REVIEW ARTICLE

Current Management and Controversies of Juvenile Angiofibromas

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ABSTRACT

Juvenile angiofibromas are benign, highly vascular lesions that are found in young male patients with an incidence of approximately 1:150,000. They are thought to arise from a residual vascular plexus in the pterygopalatine fossa at the aperture of the pterygoid canal, as a remnant of the involution of the first branchial arch artery. Juvenile angiofibromas remain challenging to treat. Early staged disease can be adequately treated by endoscopic approaches and with increasing experience, even higher staged disease has been shown to be resectable

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BACKGROUND

Juvenile angiofibromas (JAs) are benign, highly vascular lesions that are found in young male patients in the posterior nose and postnasal space arising from the posterolateral nasopharynx. They represent 0.05% of all head and neck tumors, with an incidence of approximately 1:150,000.¹ Radiological studies have identified their anatomical origin in the pterygopalatine fossa at the aperture of the pterygoid (vidian) canal.² They are thought to arise from a residual vascular plexus, as a

remnant of the involution of the first branchial arch artery.³ A national retrospective cohort study reported a median age of 15 years (10–24 years).⁴ Hormonal influence on their growth is also supported by the presence of androgen receptors on their cell membranes⁵ and the suppressive effects of flutamide.⁶

Main presenting symptoms include unilateral nasal obstruction (80%) and unprovoked unilateral epistaxis (60%).² Facial numbness, headaches, visual changes, and facial deformity can occur, depending on the extent of invasion. Nasal endoscopy typically reveals a lobulated, hypervascularized mass extending into the nasopharynx. The JAs are considered benign; however, they can invade and extend into the paranasal sinuses, orbit, cavernous sinus, and along the skull base. Forty percent present at an advanced stage and 17% of cases have intracranial involvement.⁷ The locally destructive characteristics, vascular nature, and 20% recurrence rate⁸ highlight the controversies surrounding management.

PRINCIPLES OF WORKUP AND MANAGEMENT

Biopsy is contraindicated in suspected JA due to the potential for catastrophic bleeding. Computed tomography (CT) is usually sufficient for diagnosis, characteristically revealing widening of the sphenopalatine foramen and extension into surrounding areas (Figs 1 and 2).

Fig. 1: Axial T1 fat-saturated postgadolinium image demonstrating enhancing tumor extending from the nasopharynx (long arrow), through the sphenopalatine foramen (short arrow) into the infratemporal fossa (stars)

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Figs 2A and B: Coronal T1 fat-saturated postgadolinium images of the same patient, demonstrating enhancing tumor in the nasal cavity (black star), nasopharynx (short white arrow), and sphenoid sinus (block arrow). Note the left vidian canal and foramen rotundum are destroyed and expanded by tumor (compare with the right vidian canal (back arrow) and foramen rotundum (long arrow))

Erosion of the upper medial pterygoid plate is pathognomonic, found in 98% of tumors.⁹ The CT is superior in distinguishing bony landmarks and sphenoid invasion, a significant factor in recurrence.² Contrast-enhanced magnetic resonance imaging (MRI) often shows “flow voids” typical of this vascular lesion and can differentiate it from other inflammatory lesions. The MRI further delineates intracranial or bone marrow involvement. The CT angiogram can be considered invaluable, where the blood supply can be fully delineated. Often direct tributaries from the internal carotid can be identified with this imaging modality further which aids surgical planning. Histological features include stellate and staghorn blood vessels with variable vessel wall thickness and irregular fibrous stroma containing stellate fibroblasts with small pyknotic to large vesicular nuclei (Figs 3 and 4).

There are multiple staging systems for JA (Table 1), predominantly focused on extent of invasion, the most advanced exhibiting intracranial extension. Traditionally,

the most popular systems are by Radkowski et al.,¹⁰ Fisch,¹¹ Andrews et al.,¹² and Chandler et al.¹³ (Table 1). However, the recently developed University of Pittsburgh Medical Center (UPMC) staging system¹⁴ focuses on prognostic factors for endoscopic surgery and questions which system is the most relevant to current management strategies.

