The Natural Growth Rate of Residual Juvenile Angiofibroma

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Abstract

Objectives Examine the postoperative growth rate of residual juvenile angiofibroma (JA) in a large series of patients relative to pediatric growth parameters and other prognostic factors. Establish an algorithm for postoperative surveillance of patients with JA.

Design Retrospective case series.

Setting Tertiary referral academic center.

Participants Pediatric patients undergoing surgical resection of JA between September 2005 and June 2015.

Main Outcome Measures Postoperative recurrence and tumor growth rates.

Results Thirty-eight patients were identified with a mean follow-up of 24.1 months. Sixty-eight percent (26/34) of patients achieved gross total resection, and 32% (12/38) had persistent postoperative disease. Of those with postoperative residual tumor, all had preoperative skull base involvement and residual blood supply from the internal carotid artery following embolization. Sixty-seven percent (8/12) of patients with postoperative residual tumor demonstrated radiographic stability of disease with scans being completed approximately every 6 months. Radiographic rates of disease progression ranged from 4.1 to 9.22 mm/year.

Conclusions Patients with preoperative skull base involvement and residual vascularity following preoperative embolization are more likely to have residual postoperative disease, and a longer postoperative follow-up is warranted in these patients. Progression of residual disease occurred approximately 7.5 months postoperatively. Younger patients may be more likely to need further intervention for postoperative residual disease, and postoperative imaging at 6-month intervals appears appropriate.

Keywords

- Angiofibroma
- surgery
- endoscopy
- staging system
- prognosis
- skull base
- pathology

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Introduction

The surgical management of juvenile angiofibroma (JA) and the increasing preference for an endoscopic approach¹ is described well; however, the necessary postoperative surveillance is unknown. With recurrence rates of upwards of 50% in some series, the potential implications of detecting recurrent disease are not insignificant.² Although JAs are benign, they are locally aggressive and may present as intracranial pathology. In the setting of such advanced disease, it is common to leave postoperative residual disease both for the safety of the patient and the unresectable nature given the proximity to critical structures. Furthermore, as a disease of adolescence, JAs will likely involute or fail to progress at some juncture, but the exact time at which this occurs is unknown. Some authors suggest that a surge of hormones (e.g., testosterone) during puberty may induce growth of residual tumor.³ Moreover, routine radiographs for postoperative surveillance are not without potential consequences in the pediatric population given the frequent need for sedation or anesthesia in pediatric magnetic resonance imaging (MRI) and the radiation exposure associated with computed tomography (CT).

With these uncertainties in mind, we sought to examine the postoperative tumor growth rate in a large series of patients. Radiographic tumor growth rate was compared with patient demographics, known prognostic factors, and pediatric growth parameters. Pediatric growth curves were compared with tumor growth rates as a potential surrogate for changes in hormone levels. With this data, we provide recommendations for postoperative surveillance of JA.

Methods

This retrospective review was completed with the institutional board approval from the University of Pittsburgh. Patient records with a documented history of JA and surgical treatment between September 2005 and June of 2015 were examined. Patient demographics, tumor sites, extent, and stage of disease were recorded. The University of Pittsburgh Medical Center (UPMC) staging system was used to stage all patients (►Table 1).⁴ Postoperative images were reviewed by radiologists with expertise in head and neck/neuroradiology to assess for persistent disease or recurrence of disease. Pediatric growth parameters, including height, weight, and pediatric growth curves, were collected and assessed on all patients. Patients without growth parameters or follow-up were excluded from this study.

Descriptive statistics, parametric and nonparametric statistical tests were used where appropriate, and a *p*-value of 0.05 was used to determine statistical significance (GraphPad Prism software, version 6 for Macintosh; GraphPad Software Inc., La Jolla, California, United States).

Results

Thirty-eight patients met the inclusion criteria, and their demographics are shown in ►Table 2. All patients were male with an average age of 14.4 years. All patients underwent preoperative angiography and embolization. Thirty-five (92.2%) patients

Table 1 UPMC staging system is predicated on tumor location, preoperative angiography with embolization, and relationship to the internal carotid artery

Stage	
I	Nasal cavity, medial PPF
II	Paranasal sinuses, lateral PPF; no residual vascularity
III	Skull base erosion, orbit, ITF involvement; no residual vascularity
IV	Skull base erosion, orbit, ITF involvement; residual vascularity
V	Intracranial extension with residual vascularity; M: medial extension L: lateral extension

Abbreviations: ITF, infratemporal fossa; PPF, pterygopalatine fossa; UPMC, University of Pittsburgh Medical Center.

underwent an exclusively endoscopic approach, whereas the remaining three patients (7.8%) underwent a combined endoscopic and open approach. The mean follow-up time of all patients was 24.1 months.

Twelve (31.6%) of the 38 patients had postoperative residual tumor identified by either gross residual disease or immediate postoperative radiographic evidence of residual tumor. Of these patients, two-thirds (8/12) had radiographic stability of their disease and were managed with observation alone (►Table 2). Of the remaining one-third of patients, three (3/4) of these patients underwent further surgical intervention.

