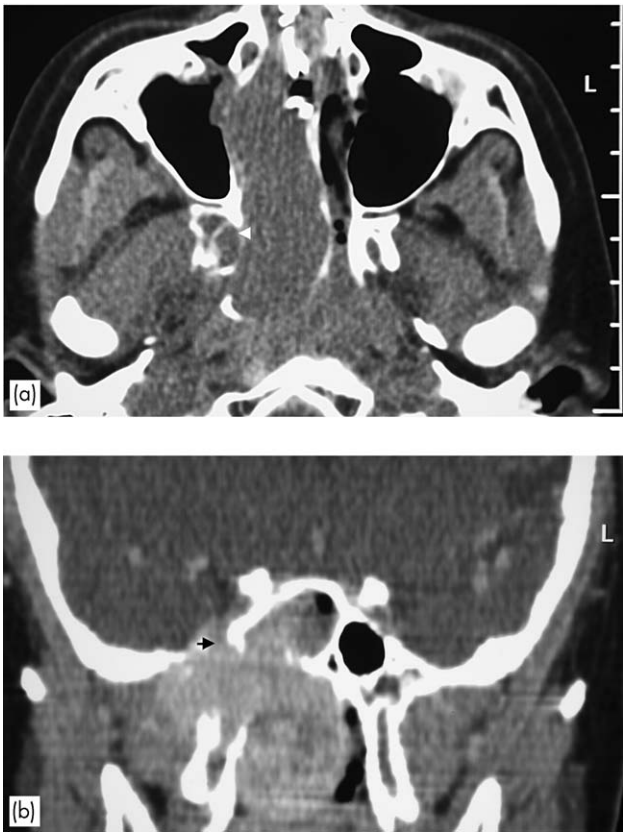

Figure 187.2 **(a)** Axial and **(b)** coronal CT images of a type 3a, right-sided, juvenile angiofibroma. There is destruction of the pterygoid plates and extension of tumour through the skull base (arrowed).

source of blood supply and as a prelude to selective embolization (**Figure 187.4**). [*]

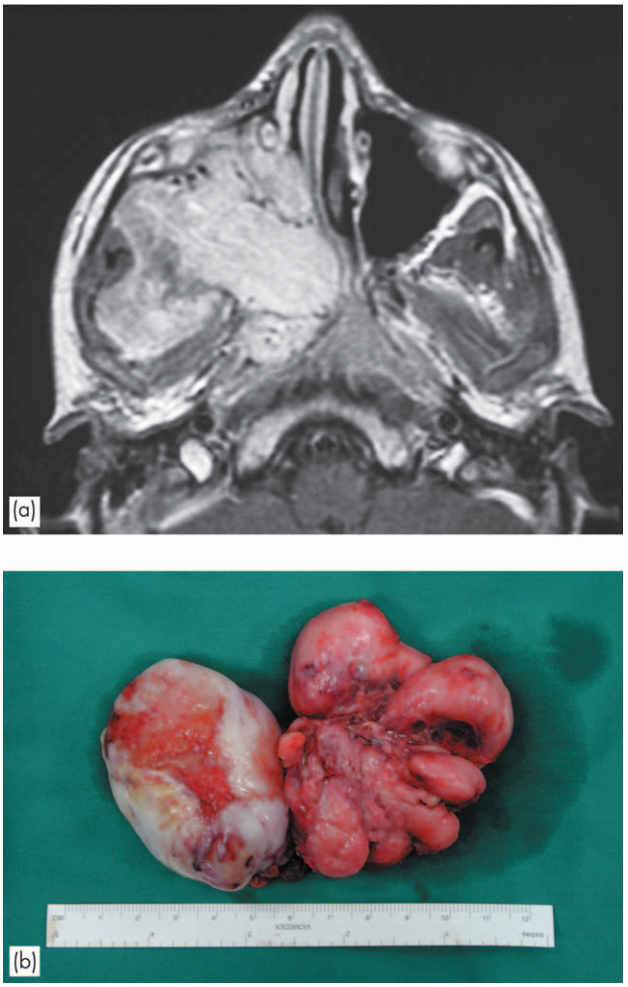

Figure 187.3 MR appearances of a type 3a, right-sided juvenile angiofibroma. It has invaded the infratemporal fossa. The operative specimen gives a more objective assessment of the tumour size.

