Chapter

Juvenile Nasopharyngeal Angiofibroma

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Abstract

Juvenile Nasopharyngeal Angiofibroma (JNA) remains one of the most enigmatic tumors encountered by laryngotologists-head neck surgeons. Its origin at a particular age in a particular sex has intrigued many. Histopathologically benign, JNAs are locally aggressive tumors with tendency to cause massive recurrent nasal bleeds. While surgery remains the gold standard treatment, a paradigm shift from open approaches to endoscopic approach is noted. Recent advances in genomic testing, radiodiagnosis and endoscopic nasal surgeries allow us to manage these tumors more efficiently. Introduction of intensity modulated radiotherapy (IMRT), stereotactic surgery, and interventional radiology (embolisation) has further helped in this cause. This chapter aims to give a brief overview of all these aspects related to JNA with the hope to initiate more ENT surgeons to contribute to further research on this benign but dangerous tumor.

Keywords: juvenile nasal angiofibroma, JNA, vascular tumor, epistaxis, pterygopalatine fossa, frog face deformity, pathways of spread of angiofibroma, staging of JNA, immunohistochemistry of JNA, open surgery for angiofibroma, endoscopic resection, treatment of angiofibroma, embolisation, CT angiography

1. Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a benign, non-encapsulated, highly vascular tumor, occurring almost exclusively in adolescent males. Although JNAs comprise of less than 0.05% of all head and neck tumors, their tendency to bleed torrentially makes them an interesting disease entity to study and treat [1].

Development of other medical fields has been instrumental in studying the origin, growth and other characteristics of this disease entity. Advancements in radiology, histopathology and endoscopic nasal surgeries have been particularly useful. We can now better diagnoses, stage and treat JNA than the previous decade.

2. History of juvenile nasopharyngeal angiofibroma

Earliest known documentation of juvenile nasopharyngeal angiofibroma is credited to Hippocrates in the 4th century BC [2]. The term "juvenile nasopharyngeal angiofibroma" was coined by Chaveau in 1906 and his works re-sparked the interest in JNA [3]. Shaheen et al. [4] reported the first female case of JNA (1930).

Harma et al. in 1959 gave a detailed clinico-pathological insight into this tumor [5]. Works of Bensch, Ewing, Som, Neffson, Moore, Handousa, Denker etc. have been vital in understanding the natural history of disease and its surgical management [6–9].

3. Relevant anatomy

3.1 Nasopharynx

Nasopharynx is a near-cuboidal shaped space with an approximate volume of 30cm^3. It is located exactly below the middle cranial fossa.

Boundaries of Nasopharynx:

- **Anterior:** Choanae and posterior margin of nasal septum. Further anteriorly lie the right and left nasal cavities.
- **Posterior:** Fascia, prevertebral muscles, basiocciput and first two cervical vertebrae.
- **Superior:** Superior wall is continuous with the posterior wall. It is formed by basisphenoid and basiocciput.
- **Inferior:** Opens into oropharynx. When the soft palate is elevated, it makes contact with the Passavant's ridge (palatopharyngeus muscle fibers); and together these from the inferior boundary of nasopharynx.
- **Lateral:** Eustachian tube openings along with the torus tuboris is the prominent structure.

Posterior to the torus tuboris, lies a deep recess called **lateral pharyngeal recess** or **fossa of rosenmuller**. Foramen lacerum lies immediately superior to the fossa of rosenmuller. Foramen spinosum and ovale are present laterally. Petrous apex and carotid canal form its posterior relation (**Figure 1**).

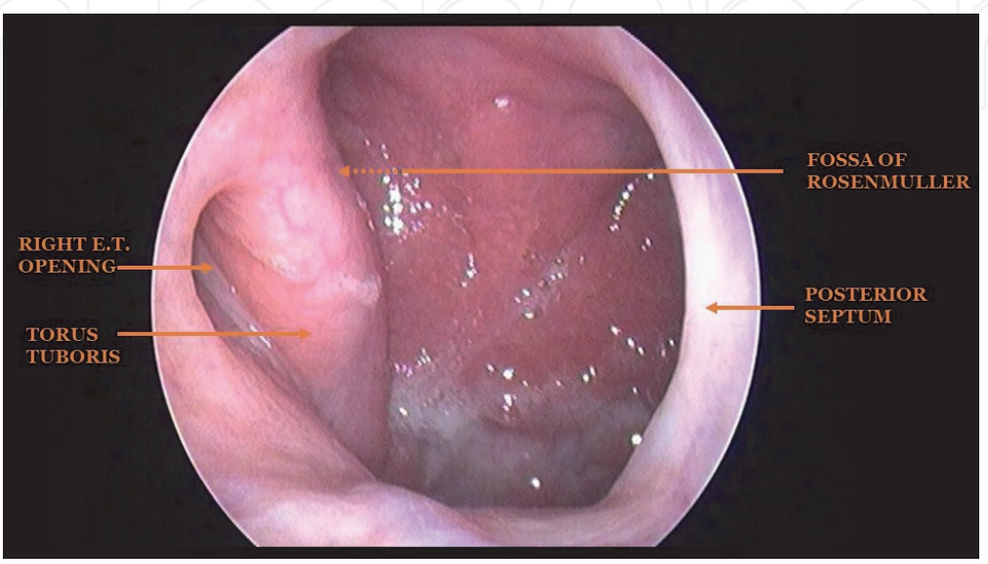

Figure 1.
Endoscopic anatomy of nasopharynx as seen through right nasal cavity (E.T.- Eustachian Tube).

3.2 Pterygopalatine fossa

Pterygopalatine fossa is a bilateral wedge-shaped space located below the orbital apex and behind the posterior wall of maxillary sinus. It communicates with other regions of skull through various canals and foramina.

Boundaries of Pterygopalatine Fossa:

- **Anterior:** Superomedial part of posterior wall of maxillary sinus.
- **Posterior:** Root of pterygoid process and anterior face of greater wing of sphenoid.
- **Medial**: Upper part of perpendicular plate of palatine bone with its sphenoidal and orbital process; sphenopalatine foramen leading to nasopharynx.
- **Lateral:** pterygomaxillary fissure leading to infratemporal fossa.
- **Superior:** Undersurface of body of sphenoid.
- I**nferior:** Pyramidal process of palatine bone with greater palatine canal.

Communications of Pterygopalatine Fossa:

- Via **sphenopalatine foramen** to nasopharynx
- Via **pterygomaxillary fissure** to infratemporal fossa
- Via **inferior orbital fissure** to orbit
- Via **greater palatine canal** to oral cavity
- Via **foramen rotundum** to middle cranial fossa
- Via **vidian (pterygoid) canal** to foramen lacerum to middle cranial fossa
- Via **palatovaginal canal** to pharynx

Contents of Pterygopalatine Fossa:

- Pterygopalatine ganglion with its branches
- Maxillary nerve (V2) and its branches
- Vidian Nerve (carrying secretomotor fibers of facial nerve from superior salivatory nucleus and sympathetic fibers from internal carotid artery via deep petrosal nerve)
- Third part of maxillary artery

4. Etiopathogenesis

Juvenile Nasopharyngeal Angiofibroma occurs almost exclusively in males and that too in adolescent period. Mean age of presentation is 14 years (range 7 years to

19 years) [10]. Isolated cases of JNAs in females or in younger/ older ages have been reported in literature [4, 11]. Exact etiology, although unknown, evidences point towards a hormonal influence on its occurrence and growth.