Juvenile angiofibroma is predominantly a surgical lesion, with resection forming the mainstay of management in primary and recurrent disease, regardless of staging. Key preoperative decision-making centers on surgical approach and use of preoperative embolization, both of which shall be assessed in more detail below.

CONTROVERSIES

Endoscopic vs Open Debate

As with many surgical techniques, there has been a recent trend toward an endoscopic approach in the resection

Fig. 3: Hematoxylin-eosin stain of juvenile angiofibroma
×100 magnification

Fig. 4: Hematoxylin-eosin stain of juvenile angiofibroma
×500 magnification

Table 1: Staging of juvenile angiofibroma

Stage	Fisch ¹¹	Chandler et al. ¹³	Andrews et al. ¹²	Radkowski et al. ¹⁰	Snyderman et al. ¹⁴
I	Limited to the nasopharyngeal cavity; bone destruction negligible or limited to the sphenopalatine foramen	Confined to the nasopharynx	Limited to the nasopharyngeal cavity; bone destruction negligible or limited to the sphenopalatine foramen	Ia: Limited to the posterior nares and/or nasopharyngeal vault Ib: With involvement of at least one paranasal sinus	Nasal cavity, medial pterygopalatine fossa
II	Invading the pterygopalatine fossa or the maxillary, ethmoid, or sphenoid sinus with bone destruction	Extends to the nasal cavity and/or sphenoid	Invading the pterygopalatine fossa or the maxillary, ethmoid, or sphenoid sinus with bone destruction	IIla: Minimal lateral extension to the pterygomaxillary fossa IIlb: Full occupation of the pterygomaxillary fossa ± superior erosion orbital bones IIlc: Extension into the infratemporal fossa or pterygoid plates	Paranasal sinuses, lateral pterygopalatine fossa; no residual vascularity
III	Invading the infratemporal fossa or orbital region (a) Without intracranial involvement (b) With intracranial extradural (parasellar) involvement	Extends to one or several of the following: antrum, ethmoids, pterygomaxillary and infratemporal fossa, orbit and/or cheek	Invading the infratemporal fossa or orbital region (a) Without intracranial involvement (b) With intracranial extradural (parasellar) involvement	IIIa Erosion of the skull base (middle cranial fossa/base of pterygoids) – minimal intracranial extension IIIb Extensive intracranial extension ± extension into the cavernous sinus	Skull base erosion, orbit, infratemporal fossa; no residual vascularity
IV	Intracranial intradural tumor (a) Without infiltration of the cavernous sinus, pituitary fossa, or optic chiasm (b) With infiltration of the cavernous sinus, pituitary fossa, or optic chiasm	Extends into the cranial cavity	Intracranial intradural tumor (a) Without infiltration of the cavernous sinus, pituitary fossa, or optic chiasm (b) With infiltration of the cavernous sinus, pituitary fossa, or optic chiasm		Skull base erosion, orbit, infratemporal fossa; residual vascularity
V					Intracranial extension, residual vascularity; M, medial extension; L, lateral extension

of JAs. This is demonstrated by Cloutier et al.,¹⁵ who reported a 45% rate of endoscopic resection in one center from 2000 to 2005, increasing to 82.9% over the following 5 years. Kamel¹⁶ was the first to publish a transnasal endoscopic approach that was recommended for JAs limited to nasopharynx, nasal cavity, and ethmoid and sphenoid sinuses. Advances in surgical technique, endoscopic equipment, imaging, and intraoperative navigation systems have made endoscopic resection an option for intracranial invasion in experienced hands.^{7,17}

Transnasal endoscopic approach was initially used for early-stage disease and with increasing experience has naturally been used for stage IIIa and IIIb JAs. Evidence for the efficacy of the endoscopic approach has been described by Khoueir et al.,¹⁸ where 54 intracranial cases of JA had been successfully resected by endoscopy alone. The approach has undeniable value in managing early and carefully selected advanced disease, avoids facial

incisions, osteotomies, and even allows access to deep and lateral areas, such as the clivus and infratemporal fossa. Tumor involvement of the roof of the cavernous sinus or roof of the infratemporal fossa can be difficult to assess endoscopically and lead to incomplete resection. In these circumstances, some centers have suggested combining an endoscopy with an open craniofacial approach.^{7,19}