TREATMENT

Hippocrates (470–410 BC) is said to have removed what he called a 'hard nasal polyp' through a midline, nose-splitting incision and it is suggested that this was a juvenile angiofibroma. The famous surgeon, Liston, at University College London performed the first successful resection of an angiofibroma on a 21-year-old man from Gibraltar on 6th September 1841.[9] The tumour had been present for at least three and a half years and filled the pharynx to the extent that it caused significant airway obstruction. It extended into his cheek and had eroded the alveolar process. The patient had experienced a

Table 187.1 Fisch staging system of juvenile angiofibromas.

Type	Details
1	Tumour limited to the nasopharyngeal cavity; bone destruction negligible or limited to the sphenopalatine foramen
2	Tumour invading the pterygopalatine fossa or the maxillary, ethmoid or sphenoid sinus with bone destruction
3	Tumour invading the infratemporal fossa or orbital region:
	(a) without intracranial involvement
	(b) with intracranial extradural (parasellar) involvement
4	Intracranial intradural tumour:
	(a) without infiltration of the cavernous sinus, pituitary fossa or optic chiasm
	(b) with infiltration of the cavernous sinus, pituitary fossa or optic chiasm

Table 187.2 Radkowski classification of juvenile angiofibromas.

Stage	Details
Ia	Limited to the nose and nasopharyngeal area
Ib	Extension into one or more sinuses
IIa	Minimal extension into pterygopalatine fossa
IIb	Occupation of the pterygopalatine fossa without orbital erosion
IIc	Infratemporal fossa extension without cheek or pterygoid plate involvement
IIIa	Erosion of the skull base (middle cranial fossa or pterygoids)
IIIb	Erosion of the skull base with intracranial extension with or without cavernous sinus involvement

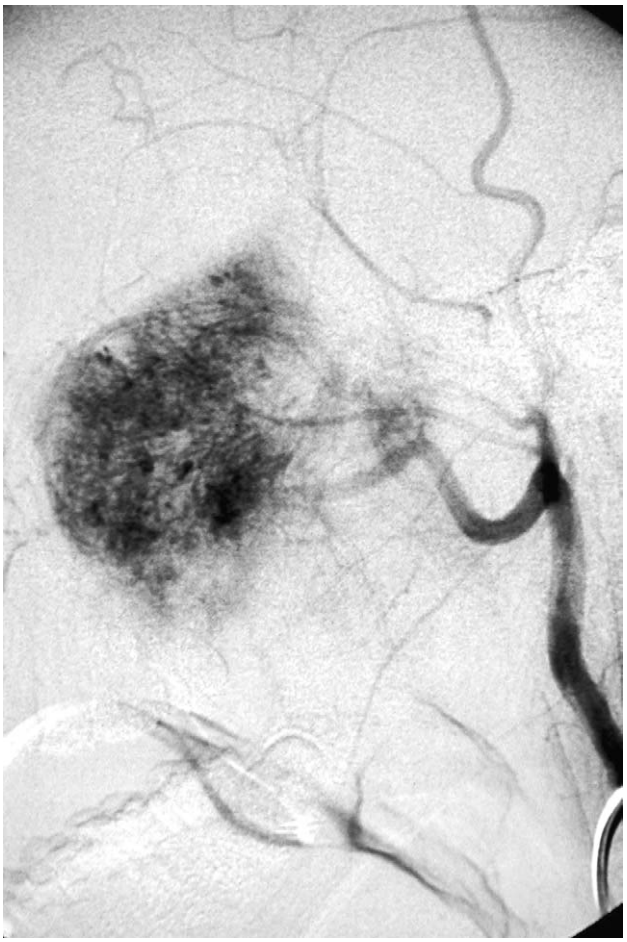

Figure 187.4 External carotid angiogram of a juvenile angiofibroma demonstrating its blood supply from the internal maxillary artery which is much larger than normal.

number of severe epistaxes, losing two to three pints of blood on each occasion. Liston removed the tumour by performing a total maxillectomy through a Weber–Fergusson incision without anaesthesia! The patient bore the procedure 'with remarkable fortitude'. He was discharged 24 days later able to eat a normal diet! Histopathological examination of the operative specimen showed the tumour had a 'fibro-vascular nature.'