4.1 Theories of origin

1. **Ringertz Theory (1938):** JNA arises from the periosteum of the skull base [12].

2. **Som- Neffson Theory (1940):** If bones forming the skull base grow in a disproportionate manner, it results in the hypertrophy of underlying periosteum. Additional stimulation by hormones can result in formation of a tumor in nasopharynx [6].

3. **Bensch- Ewing Theory (1941):** Between the basi sphenoid and basi occiput, exists an embryonic fibrocartilage. This embryonic fibrocartilage proliferates to form a tumor [7].

4. **Brunner's Theory (1942):** JNA arises from conjoined buccopharyngeal and pharyngobasilar fascia [13].

5. **Martin's Theory (1948):** Imbalance between estrogens and androgens during adolescence causes JNA. Increased estrogen stimulation and/ or decreased androgen stimulation is suggested as the probable cause [14].

6. **Sternberg's Theory (1954):** JNAs are nothing but hemangiomas of nasal cavity and skull base [15].

7. **Handousa's Theory (1954):** JNA is a true neoplasm arising from periosteum of basi sphenoid [9].

8. **Osborn's Theory (1959):** Two theories were given by him. JNA is a fetal erectile tissue which proliferates under hormonal influence **(Pseudo-tumor theory)**. Or, JNA is a true hamartoma **(True tumor theory)** [16].

9. **Girgis- Fahmy's Theory (1973):** Histopathological resemblance between JNA and paragangliomas was noted by Girgis and Fahmy. The growing edge of JNA showed cell nests of undifferentiated epitheloid cells. They called this pattern "Zellballen" (German- ball of cells). JNAs belong to the same disease entity as paragangliomas [17].

10. **Hamartoma and Vascular Malformation Theory:** This is the most accepted theory at present. Although, the dilemma still exists between JNA being a hamartoma or a vascular malformation, influence of sex-hormones is an accepted notion. While some consider JNAs to be true neoplasms, other studies reveal these to be only vascular malformations [18–20].

11. **Branchial Arch Artery Theory (Bernhard Schick, 2004):** Incomplete regression of first branchial arch artery has been proposed. First branchial arch artery regresses near pterygoid base and sphenopalatine foramen, and is finally incorporated into sphenopalatine and maxillary artery. This explains

the anatomical location of the tumor at pterygoid base/ sphenopalatine foramen as well as its supply by maxillary artery. This also explains the need to drill pterygoid base to remove tumor remnants in this site of origin so as to avoid tumor recurrence. As first branchial arch artery is connected to C4-segment of internal carotid artery (ICA), its incomplete regression also explains how JNAs acquire blood supply from ICA despite no anatomical proximity [21].

4.2 Site of origin

Juvenile nasopharyngeal angiofibroma can arise from any one of the following sites:

1. *SPHENOPALATINE FORAMEN:* Upper margin of the sphenopalatine is considered as the most common site of origin of JNA. Sphenopalatine foramen is the point of trifurcation of 3 bones: palatine (perpendicular plate, orbital process and sphenoidal process), vomer (horizontal ala) and sphenoid (specifically root of pterygoid process).

2. *VIDIAN CANAL:* Vidian canal/ pterygoid canal arises from the anterior wall of foramen lacerum and opens into the posterior wall of pterygopalatine fossa. Literature states this as potential site of origin in cases with laterally extended JNAs having little/ no involvement of sphenopalatine foramen/ nasopharynx.

3. *PTERYGOID WEDGE:* Pterygoid wedge is found to be the most common site of recurrence [22]. Drilling of pterygoid wedge during primary surgery significantly reduces the risk of recurrence. First branchial arch artery theory for origin of JNA supports the same. Recent studies have been conclusively able to prove the same.

4.3 Factors for etiopathogenesis

Scientists are still looking out for exact etiological factors and how these affect the growth of the tumor. Following factors should be considered:

1. *Hormones:* Occurrence of tumor in males during adolescence phase strongly indicates hormonal influence on tumor growth initiation. An imbalance between testosterone, estrogen and progesterone has been theorized as an etiological factor. This allows the use of flutamide therapy as an adjuvant therapy for its treatment. Flutamide has been found to be effective in postpubertal patients as opposed to prepubertal patients [23].

2. *Genetic alterations:* gains and losses in the regions of 4q, 6q, 8q, 12, 17, 22q, X and Y –chromosomes are present in patients of juvenile nasopharyngeal angiofibroma [19, 24–26]. Over expression or under expression of p53 on chromosome 17 has been implicated in tumor cells [27–30]. Her-2/neu receptors (encoded by Her-2 gene on chromosome 17) have also a role in JNA [29].

3. *Molecular pathology:* Cytokines such as transforming growth factor beta-1 (TGFβ-1) and Insulin-like growth factor-2 (IGF2) are involved in the growth of this tumor. Vascular endothelial growth factor (VEGF) and platelet derived

growth factor (PDGF) have been implicated as most important factors for neoangiogenesis [28, 30]. AURKB, FGF18, and SUPT16H can act as potential molecular markers in JNA [31].

5. Pathology

MACROSCOPIC: On gross examination, the tumor appears as a polypoidal, non-encapsulated, red to gray colored mass with spongy appearance. Mean size is 4 cm.

MICROSCOPIC: The tumor has a fibrous stroma with abundant blood vessels. The blood vessels are of variable sizes without any organized layout. Elastin fibers in the blood vessels are typically absent while the muscle layer maybe absent, focal (pad-like) or circumferential. This accounts for profuse bleeding in these tumors as these blood vessels are unable to contract to achieve effective hemostasis.

The fibrous stroma has varying amounts of fine and coarse collagen fibers. Plump spindle, angular, or stellate-shaped cells are also seen. Rarely, mast cells may be present. The nuclei of stromal cells generally lack any characteristic features; although, multinucleated pleomorphic cells are not uncommon.

The vascular and fibrous elements vary in proportion within the same tumor and with the tumor age. While the fibrous component is more towards the centre of the tumor, peripheral areas have abundance of vascular elements. Also, newer lesions have predominantly vascular component while long standing tumors are enriched with fibrous tissue.

Embolised specimens show myxoid changes with areas of infarction. Embolic agent can be seen in the tumor vessels. Post flutamide therapy or radiotherapy specimens show a significant increase in fibrous component (**Figure 2**).

IMMUNOHISTOCHEMISTRY: Immunohistochemistry (IHC) tests act as ancillary tests for juvenile nasopharyngeal angiofibroma. Various IHC tests are described in the **Table 1**.