A wide array of open surgical approaches have been described, including midfacial degloving, transpalatal, LeFort I osteotomies, lateral rhinotomy, transfacial, craniofacial, and infratemporal approaches.¹⁴ Midfacial degloving entertains popularity in comparison with lateral rhinotomy due to its avoidance of facial scars and provision of access through both the nasal cavity and maxillary sinus. Augmentation is possible with the preauricular-subtemporal-infratemporal approach for tumors extending into the middle cranial fossa or craniofacial-subcranial approaches for tumors extending

into the anterior fossa.²⁰ A significant disadvantage of the transpalatal approach is its poor exposure of larger tumors and subsequent increased chance of recurrence.²¹ In contrast, the infratemporal craniofacial approach has been advocated in the removal of JAs with intracranial extensions, combined with subtemporal craniectomy.^{12,22} Successful resection of JAs is also described via Le Fort I osteotomies, which allow for resection of intracranial lesions, but have a 40% complication rate in advanced JAs.²³ Our unit considers even the most advanced JAs to be resectable via midfacial degloving, although in widespread recurrent disease this may, in rare circumstances, need to be augmented by combined approaches.

Hemostatic control with endoscopy has been previously considered challenging due to the limited access; however, a number of studies have indicated significantly less intraoperative blood loss with this method.²⁰ A systematic review of 1,047 cases looked at the average blood loss for the endoscopic approach which was 544 mL compared with 1579.5 mL via open techniques.²⁴ Intracranial involvement appears to be converse with an estimated blood loss (mean 1500 mL) in open procedures, compared with a mean of 2998 mL observed during endoscopic resection ($p < 0.05$).⁷ As such, intracranial involvement may ultimately lead surgeons to choose an open approach.

Ensuring adequate resection is paramount in preventing recurrence. Endoscopy has the benefit of magnification and some authors consider it to improve ability to distinguish normal tissue from tumor. Studies have, however, remained inconclusive on this endoscopic benefit. Boghani et al's²⁴ systematic review of published individual patient data concluded that although recurrence rates were less for endoscopic resections (10.8 *vs* 14.5%), the difference was not significant. However, a significantly lower recurrence rate was reported endoscopically (4.7%) in comparison with open resection (20.6%) when the same systematic review looked at aggregate patient data (APD). It should be noted that the APD series is predominantly from single-center studies with large series and therefore, more experienced surgeons, which may explain why there is a significant difference in recurrence rates. The different open approaches are also not distinguished between, so it is not possible to tell whether some have better recurrence rates than others.²³

Embolization

The benefits of minimizing intraoperative bleeding in JA resection include improved visualization and subsequent reduced chances of cerebrospinal fluid leak, cranial nerve and vascular injury. Poor visualization and excessive blood loss can ultimately prevent the complete

removal of a lesion and require future staged resections. Blood transfusion and anemia have their own additional complications.

Most surgeons now endorse preoperative embolization of the branches of the external carotid artery (ECA) 24 to 48 hours before surgery with the aim of reducing intraoperative blood loss by up to 70%.²⁰ This is supported by a systematic review that shows significantly lower blood loss in endoscopic cases, from an average of 828.3 mL without embolization to 406.7 mL with embolization. However, blood loss in the open group was significantly greater after preoperative embolization, perhaps due to the selection bias of larger tumors with more vascular involvement undergoing open resection.²⁴ The branches of the internal carotid artery (ICA) are usually not embolized due to the increased risk of intracranial embolic events. Higher stage tumors and those with a blood supply from the ECA and ICA suffer significantly greater blood loss in comparison with smaller tumors and those supplied by ECA alone.²⁵

Embolic substances used include coils, microparticles, liquid glue, polyvinyl alcohol, and an ethylene vinyl alcohol polymer, Onyx (ev3, Irvine, CA). The latter is statistically superior in reducing blood loss, reducing number of transfusions and increasing the number of lesions amenable to endoscopic resection when compared with particulate embolization.^{26,27} Additional advantages of Onyx include pigmentation of the tumor, more extensive tumor necrosis, embolization by fewer catheterizations, superior devascularization on angiograms, and no recurrence at follow-up.²⁷