In the years that followed it became apparent that a large number of these tumours could be removed relatively safely by open approaches but not without significant morbidity. A number of patients also died as a direct result of blood loss. Attempts were made to reduce the blood supply of the tumour preoperatively and to shrink them by chemical means. Very extensive tumours were treated by radiotherapy as were recurrences. Strategies for the surgical management of these tumours have evolved over the intervening years and never more quickly than in the last decade with the advent of endonasal endoscopic techniques.[10]

PREOPERATIVE EMBOLIZATION

The role of preoperative embolization in the surgical management of this tumour is controversial. While some surgeons regard it as essential, others have less strict views or frankly disagree. There is little doubt that for small tumours the blood supply is predictable, usually the terminal branches of the internal maxillary artery, and these can be controlled easily at the time of surgery. Embolization in such cases would seem to be unnecessary. More extensive tumours acquire a blood supply from other vessels, branches of both the external and internal carotid circulations. Surgical resection of these tumours can be formidable and preoperative selective embolization, some days before surgery, is prudent at the very least. It is the medium-sized tumours where the benefits of preoperative embolization are doubtful. Intraoperative blood loss after embolization is certainly less.[11] The maxillary or external carotid artery can be controlled or ligated relatively easily at an early stage in any open procedure, regardless of whether embolization has been undertaken or not. [**]

It might be thought that any measure undertaken to improve operative conditions might influence the adequacy of resection and reduce the rate of recurrence. On the contrary, recurrence rates seem to be increased by preoperative embolization.[12] Perhaps shrinkage of the tumour makes it more difficult to define its entirety at the bottom of a deep and bloody operative field.

PREOPERATIVE CHEMOTHERAPY

Other means of reducing tumour size before surgery have also been evaluated. Oestrogens have been reported to induce shrinkage in some but their effect is variable and not without complications. At the very least, oestrogen therapy delays surgery and the secondary feminizing effects are certainly unwanted by an adolescent boy. In a small series of patients given the nonsteroidal androgen receptor blocker, flutamide, tumour shrinkage of up to 44 percent was reported by Gates *et al.*[13] Flutamide is regularly used in the management of prostatic cancer. While not without side effects, nausea, breast tenderness and gynaecomastia, these effects were only temporary and disappeared completely at the end of therapy. It seemed that this drug might have a role in the preoperative preparation of patients with very advanced tumours, certainly those with intracranial extension. Unfortunately, in a pilot study of seven patients with stage IV disease undertaken by Labra *et al.*[14] the mean shrinkage achieved was 7.5 percent (median 6.1 percent, range 4.8–11.1 percent) and this was considered to be insignificant. [**/*]

SURGICAL RESECTION – TECHNIQUES AND APPROACHES

Until relatively recently, most small tumours were resected either through a transpalatal approach, lateral rhinotomy or mid-facial degloving approach. Open approaches can be used for tumours of all stages and certainly were the only option before the application of endonasal endoscopic techniques became more widespread. Nowadays, stage Fisch 1, 2 and some type 3 tumours are suitable for endoscopic resection using one or two surgeon techniques.[15, 16, 17, 18, 19]

There is much to be gained by endonasal endoscopic techniques, for example, reduced intraoperative blood loss, fewer postoperative complications and a reduced length of hospital stay. It is difficult to know how real these claims are as no prospective trials have been undertaken and those reported are either small case series or rely on historical controls. Furthermore, the tumours resected by endoscopic techniques tend to be relatively small. Fisch type 3 tumours suitable for endoscopic resection have limited medial invasion of the infratemporal fossa. Larger tumours and those extending across or through the skull base present a very different surgical challenge which the enthusiastic endoscopist should consider carefully before embarking on a potentially life-threatening procedure.