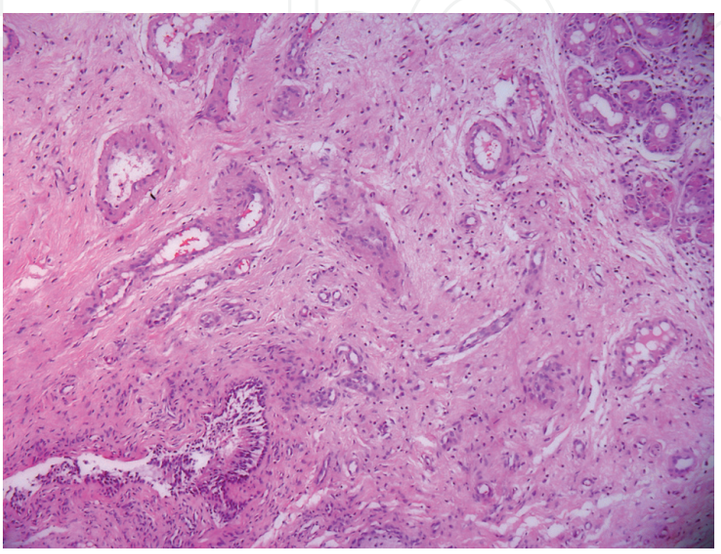

Figure 2.
Histopathological section of JNA as seen under a microscope. Multiple blood vessels of varying diameters are seen in a fibrous stroma.

IMMUNOHISTOCHEMISTRY			
TEST ANTIBODY	**TUMOR COMPONENT**	**TUMOR CELLS**	**STAINING PATTERN**
1. Vimentin	Vascular & Fibrous	All tumor cells	Cytoplasmic
2. Androgen receptor	Vascular & Fibrous	All stromal cells and endothelial cells	Nuclear
3. VEGF	Vascular & Fibrous	Stromal and vascular cells	Cytoplasmic
4. PDGF	Vascular & Fibrous	Stromal and vascular cells (+/−)	Cytoplasmic
5. IGF-2	Vascular & Fibrous	Stromal and vascular cells (+/−)	Cytoplasmic
6. TGF- β	Vascular & Fibrous	Stromal and vascular cells (+/−)	Cytoplasmic
7. SMA (Smooth Muscle Actin)	Vascular	Smooth muscle cells in blood vessels	Cytoplasmic
8. Desmin	Vascular	Cells in walls of larger blood vessels	Cytoplasmic
9. FVIIIRAg	Vascular	Endothelial cells	Cytoplasmic
10. CD31	Vascular	Endothelial cells	Cytoplasmic
11. CD34	Vascular	Endothelial cells	Cytoplasmic
12. ER	Vascular	Vascular cell nuclei (+/−)	Nuclear
13. PR	Vascular	Vascular cell nuclei (+/−)	Nuclear
14. CD117 (c-kit)	Fibrous	Stromal cells	Cytoplasmic
15. β Catenin	Fibrous	Stromal cells	Nuclear

Table 1.
Immunohistochemistry (IHC) tests for JNA.

6. Spread of JNA

JNA arises at the upper lip of sphenopalatine foramen. As it grows further, it spreads along the path of least resistance to involve many vital structures.

6.1 Medial extension

From sphenopalatine foramen, it extends into the nasopharynx and grows submucosally. It can occupy the entire nasopharynx to produce bilateral nasal obstruction and nasal intonation of voice (rhinolalia clausa). Recurrent epistaxis often starts at this stage only. The tumor mass may depress the soft palate or hang in the oropharynx. Blockage of eustachian tube(s) results in conductive hearing loss (otitis media with effusion).

6.2 Anterior extension

i. It enters the ipsilateral nasal cavity first to cause unilateral nasal obstruction and epistaxis. Here it may acquire secondary attachments.

ii. As the tumor grows further within the ipsilateral nasal cavity, it pushes the nasal septum towards the opposite side to produce contralateral nasal obstruction as well.

iii. Further tumor growth allows it to involve ethmoidal sinuses. This results in flattening of the nasal bridge and an increase in the intercanthal distance.

An associated proptosis gives a classical '**frog- face deformity**' to the patient.

iv. The tumor may encroach upon and erode anterior wall of sphenoid sinus. It may further invade the sphenoid sinus.

6.3 Lateral extension

Lateral growth of the tumor results in the involvement of pterygopalatine fossa. Pterygopalatine fossa is a small wedge-shaped cavity, which can be considered as a cross-section/ junction point of many important 'highways'.

i. As the mass lesion fills the pterygopalatine fossa, it causes anterior bowing of the posterior wall of maxillary sinus **(Antral Sign/ Holman- Miller Sign)**.

ii. From pterygopalatine fossa, it can extend into the orbit via the inferior orbital fissure. This produces proptosis. Further involvement of orbital apex results in loss of vision. Involvement of extraocular muscles produces diplopia.

iii. From pterygopalatine fossa, tumor grows laterally to invade infratemporal fossa via the pterygomaxillary fissure. This causes facial swelling and fullness in the cheek region. Erosion of the anterior face of greater wing of sphenoid causes entry of tumor into the middle cranial fossa.

iv. From pterygopalatine fossa, it can grow along the vidian canal to reach foramen lacerum. Foramen lacerum opens in the middle cranial fossa, providing easy access to the tumor for intra cranial extension.

6.4 Posterior extension

i. The tumor can erode the pterygoid process posteriorly and spread downwards into the pterygoid fossa. It can reach as far as the parapharyngeal space.

ii. Tumor growth in the posterolateral part of nasopharynx can cause extension into the fossa of rosenmuller. Further posterolateral growth into the apex of this fossa results in intracranial extension by eroding the carotid canal and petrous apex.

6.5 Inraorbital extension

The tumor can involve the orbit through the following routes-

i. Sphenopalatine foramen ➜ pterygopalatine fossa ➜ via inferior orbital fissure ➜ enters orbit.

ii. Sphenopalatine foramen ➜ nasopharynx and nasal cavity ➜ erodes lamina papyracea ➜ enters orbit.

6.6 Intracranial extension

The tumor can have intracranial extension through the following routes:

i. Sphenopalatine foramen ➜ pterygopalatine fossa ➜ infratemporal fossa ➜ erosion of anterior face of greater wing of sphenoid AND/ OR through foramen ovale causing its widening ➜ middle cranial fossa. The tumor lies lateral to Internal Carotid Artery (ICA) and Cavernous Sinus (CS) in such cases.

ii. Sphenopalatine foramen ➜ pterygopalatine fossa ➜ via inferior orbital fissure ➜ orbit ➜ growth within orbit towards orbital apex and superior orbital fissure ➜ middle cranial fossa. The tumor lies anterolateral to ICA and lateral to CS.

iii. Sphenopalatine foramen ➜ nasopharynx and nasal cavity ➜ erosion of floor and anterior wall of sphenoid sinus to invade sphenoid sinus ➜ erosion of roof of sphenoid sinus ➜ intracranial spread. The tumor lies medial to ICA and lateral to pituitary gland.

iv. Sphenopalatine foramen ➜ pterygopalatine fossa ➜ pterygoid (vidian) canal ➜ foramen lacerum ➜ middle cranial fossa. Encasement of ICA is seen early.

v. Sphenopalatine foramen ➜ nasopharynx ➜ fossa of rosenmuller ➜ erodes carotid canal and petrous apex ➜ intracranial spread.

vi. Sphenopalatine foramen ➜ nasopharynx ➜ nasal cavity ➜ through cribriform plate ➜ anterior cranial fossa (rare route for intracranial extension).