If the tumor feeding vessels cannot be safely embolized or are inaccessible, then further options include intratumoral embolization and surgical strategies, such as isolation and ligation of the internal maxillary artery, radiofrequency ablation, hypotensive anesthesia, division into vascular segments, diathermy of the sphenopalatine artery, cauterization of the vidian artery (the predominant feeding vessel of the ICA), and staging of surgery.²⁰ However, preoperative embolization is not without its complications, including emboli causing ischemic events and amaurosis²³ and vision loss due to central retinal artery occlusion.^{28,29} Some authors have proposed that embolization obscures the margins of JAs intraoperatively, leading to incomplete resection.³⁰ It has also been linked to recurrence in sphenoid invasion, leading to the suggestion that this anatomical feature on imaging should be a contraindication to embolization.²

Despite its potential flaws, preoperative embolization has become an accepted standard that particularly augments the clear visual fields necessary in endoscopic resection. For larger and more invasive tumors, embolization may not be possible due to the high risk of stroke. In these

cases, open surgery is not only indicated for adequate resection, but for hemostatic control during surgery.

Staging

Embolization of branches of the external carotid allows the remaining blood supply from branches of the ICA to be delineated and is accounted for in the UPMC staging system¹⁴ (Table 1). Other popular staging systems by Radkowski et al.,¹⁰ Fisch,¹¹ Andrews et al.,¹² and Chandler et al.¹³ were established up to 20 years previously when open resection was the sole approach. These staging systems depend on the extent of invasion, with advanced stages being associated with skull base involvement and intracranial extension.

The UPMC staging system not only accounts for the vascularity of JAs but also the route of skull base extension. Its creators argue that UPMC staging can be applied to open and endonasal approach and found that residual vascularity after ICA (ECA) embolization (UPMC IV and V) correlated most strongly with blood loss, residual or recurrent tumor, and need for multiple procedures when compared with other staging systems.^{14,30} Preoperative embolization can thus effectively downstage tumors to a level associated with less perioperative risk. In two case series, they concluded that extent of disease and invasion of anatomical sites were less important in predicting complete resection with endonasal techniques. However, the review does not include open resection and has a median follow-up of 13.8 months. Other studies have shown the staging system by Andrews to correlate better with estimated surgical blood loss than UPMC ($p < 0.008$ vs $p < 0.015$), which is also only applicable where embolization is implemented. Opposing results mean multicenter studies are required to determine if a single staging system is superior in modern-day practice.

Management of Residual Disease and Recurrence

Unresectable disease is uncommon in JA management, but extensive invasion into poorly accessible anatomical regions or encasement of neurovascular structures means that on occasion small amounts of tumor are left *in situ*. If residual disease is suspected or detected on imaging, some surgeons are aggressive in their approach and proceed to total tumor removal, while others monitor residual disease to reduce the risk of morbidity from multiple procedures.²¹ Magnetic resonance imaging is considered superior in postoperative monitoring due to its superior sensitivity in distinguishing postoperative changes from recurrence.²⁰

Radiotherapy may be considered in unresectable advancing disease, with a regimen of 36 Gy at 1.8 Gy per treatment.³¹ However, the effectiveness of radiotherapy is limited and routine use in residual disease should be avoided due to long-term effects in a young population that include growth retardation, temporal lobe necrosis,³² and sarcomatous transformation.³³ Intensity-modulated radiation therapy³⁴ and proton beam therapy³¹ may help to reduce late radiation damage and offer superior target coverage, but are currently not supported by robust evidence in JA.

Recurrence of JAs commonly occurs early, between 12 and 24 months.^{2,21} Spontaneous regression has been observed^{35,36} and therefore, in a benign lesion that may not progress, serial imaging, endoscopic examination, and close observation are acceptable follow-up strategies.

CONCLUSION

Juvenile angiofibromas remain challenging to treat and current controversies center around the optimal approach to ensure complete resection. Early staged disease can be adequately treated by endoscopic approaches and with increasing experience, even higher staged disease has been shown to be resectable. Open approaches are reserved for more invasive disease, particularly those with intracranial involvement. We would advocate open approaches for very extensive JA for access and for both hemostatic control and full resection of disease.

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