Endoscopic endonasal techniques

Preoperative embolization is usually undertaken, notwithstanding its doubtful benefit. After the induction of anaesthesia the nose is prepared with a vasoconstrictor solution, 4 percent cocaine or epinephrine 1:10,000. The anterior end of the middle turbinate is resected at the outset of the procedure (**Figure 187.5**).

An anterior ethmoidectomy together with removal of the medial wall of the maxillary sinus gives access to the posterior wall of the antrum. This is then removed to achieve complete lateral exposure of the tumour (**Figure 187.6**). Dissection then continues into the sphenoid until its rostrum is reached following which the tumour can be peeled inferiorly (**Figure 187.7**).

A similar technique can be used to deliver the lateral extension of the tumour into the operative field (**Figure 187.8**). Throughout this process it is necessary to use bipolar diathermy and ligaclips to control the feeding blood vessels.[20] The use of a second surgeon accessing the nasal cavity through the contralateral nostril aids the resection of larger tumours. The second surgeon can apply traction to the tumour and improve visibility by additional suction.

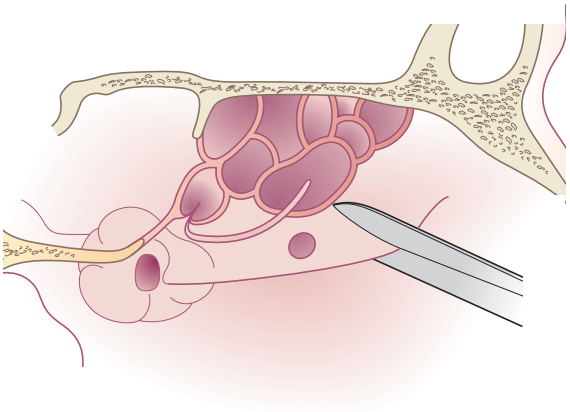

Figure 187.5 The anterior end of the middle turbinate is removed to gain access and improve visualization of the tumour.

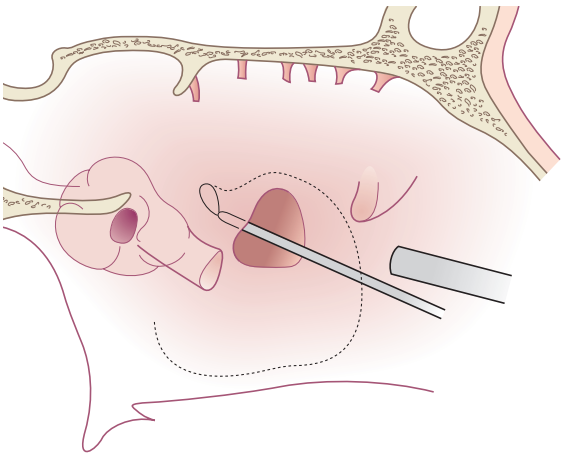

Figure 187.6 An anterior ethmoidectomy and resection of the medial antral wall is undertaken.

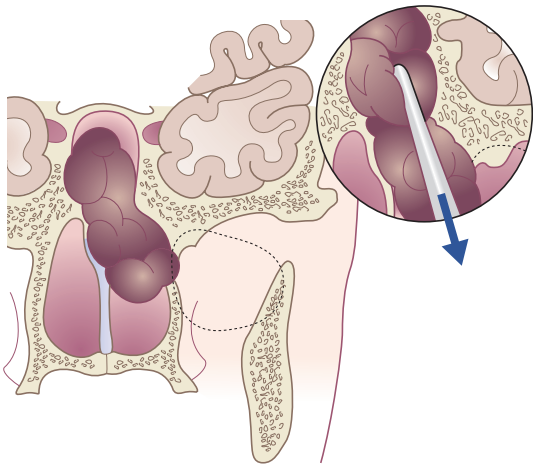

Figure 187.7 Extraction of the tumour from the sphenoid.