7. Clinical features

7.1 Age/sex

The patient is almost invariably male in his second decade of life. Mean age of presentation is 14 years (reference).

7.2 Symptoms

The patient may have one or more of the following symptoms

i. *Nasal bleed:* any adolescent male presenting with recurrent nasal bleeds should always raise the suspicion of angiofibroma. Nasal bleeds are usually massive and often require an intervention to control them.

ii. *Nasal obstruction:* initially unilateral. Later, bilateral nasal obstruction develops owing to involvement of entire nasopharynx or pushing of nasal septum to the other side

iii. *Nasal discharge:* mucopurulent nasal discharge due to pent up secretions in the nasal cavity followed by secondary infection.

iv. *Hyposmia/ Anosmia*: mechanical obstruction due to tumor mass of olfactory area can cause decreased sense of smell.

v. *Weakness and irritability:* easy fatiguability and irritability due to frequent nasal bleeds causing chronic anemia.

vi. *Voice change:* Voice takes a nasal intonation owing to the tumor mass in the nasopharynx (rhinolalia clausa). Tumor mass depressing the soft palate causes 'plummy voice'.

vii. *Facial swelling:* ipsilateral cheek swelling results when JNA involves the infratemporal fossa.

viii. *Facial deformity:* flattening of dorsum of nose with increased intercanthal distance and proptosis results in 'frog face deformity'.

ix. *Headache:* headache may result from chronic rhinosinusitis, or chronic anemia, or intracranial extension of tumor.

x. *Otological/ Aural symptoms*: eustachian tube blockade in nasopharynx results in serous otitis media causing conductive hearing loss and heaviness in ears.

xi. *Ocular symptoms*: involvement of orbit causes proptosis, double vision, or even loss of vision.

xii. *Intracranial symptoms:* headache, seizures, loss of consciousness owing to intracranial spread of tumor.

7.3 Anterior rhinoscopy

Mucopurulent discharge in the involved side is seen. Tumor mass may also be visualized. Septum is often deviated towards contralateral side.

7.4 Posterior rhinoscopy

Mass lesion is visualized in the nasopharynx.

7.5 Diagnostic nasal endoscopy

Examination with a Hopkin's rigid rod lens 0° endoscope reveals a fleshy mass lesion. It is usually covered in mucopurulent secretions which require gentle suctioning. Probing is avoided as it can complicate into profuse nasal bleed.

8. Investigations

8.1 Biopsy

Though for any nasal mass, golden rule is that biopsy is preceded by radiological imaging to ascertain origin, extent, and nature of the disease; in vascular tumors such as JNAs, biopsy is contraindicated. Risk of bleeding during and/ or after the procedure outweighs any added advantage we may get out of preoperative biopsy.

8.2 X-ray PNS

Water's view (Occipitomental view)/ Peer's view (Occipitomental view with open mouth) shows haziness of the involved sinus. Lateral view shows anterior bowing of posterior wall of maxillary antrum (**Holman Miller sign**).

8.3 CT NOSE–PNS

Contrast enhanced computed tomographic imaging is the investigation of choice for JNA. Infact, the diagnosis of JNA is confirmed by presence of a mass in nasopharynx and pterygopalatine fossa that enhances after contrast administration on CECT. CECT is a non-invasive procedure that forms the basis for JNA diagnosis and staging.

Lloyd's criteria for diagnosis of JNA on CECT [32]:

i. mass lesion in the nasopharynx/ nasal cavity and pterygopalatine fossa

ii. erosion of posterior bony margin of sphenopalatine foramen with extension to the upper medial pterygoid plate.

Holman Miller sign/ Antral sign: anterior bowing of the posterior wall of maxillary antrum. This is due to the tumor mass completely filling the pterygopalatine fossa.

Hondousa Sign: widening of the gap between the maxillary body and ramus of mandible. This occurs when the tumor mass involves infratemporal fossa.

Ram Haran Sign: In JNA patients, coronal cuts of CT Nose- PNS show widening of the pterygoid wedge. It appears as a quadrilateral area rather than normal triangular area [33].

Chopstick Sign: CECT when used for post-operative surveillance to detect residual/ recurrent tumor, shows 'floating' medial and lateral pterygoid plates in cases where the root of pterygoid base is drilled. These pterygoid plates are visualized separately to give appearance of a pair of chopsticks.

8.4 MRI

Contrast enhanced MRI (CE-MRI) is the investigation of choice for advanced JNA tumors, particularly those with intracranial, intra-orbital, or parapharyngeal space involvement. It can accurately determine the extent of the tumor. 'Salt and pepper' appearance on contrast MRI is characteristic to any vascular tumor, resulting due to flow-void areas (T2WI and contrast enhanced T1WI) [22, 34].

Fat Suppression MRI: This has an immense potential in detecting bone invasion by tumor. In fat-suppression MRI sequence, a normal pterygoid wedge should be hypointense owing to fat-rich marrow. Any iso−/hyper-intensity in that area indicates invasion by the tumor, therefore, requiring bone drilling to avoid recurrence.

MRI is also the preferred modality for post-operative long-term surveillance because of its superior soft tissue differentiation quality without any radiation exposure.

8.5 CT-angiography

CT angiography is useful to identify the feeder vessel(s) to the tumor. Internal maxillary artery is the most common feeder vessel for JNA. JNA may additionally acquire blood supply from ascending pharyngeal artery, contralateral external carotid artery branches, ipsilateral or contralateral internal carotid artery and its branches (ophthalmic, meningohypophyseal, vidian artery).

Knowledge about the feeding vessel and its site of entry into the tumor is absolutely critical to decide the surgical approach for JNA excision. For example, where feeder vessels are located posterior to the main tumor mass without direct access, open approach is preferred to endoscopic approach.

8.6 Digital subtraction angiography (DSA)

DSA is used in preoperative phase to identify the feeder vessel and its preoperative embolization. Selective vessel angiography in DSA allows to determine the exact branch(es) supplying the tumor and its selective embolization. JNA shows a characteristic *'tumor blush'* in DSA of external carotid artery. This can also help in predicting the expected blood loss during tumor resection [35].

9. Staging of JNA

Various staging systems have been proposed over the years, each with its own merits and demerits.

9.1 Session's staging system, 1981

Table 2

SESSION'S STAGING SYSTEM	
STAGE	**TUMOR EXTENSION**
IA	Involvement of the nose or nasopharyngeal vault
IB	Extension into one or more sinuses
IIA	Minimal extension into the pterygopalatine fossa
IIB	Full occupation of the pterygopalatine fossa
IIC	Infratemporal extension (± involvement of the cheek)
III	Intracranial extension

Table 2.
JNA staging system by Sessions, 1981 [36].

9.2 Chandler's staging system, 1984

Table 3

CHANDLER'S STAGING SYSTEM	
STAGE	TUMOR EXTENSION
I	Involvement of the nasopharyngeal vault
II	Extension into nasal cavity or sphenoid sinus
III	Extension into maxillary sinus, ethmoid sinus, pterygopalatine fossa, infratemporal fossa, cheek, palate
IV	Intracranial extension

Table 3.
JNA staging system by Chandler, 1984 [37].