The most common site of residual disease was the infratemporal fossa, while the cavernous sinus and middle cranial fossa were also common (►Fig. 1). Of patients with postoperative residual disease, the mean duration of follow-up was 37 months with a modal time of interval imaging of 6 months. Patients with postoperative residual disease were

Table 2 Clinical characteristics of patients

Number of patients	38
Age (y), median (25–75th percentile)	14.4 (11.9–16.3)
Sex	All males
Previous treatment at another institution (n)	11
Preoperative embolization (%)	100
Surgical Approach (%)	
Endoscopic endonasal approach	47.3
Multiple endoscopic approaches	42.1
Combined endoscopic and open	7.8
Follow-up (mo), mean (25–75th percentile)	24.1 (1.8–37.9)
Residual tumor (n)	12
Stable (observation)	8
Requiring further surgery	4

Fig. 1 Illustrative MRI example of patient with gross postoperative residual extending into the left parapharyngeal space with subsequent regrowth of disease and further resection. (a) Initial presentation, (b) primary postoperative MRI with residual disease, (c) regrowth of residual disease, (d) complete resection of regrowth of disease. MRI, magnetic resonance imaging.

more likely to have a more advanced stage of disease (UPMC stage IV or V) at presentation when compared with patients who achieved gross total resection ($p = 0.008$) (► **Table 3**). In patients with further growth of their disease, the rate of radiographic progression ranged from 4.1 to 9.2 mm/year, with a median time to progression of disease of 7.5 months. Patients with further growth of disease ranged from 11.1 to 16.5 years of age (► **Table 4**). All patients with regrowth of

postoperative residual disease had UPMC Stage V with lateral extension (V_L) (► **Table 1**) at the time of presentation.

Three of the four cases with regrowth of postoperative residual underwent further endoscopic endonasal resection, while the fourth case may require further resection in the future given persistence of disease in the infratemporal and middle cranial fossa. Two of the three patients undergoing reresection achieved total resection without further evidence

Table 3 Comparison of stage of disease in patients who achieved gross total resection versus those with postoperative residual disease

	Number (%)	<i>p</i> Value
Gross total resection	26	
UPMC stage I–III	11 (100)	
UPMC stage IV or V	13 (58)	
Postoperative residual disease	12	
UPMC stage I–III	0 (100)	
UPMC stage IV or V	12 (100)	$p = 0.008$

Abbreviation: UPMC, University of Pittsburgh Medical Center.
Note: The *p*-value indicates comparison between patients with stage I–III disease and stage IV–V disease.

Table 4 Clinical characteristics of patients with regrowth of residual postoperative disease

UPMC Stage V_L (%)	100
Modal time of interval scan (mo)	6
Rate of radiographic progression of disease (mm/y)	4.1–9.2
Time to progression of disease (mo), median (range)	7.5 (6–15)
Age range of patients with progression (y)	11.1–16.45
Management	
Further surgery	3
Observation alone	1

Abbreviation: UPMC, University of Pittsburgh Medical Center; V_L , Stage V with lateral extension.

Fig. 2 Comparison of anatomical subsite of postoperative residual disease in patients with stability of postoperative residual (blue) as compared with patients with progression of their disease (red). CS, cavernous sinus; IOF, inferior orbital fissure; ITF, infratemporal fossa; MCF, middle cranial fossa; Meckel's, Meckel's cave.

of regrowth, while the remaining patient continued to be observed with small foci of persistent disease in the infratemporal fossa, cavernous sinus, and orbit. An illustrative example of patient with residual disease in the parapharyngeal space, regrowth of his disease, and subsequent resection is depicted in ►Fig. 1.

When patients with stable residual disease were compared with those with progression of their residual disease, there was no difference between the anatomical subsites of residual disease or when compared on the basis of intradural or extradural residual ($p = 1.0$, ►Fig. 2). Patients who required further surgical intervention for residual tumor tended to be younger than those who did not require further treatment with an average age of 11.6 years as compared with 14.2 years, but this was not statistically significant ($p = 0.18$, ►Fig. 3). Collection rates of patients' height and weight at regular intervals were inconsistent and could not be compared statistically. Six patients, three with stability of residual disease and

three with progression of residual disease, had growth parameters recorded at an exact 6-month follow-up appointment. The patients with progression of disease demonstrated a mean change in height of 4.43 cm as compared with 0.33 cm in patients who had stability of their disease ($p = 0.15$, ►Fig. 4).

Discussion

The appropriate postoperative follow-up for JA remains controversial; however, based on these results, patients with skull base involvement and residual vascularity following preoperative embolization are more likely to have residual postoperative disease. With the inherent risk of potential progression of residual disease, a longer postoperative follow-up is warranted in these patients.