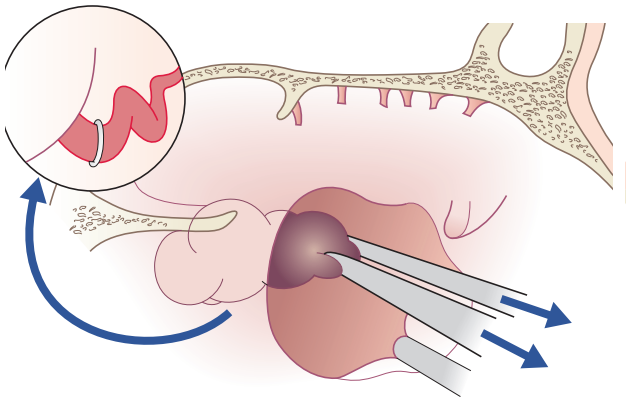

Figure 187.8 Resection of the lateral extension of the tumour and use of ligaclips to control bleeding from the feeding artery.

Open approaches

Access for open approaches has changed over the last 20 years. Transpalatal and lateral rhinotomy approaches have largely, but not completely, given way to mid-facial degloving and infratemporal approaches that were popularized in the 1980s. Most surgeons now have adopted the technique of mid-facial degloving for the resection of juvenile angiofibromas. Using the exposure afforded by this approach, the anterior, medial, lateral and posterior walls of the maxillary antrum can be removed. This produces a very large cavity that is confluent with the nasal cavity and post-nasal space and gives adequate access for tumour removal together with control of its blood supply. Extensions into the inferior part of the orbit and infratemporal fossa can also be removed (**Figure 187.9**).[21]

Extensive juvenile angiofibromas are better resected through skull base approaches, preferably undertaken by a combined otorhinolaryngological and neurosurgical team. It may be that the intranasal component can still be removed endoscopically or that endoscopic guidance may facilitate the removal of paranasal extensions. However, the components of tumour in the cavernous sinus and any intradural disease demands adequate exposure and this can only be achieved with a subtemporal pre-auricular infratemporal fossa approach, usually combined with a modified middle fossa craniectomy.[22]

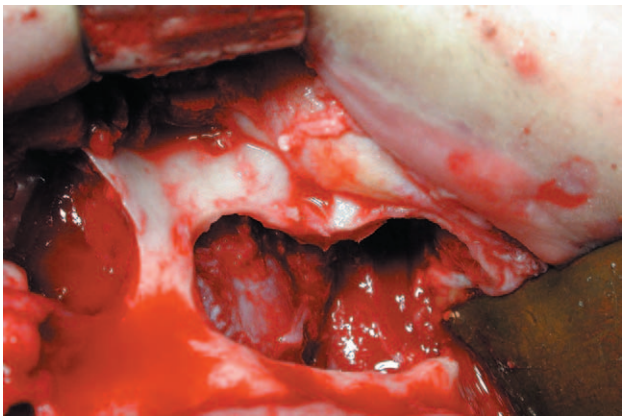

Figure 187.9 A mid-facial degloving approach to the pterygopalatine fossa. The anterior, medial, lateral and posterior walls of the antrum have been removed while preserving the infra-orbital nerve and a rim of bone around the nasal aperture.

Radiotherapy

Several centres have reported results for the treatment of advanced disease by radiotherapy.[23, 24, 25] External beam radiation was delivered in several fractions to achieve a total tumour dose of 30–55 Gy. All series report that regression of angiofibromas after radiotherapy is very slow indeed, often taking two to three years before 'radiological stabilization' is achieved. In other words, reduction in the size of the tumour takes place, but residual tumour remains. Local control rates of 80–85 percent have been achieved as assessed by clinical examination. In most series, residual disease was not assessed by interval scans unless new symptoms or signs developed. The radiation oncologists relied upon mirror examination of the nasopharynx and clinical criteria rather than objective image data to determine outcome. Treatment failure was apparent, usually within the first two to three years, and surgical salvage was generally successful in all these patients. There are no reports on the efficacy of gamma-knife therapy as yet, though some patients must have been treated by this means. [**]