9.3 Andrews-Fisch's staging system, 1989

Table 4

ANDREWS-FISCH'S STAGING SYSTEM	
STAGE	**TUMOR EXTENSION**
I	Confined to nose or nasopharyngeal vault
II	Invasion of the pterygopalatine fossa or maxillary/ ethmoid/ sphenoid sinuses with bone destruction
IIIA	Extension into the infra- temporal fossa or orbit
IIIB	Intracranial but extradural extension (parasellar area)
IVA	Intracranial intradural extension **without** involving **c**avernous sinus/ **o**ptic chiasma/ **p**ituitary fossa (*mnemonic C-O-P)*
IVB	Intracranial intradural extension involving **c**avernous sinus/ **o**ptic chiasma/ **p**ituitary fossa

Table 4.
JNA staging system by Andrew- Fisch, 1989 [38].

9.4 Radkowski's staging system, 1996

Table 5

RADKOWSKI'S STAGING SYSTEM	
STAGE	**TUMOR EXTENSION**
IA	Involvement of the nose or nasopharyngeal vault
IB	Extension into one or more sinuses
IIA	Minimal extension into pterygopalatine fossa
IIB	Complete extension into pterygopalatine fossa
IIC	Extension into infratemporal fossa/ posterior to pterygoid plates
IIIA	Minimal skull base involvement (middle cranial fossa/ base of pterygoid plates)
IIIB	Extensive intracranial involvement ± involvement of cavernous sinus

Table 5.
JNA staging system by radkowski, 1996 [39].

9.5 Endoscopic system of staging

9.5.1 UPMC (University of Pittsburgh Medical Center)/ Snyderman, 2010

Only valid for tumors which are preoperatively embolised (**Table 6**).

UPMC/ SNYDERMAN'S STAGING SYSTEM	
STAGE	**TUMOR EXTENSION**
I	Nasal cavity, medial pterygopalatine fossa
II	Paranasal sinuses and lateral pterygopalatine fossa, no residual vascularity
III	Skull base erosion, orbit, infratemporal fossa, no residual vascularity

UPMC/ SNYDERMAN'S STAGING SYSTEM	
STAGE	**TUMOR EXTENSION**
IV	Skull base erosion, orbit, infratemporal fossa, with residual vascularity from ICA
V	Intracranial extension with residual vascularity from ICA
VM	Medial cavernous sinus
VL	Middle cranial fossa

Table 6.
JNA staging system by Snyderman/ UPMC, 2010 [40].

10. Treatment

Choice of treatment depends on the size and extent of the tumor. Treatment modalities include surgical excision (open v/s endoscopic approach) and non-surgical adjuvant therapy (embolization/hormonal/ radiotherapy) or their combination(s).

10.1 Surgical treatment of JNA

Complete excision of the entire tumor mass should be the aim of any surgical procedure and the approach selected accordingly. Though the advancements in endoscopic surgery have minimized the need for open approaches, the surgeon should be well versed with all the techniques.

10.1.1 Open surgical approach

In general, open approaches have the advantage of providing a wide exposure. But this comes at the cost of higher morbidity, increased hospital stay, and some degree of cosmetic deformity.

10.1.1.1 Transpalatal approach

This is the shortest and most direct approach for tumors limited to nasopharynx with/ without minimal extension into sphenoid sinus/ choana [41, 42].

A U-shaped incision (Wilson's incision) is made 2.5 cm anterior to the junction of hard and soft palate. Submucoperiosteal flap is elevated posteriorly till the soft palate to bare the underlying horizontal plate of palatine bone. Soft palate and hard palate are separated. Bone is removed from the posterior part of hard palate to visualize the entire nasopharynx along with the tumor.

This approach has the advantage of good post-operative healing with no visible scar.

10.1.1.2 Transnasal- maxillary approach

10.1.1.2.1 Lateral rhinotomy

Lateral rhinotomy was first described by Irwin Moore in 1917 [43].

The incision is started 5 mm anterior and superior to the medial canthus and continued inferiorly along the deepest portion of the nasomaxillary groove. At its inferior end, it is curved medially in the crease beneath the ala. Skin flaps are

elevated over the maxilla and nasal bones. Medial wall of maxillary antrum is removed.

This provides adequate exposure for tumors extending into the nasal cavity and/or sinuses with minimal extension into the pterygopalatine fossa.

Adequate healing allows for an inconspicuous scar mark, well hidden within the facial creases.

10.1.1.2.2 Extended lateral rhinotomy

The lateral rhinotomy incision is further extended inferiorly along the ipsilateral ridge of the philtrum and continued to split the upper lip in paramedian position. After dividing the upper lip, incision is continued laterally along the gingivobuccal sulcus upto the first molar. This approach is required in cases needing exposure beyond the infraorbital neurovascular bundle.

10.1.1.2.3 Extended subtoal maxillectomy

The main objective of this approach is to expose the maxillary antrum and remove its medial, anterior and posterolateral walls along with perpendicular plate of palatine bone. Orbital floor and alveolar arch are left intact. This converts the maxillary sinus, nasal cavity, nasopharynx, pterygopalatine fossa and infratemporal fossa into a single large accessible cavity.

This wide exposure is required for large tumors spilling in the infratemporal fossa. Lateral most aspect of these tumors is identified. Feeder vessel in the form of internal maxillary artery (most common feeder vessel) is identified as it enters the lateral aspect of the tumor in the infratemporal fossa and ligated before starting with the tumor dissection. Ascending pharyngeal artery maybe seen entering and supplying the tumor at its posterior aspect. It is also identified and ligated. This allows for minimal blood loss during the tumor dissection and delivery. Tumor delivery is done in-toto through transnasal/ transoral route or in a piecemeal fashion.

Two pathways for this approach have been described:

I. **Weber-Ferguson's Incision:** The incision starts just below the lateral canthus upto the medial canthus in the subciliary crease. It is continued inferiorly along the nasomaxillary groove and turned medially at alar crease. It is again curved inferiorly along the philtrum to split the upper lip. Gingivobuccal incision is extended laterally upto the first molar area. Ectropion, cheek anesthesia, and an unsightly scar are often encountered complications of this approach.

II. **Mid Facial Degloving:** A complete transfixation incision is placed in the anterior nasal septum followed by bilateral intercartilagenous incisions between upper and lower lateral cartilages. Incision over the pyriform aperture is made on both sides. A sublabial incision between the two upper second molars is made and dissection continued superiorly to join it with the nasal incisions. Entire skin and soft tissue flap is retracted superiorly to reveal the whole midface skeleton. Although more technologically challenging, this approach has the advantage of no visible scar. Cheek anesthesia is an almost inevitable complication. Nasal vestibular stenosis has also been reported with the use of this approach.

10.1.1.2.4 Le fort-I approach

An incision is made in the gingivobuccal sulcus between the two upper second molars. Periosteum is elevated to expose maxilla in its anterior and lateral aspect. Horizontal osteotomies from pyriform aperture to pterygomaxillary fissure and from pyriform aperture to palatine canals are made. Nasal septum is freed from anterior nasal spine and maxillary crest. Pterygoid dysjuctioning allows easy down fracturing of maxilla to achieve a wide exposure of the tumor extending into multiple paranasal sinuses, infratemporal fossa or intracranial space. After tumor excision, fixation of mid facial skeleton is achieved using titanium plates. This approach provides the widest possible exposure without any external scar [44].