In this series of patients, even advanced stage disease could be successfully managed almost exclusively with endoscopic approaches alone. Intuitively, patients with advanced stage disease were more likely to have postoperative residual tumor.

Fig. 3 Average age of patients with stability of residual disease as compared with patients who required further surgical treatment of residual disease. Error bars indicate standard error.

Fig. 4 Comparison of postoperative changes in height in six patients with stability of their disease as compared with patients with progression of their disease. Data labels indicate total growth (cm) at 6-month postoperative visit.

The most common sites of postoperative residual disease can be technically difficult to manage and include anatomical subsites, such as the infratemporal fossa, cavernous sinus, and middle cranial fossa. In line with the literature, the majority of cases with postoperative residual disease failed to progress.^{2,5} In the presented series of patients, progression of disease was seen only in patients with UPMC Stage V_L disease, intracranial disease with postembolization residual blood supply from the internal carotid artery and extension of tumor lateral to the internal carotid artery. Progression of disease was typically seen within the first 7.5 months and no later than 15 months postoperatively. Early progression or recurrence is in-line with other reports; however, recurrence later than 15 months has been reported.^{3,5} While we did not witness progression of residual disease beyond the age of 16.5 years, there is a case report of a patient who developed recurrence 20 years following resection of a JA, at age 36, following administration of exogenous testosterone therapy.³

All patients who underwent further surgery for regrowth of residual disease in this study underwent further endoscopic endonasal resection with curative intent. Two of these three patients achieved total resection, while the remaining patient had small, but measurable, foci in the infratemporal fossa, cavernous sinus, and orbit. Certainly, radiation therapy or radiosurgery would have been or is a potential option for these patients with residual disease. There is evidence that stereotactic radiosurgery can be an effective adjuvant modality; however, it is avoided in this patient population because of the relatively unknown long-term consequences in young patients.⁶ Our outcomes suggest that with a highly functioning team, most recurrences can be safely removed, even when in proximity to the internal carotid artery.

When a comparison is made between patients with residual postoperative disease who achieved stability of their disease against those who had progression of their disease, the statistical evaluations between these two groups are limited by a small sample size. Although none of these comparisons are statistically significant, some trends are worth noting. In cases with residual postoperative disease, there was an increased frequency of progression in patients with residual disease in the infratemporal and middle cranial fossa subsites. Moreover, patients who required further treatment of their progression of disease tended to be younger than those who demonstrated stability of their disease. Finally, progression of postoperative residual disease may be accompanied by a change in height, which may be representative of an underlying shift in the patient's

hormonal profile. Taken as a whole, these findings suggest that younger patients may be more likely to have progression of residual disease, especially when their disease is resected prior to a growth period (change in height).

Although JA is a disease of adolescence, there is no consensus regarding postoperative imaging guidelines. In our series, we demonstrate safe surveillance with modal magnetic resonance imaging (MRI) time of every 6 months. MRIs are most critical during the first year after surgery. The initial MRI may be difficult to interpret due to postoperative changes and proximity to vascular structures, but provides a baseline for comparison with subsequent imaging. In the absence of residual disease, surveillance beyond 2 years is probably unnecessary. If there is evidence of residual disease, closer follow-up is warranted for younger patients entering a growth phase. We recommend that such patients be followed up for at least 3 years or until the end of puberty to confirm stability or regression of residual disease. Ultimately, younger, prepubescent patients may be more likely to need further intervention for residual disease; however, a multi-institutional review with more robust statistical power and a prolonged follow-up are necessary to better characterize the postoperative progression and appropriate surveillance for this rare pathology.

Conflict of Interest

None.

References

- 1 Khoueir N, Nicolas N, Rohayem Z, Haddad A, Abou Hamad W. Exclusive endoscopic resection of juvenile nasopharyngeal angiofibroma: a systematic review of the literature. *Otolaryngol Head Neck Surg* 2014;150(03):350–358
- 2 Boghani Z, Husain Q, Kanumuri VV, et al. Juvenile nasopharyngeal angiofibroma: a systematic review and comparison of endoscopic, endoscopic-assisted, and open resection in 1047 cases. *Laryngoscope* 2013;123(04):859–869
- 3 Riggs S, Orlandi RR. Juvenile nasopharyngeal angiofibroma recurrence associated with exogenous testosterone therapy. *Head Neck* 2010;32(06):812–815
- 4 Snyderman CH, Pant H, Carrau RL, Gardner P. A new endoscopic staging system for angiofibromas. *Arch Otolaryngol Head Neck Surg* 2010;136(06):588–594
- 5 Hofmann T, Bernal-Sprekelsen M, Koele W, Reittner P, Klein E, Stammberger H. Endoscopic resection of juvenile angiofibromas—long term results. *Rhinology* 2005;43(04):282–289
- 6 López F, Triantafyllou A, Snyderman CH, et al. Nasal juvenile angiofibroma: current perspectives with emphasis on management. *Head Neck* 2017;39(05):1033–1045