COMPLICATIONS

Recurrence is by far the most common complication encountered and is reported in up to 25 percent of patients regardless of the method of treatment. Further recurrences may develop in up to 40 percent of these

patients. Not surprisingly, recurrence is more likely in patients with advanced disease and in those treated by inexperienced surgeons. As stated previously, preoperative embolization is not associated with a reduced rate of recurrence as might be expected. The one single factor that seems to correlate with recurrence is the age of the patient at the time of presentation. The younger the patient the more likely that future recurrence will develop. [**/*]

From a surgical standpoint, most recurrences develop as a consequence of invasion of the basisphenoid. A more meticulous exploration of this area at the time of primary surgery has been reported to have a dramatic effect on the rate of recurrent disease.[26] Rather than rely on macroscopic clearance of disease, drilling out the basisphenoid ensures that no residual tumour remains in the pterygoid canal or cancellous bone of the sphenoid.

In view of the very high incidence of recurrent disease, prolonged clinical and radiological monitoring is necessary for all these patients. Disease-free status five years after primary surgery probably represents cure. The same cannot be said for those who have experienced recurrent disease.

Interestingly, few surgeons have quoted complications other than recurrence. It is unlikely that this is the only possible complication, but rather that all others pale into insignificance in comparison. Surgically induced infraorbital nerve sensory deficits are recognized as a potential complication of mid-facial degloving, as is nasal vestibular stenosis.[27] Prolonged nasal crusting is also common and this may well develop into ozaena. Regular nasal douching with saline and the use of glucose in glycerine drops can do much to alleviate this unpleasant complication. With more extensive resections, ocular problems may be experienced. Displacement of the globe caused by loss of bony support, ophthalmoplegia and visual loss must have been experienced by some, but perhaps not considered a complication so much as the unavoidable consequence of a complete craniofacial resection.

Late complications also develop following radiotherapy and are relatively common. Up to 33 percent of patients in the reported series have been affected. Growth retardation, panhypopituitarism, temporal lobe necrosis, cataracts, radiation keratopathy, together with skin, thyroid and nasopharyngeal malignancies were the most common problems encountered in the first 10–15 years after treatment. Some second neoplasms have developed in the radiation field at an even later date. Whatever the success rate of radiotherapy to control disease, it has to be remembered that even 30 years after radiotherapy the patient will still be very young[28] and none of these reported complications is negligible. Furthermore, it must be recognized that all patients with residual disease are at risk of future regrowth or recurrence. For these patients, lifetime monitoring and assessment is necessary. Serial interval MR imaging should become a standard of care for these patients.

KEY POINTS

- Angiofibromas should be suspected whenever a young male patient complains of unilateral nasal obstruction, particularly if they have been experiencing epistaxes.
- The diagnosis should be made on the basis of imaging and not biopsy.
- Complete surgical resection is the treatment of choice with radiotherapy being reserved for those in whom this is not possible or who develop recurrence.
- There is a high rate of recurrence.
- Recurrence rates can be reduced by meticulous dissection of the sphenopalatine foramen.
- Recurrence usually becomes evident within two to three years of the initial resection.
- Response to radiotherapy is very slow, the effect may not be fully apparent for one to two years.

Best clinical practice

- ✓ Both CT and MR images should be acquired and clinical staging made on the basis of these data.
- ✓ Angiography and embolization is advised for those undergoing endoscopic endonasal resection and for those with intracranial extension.
- ✓ Patients should have interval imaging for at least five years before being declared disease free and cured.

Deficiencies in current knowledge and areas for future research

- ➤ The precise molecular mechanisms involved in the development of this tumour.
- ➤ Long-term outcome data for patients treated by endoscopic endonasal techniques.
- ➤ Outcome data for patients treated by gamma-knife or stereotactic radiotherapy.

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