10.1.1.3 Transfacial approach

10.1.1.3.1 Maxillary swing

A Weber-Ferguson incision is combined with the splitting of the hard palate [45, 46]. Multiple osteotomies are done and maxilla is disarticulated. Overlying skin and muscles are NOT dissected. Rather they are raised as a single flap along with underlying maxillary and zygomatic bone (**cheek masseter maxillary flap**). After tumor excision, maxilla is repositioned and fixed with titanium plates followed by layered suturing of the skin incision.

This approach provides accessibility to nasopharynx, paranasal sinuses, infratemporal fossa, parapharyngeal space and intracranial space. Malocclusion of upper jaw and palatal fistula are some uncommon but difficult to manage complications associated with this procedure [47].

10.1.1.3.2 Maxillary removal and reinsertion (MRR)

MRR starts as a midfacial degloving approach through a sublabial incision [48]. Partial osteotomy at nasofrontal angle allows extended degloving of midface. Multiple osteotomies are made to resect and remove the maxillary bone. Tumor is resected. Maxilla is repositioned at its original anatomical position and secured with titanium plates/ absorbable plates.

Wide exposure for tumor resection from infratemporal fossa, parapharyngeal space, and middle and anterior cranial fossa is achieved. Such extensive resections can cause malocclusions, visual disturbances and disruption of growth centres in the maxillary bone, resulting in future cosmetic deformities.

10.1.1.4 Infratemporal fossa approach

Fisch Type C and **Fisch Type D** are the two most commonly used approaches for extensive JNAs. Infratemporal approaches are suitable for gaining excess to infratemporal fossa, middle cranial fossa and lateral cavernous sinus [49]. Good resection rates are achieved with low recurrence rates. Major complications of Fisch Type C approach are a permanent conductive hearing loss, cosmetic deformity and loss of facial sensation. Fisch Type D approach was later added with the advantage of avoiding a visible facial scar, hearing loss and ability to convert as Type C approach as and when required [50, 51]. However, these approaches fail to resect tumors extending medial to the abducent cranial nerve in the cavernous sinus [52].

10.1.1.5 Craniofacial resection

A combination of infratemporal fossa approach and transfacial approach is required in certain cases with advanced stage angiofibromas [52]. This approach allows access to the infratemporal fossa, middle and anterior cranial fossa, and entire cavernous sinus (both medial and lateral aspects). An added enhanced exposure to the nasopharynx, paranasal sinuses and pterygopalatine fossa facilitates complete tumor excision. Facial skeletal growth retardations and facial asymmetry is rare [53].

10.1.1.6 Combined open approach

Large primary tumors or recurrent tumors may necessitate the need for using more than one open approach in the same sitting. These combinations can be tailor –made depending on size of the tumor, involvement of vital structures, and surgeon's expertise in one or more approaches. Some commonly used combined approaches are-

i. **Transapalatal + Lateral Rhinotomy:** In large tumors, not amenable to single approach surgery, this was the most common approach used earlier.

ii. **Sardana's Approach:** Sublabial approach combined with a partial transpalatal approach (without removing bone from posterior part of hard palate) [54].

iii. **Midface Degloving + Transzygomatic Approach:** This achieves a wide exposure with radical tumor excision and good hemostasis [55].

iv. **Triple Approach of Hiranandani:** Combination of lateral rhinotomy with transpalatal approach with Caldwell-Luc's approach [56].

v. **Craniofacial Resections:** Infratemporal fossa approach combined with transfacial approach. Craniofacial resections can be included in this category as well [52].

10.1.2 Endoscopic approach

Last decade has seen a paradigm shift from open approach to transnasal endoscopic approach. In today's time, endoscopic surgery can be regarded as the most rapidly advancing surgical field. As the surgeon's familiarity with the endoscopes is increasing, hard to reach anatomical regions are also becoming more accessible, thereby, widening the horizon for this approach. Tumors, which were earlier labeled as operable via an open approach only, can now be easily and completely resected using endoscopic approach.

Endoscopic surgery has the advantage of better illumination and magnification, lower morbidity, and shorter duration of hospital stay which ultimately leads to cost saving. Advantage of no visible facial scar adds to the cosmetic viability of this approach.

10.1.2.1 Surgical considerations for endoscopic jna surgery

1. Tumor size and extent decides the exact endoscopic approach required. While smaller tumors are managed via an endonasal approach; medium to large sized tumors require an endoscopic Denker's / Sturman- Canfield or a more extensive transpterygoid approach [57, 58].

Extended anterior skull base approaches are recommended for intracranial lesions [59].

1. Exposure is the key to a successful surgery. Adequate exposure allows identification of tumor limits, delineation of feeder vessels, and assessment of tumor's relation with vital structures. Most of the surgical time is spent in achieving this exposure before starting off with the tumor resection.

2. It is always advisable to identify and ligate the feeding artery first (usually internal maxillary artery), before starting with tumor dissection.

3. Posterior septectomy, wherever required, is recommended. This greatly increases the access to the tumor.

4. Dissection is carried along the tumor pseudocapsule from lateral to medial direction. Any injury to tumor surface can provoke massive bleeding.

5. For larger tumors, a four-handed technique is recommended [22]. For large tumors with extensive lateral extension into infratemporal fossa/ parapharyngeal space, the four-port Bradoo's technique is a worthy option [60].

6. Drilling of pterygoid base at the end of the procedure should be a routine practice, so as to minimize the recurrence rates (**Figures 3–8**).

7. The operative room should have the availability of hemostatic materials like SURGICEL, FLOSEAL, TIS SEEL and a functioning bipolar cautery. Access to a blood bank is recommended.

8. Coblation is a plasma based device that can be used for surface coagulation of the tumor without causing any collateral thermal damage. This shrinks the tumor and also greatly reduces intra-op bleeding.

9. During preoperative planning stage, it is imperative to discuss with the patient, the possibility to convert an endoscopic approach into an open approach at any given time during the surgery.

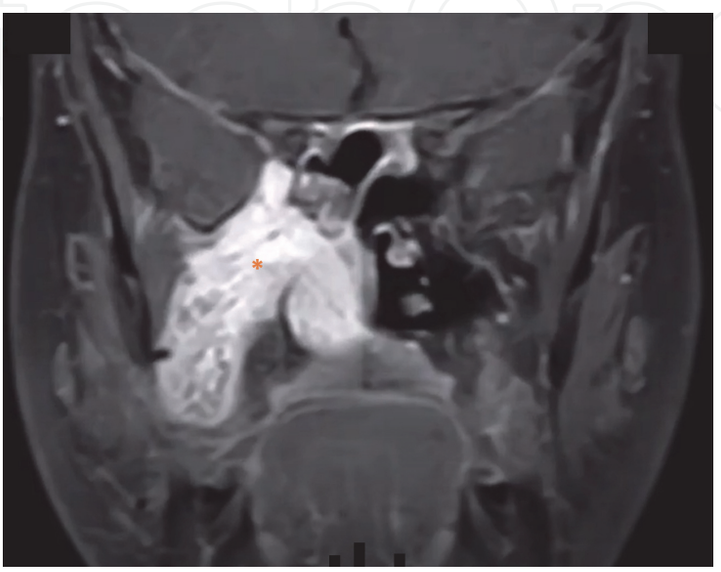

Figure 3.
CE-MRI showing hyperintense tumor (*) with massive lateral extension into infratemporal fossa.

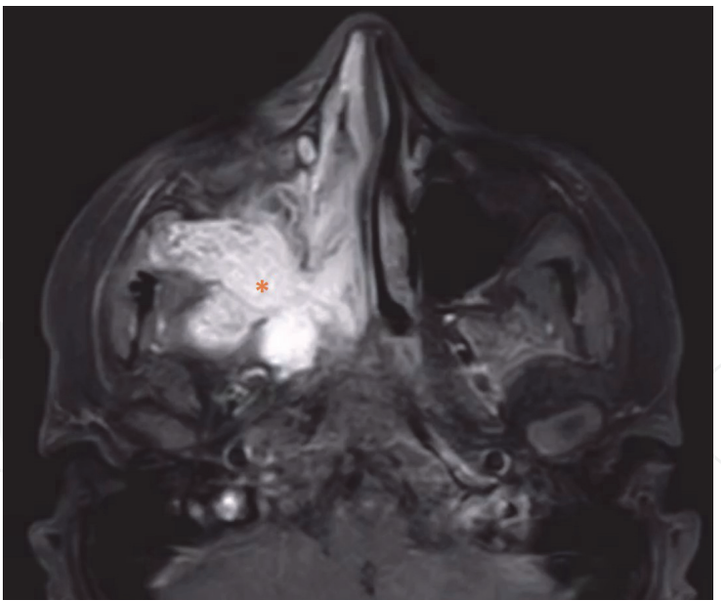

Figure 4.
CE-MRI showing hyperintense tumor (*) in the infratemporal fossa.

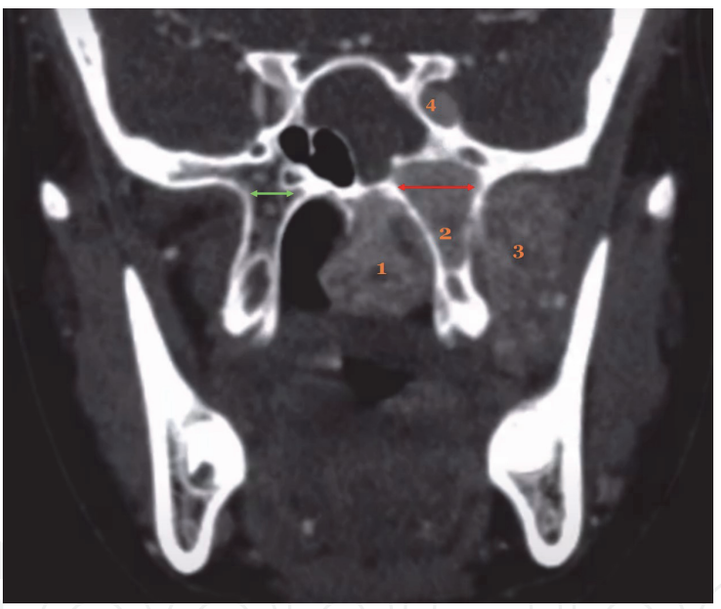

Figure 5.
CECT showing JNA occupying nasopharynx (1), pterygoid wedge (2), infratemporal fossa (3) and intracranial space (4). Notice the widening of left pterygoid wedge (red arrow) as compared to the right normal pterygoid wedge (green arrow)- Ram Haran Sign.

10.1.2.2 Contraindications to endoscopic approach

i. Broad skull base infiltration

ii. extensive blood supply from ICA

iii. encasement of ICA

iv. brain infiltration

Considering the pace of progress in endoscopic techniques, it would not be surprising if some more indications are added by the time this chapter reaches the readers.

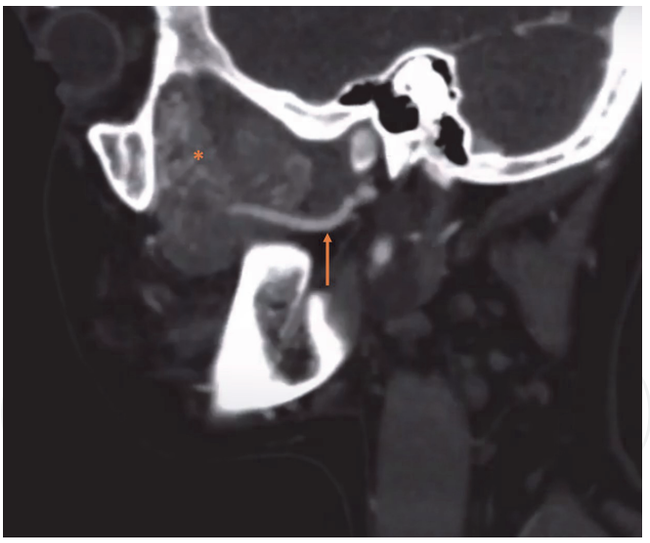

Figure 6.
CT angiography showing a vascular tumor (*). Notice the internal maxillary artery supplying this tumor (orange arrow).

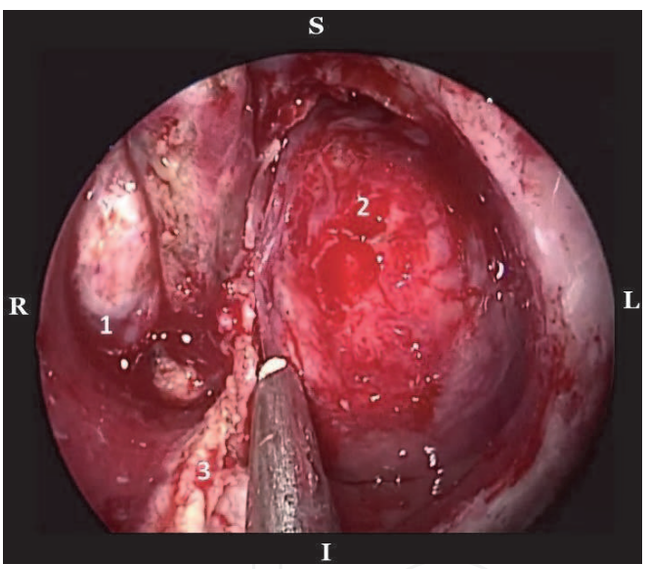

Figure 7.
Endoscopic view through left nasal cavity: Medial and posterior walls of left maxillary sinus and left inferior turbinate have been removed. 1-nasopharyngeal component of JNA; 2- pterygopalatine fossa + infratemporal fossa component of JNA; 3- remnants of left inferior turbinate; R- right, L- left, S- superior, I- inferior.

10.2 Non-surgical treatment of JNA: adjuvant treatment modalities

Though Juvenile angiofibroma is now an established surgical entity, there has been an era when medical management alone was the rule for extensive tumors especially those with intracranial extension. With paradigm shift towards more aggressive surgical procedures for all stages of the tumor, other treatment modalities are now valued as adjuvant therapy only.

10.2.1 Embolization

Transarterial embolization (TAE) is done preoperatively to decrease the blood flow to the tumor, thereby, reducing the intraoperative blood loss and need for blood transfusion. This is particularly useful for tumors with advanced stage.

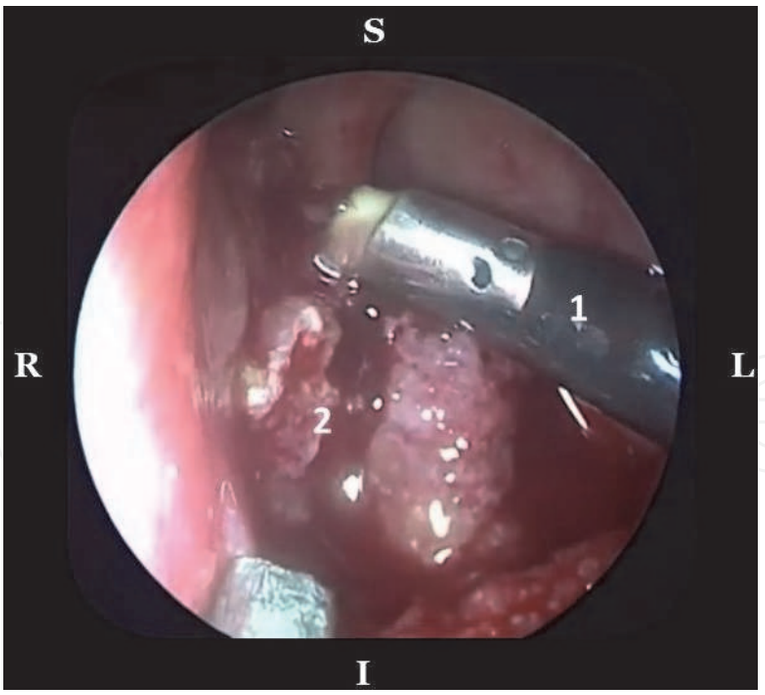

Figure 8.
Coblation wand being used in juvenile nasopharyngeal angiofibroma endoscopic surgery. 1- coblation wand, 2- tumor, R- right, L- left, S- superior, I- inferior.

Smaller tumors have less vascularity and can be resected easily even without preoperative embolization [61].

The procedure is usually done 24 to 48 hours before the scheduled surgery. Further surgical delay is not appreciated/recommended as tumor gains collateral blood supply through neoangiogenesis. A wide variety of materials are available as embolic agents: microspheres, gelatin sponge, Teflon particles, gel foam, poly-vinyl alcohol, polystyrene, silicone particles, silk, cyanoacrylate, sodium tetradacyl sulphate, autogenous clot, duramater, muscle fragments, etc. 300–500 micrometer spheres are preferred owing to greater blocking capacity of vascular lumen [62].

The procedure is not without complications. Cerebral ischemia and vision loss are known complications following embolic agent migrating to ICA system. Rare complications like cerebral edema, hemiplegia and aphasia have also been reported [63].

Direct Puncture Therapeutic Embolization (DPTE) is a new concept for tumor embolization. Embolizing agent is a mixture of n-butyl cyanoacrylate [NBCA], lipiodol, powdered tungsten with/without absolute ethanol. Under fluoroscopic visualization, embolizing agent is injected directly into the tumor through a percutaneous route or a transoral/ transnasal/transpalatal route [64].

This results in almost complete filling of tumor microvasculature with irreversible occlusion of embolized vessels. Tumor gains a dark color (due to tungsten powder with blue dye) which helps to better distinguish it from surrounding normal tissue. Direct cytotoxicity of absolute ethanol has shown good therapeutic effects.

DPTE alone or in combination with TAE has shown to have better devascularisation effects than TAE alone [65, 66].

10.2.2 Hormonal therapy

Hormonal influence on growth of JNA has been speculated since long. An interplay between estrogens and androgens has been associated with tumor proliferation and its spontaneous involution. Various hormonal therapies are recommended based on these concepts.

Estrogen therapy: exogenous estrogen has been tried traditionally with the aim of decreasing tumor size and vascularity. Lack of conclusive therapeutic advantage, feminizing side effects and propensity towards cardiovascular side effects have rendered its place to be of historical significance only.

Anti-androgen therapy: Flutamide is a non-steroidal androgen receptor blocker drug, primarily used in prostatic cancer. It binds with the androgen receptors, thereby blocking the action of testosterone. Recently, it has been proven that the response to flutamide therapy is much more pronounced in post-pubertal patients as compared to pre-pubertal patients [23].

Flutamide therapy is recommended as a six week preoperative adjuvant therapy for intracranial and intraorbital lesions, recurrent lesions and those with their blood supply primarily from ICA.

10.2.3 Radiotherapy

Low dose radiotherapy is used for angiofibromas extending intracranially, not amenable to primary surgery. Typically, total radiation dose of 3,500 cGy is given over 3 weeks. A successful response in terms of decreased tumor size and vascularity is seen over several months in 80% of the patients [67, 68]. Those showing no response/incomplete response by 2 years post radiotherapy are deemed as failures and taken up for salvage surgery.

There are numerous side effects to use of radiotherapy at a young age. Posterior capsular opacities, glaucoma, optic nerve atrophy, xerostomia, hypopituitarism, cerebral necrosis, osteoradionecrosis of mandible, skull base osteomyelitis, risk of developing new head–neck tumors later in life, potential malignant transformation of angiofibromas are few of the complications associated with the use of radiotherapy in head and neck region.

Intensity Modulated Radiotherapy (IMRT) allows higher doses to be given to the lesion without damaging adjoining normal tissues. Multiple beams from different directions converge onto the tumor shape so that the target area has the highest dose strength with relative sparing of surrounding vital structures.

Gamma Knife makes use of radiation beams from 201 sources, converging onto a single point. This causes retardation of further tumor growth. **Cyber Knife** is a type of stereotactic radiosurgery which uses a robotic arm to deliver radiations to a point source. These are being applied in association with other treatment modalities to achieve desired results in large angiofibromas [69, 70].

11. Conclusion

Juvenile nasopharyngeal angiofibroma, although an old disease entity, is still fascinating medical experts all over the world. Although still largely unknown, with advanced genetic and molecular studies, we have moved a step closer to find the origin and etiology of this disease. At present, surgery is the mainstay of treatment with endoscopic approach replacing the conventional open approach. Future considerations can be focused on therapeutic embolisation, stereotactic radiotherapy and targeted molecular therapy for a non-surgical cure.

Acknowledgements

I wish to express my sincere gratitude towards Dr. Anupama Mahajan, Dr. Stuti Mahajan and Dr. Anugeet Sethi for their constant moral support. I am fortunate to

have worked with Dr. Rajesh Choudhary and Dr. Bikramjeet Singh on numerous juvenile nasopharyngeal angiofibroma cases. A special vote of thanks to Dr. Rohan Sardana and Dr. Karamjeet Singh Gill for providing valuable insight into the pathology of this disease. I shall always be indebted to ENT Department of my alma mater VMMC & Safdarjung Hospital, New Delhi.

Conflict of interest

The authors declare no conflict of interest.

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