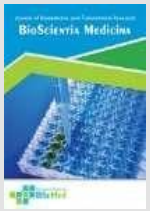
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Angiofibroma Beyond the Nasopharynx: Diagnostic Challenges and Endoscopic Management of Two Atypical Cases Arising from the Ethmoid and Sphenoid Sinuses

Dolly Irfandy[1*], Bestari Jaka Budiman[1], Jihan Mudrika Rahmi[1], Auzy Yoana Khalisha[1], Hippocrates Kam[2]

[1]Department of Otorhinolaryngology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Department of Vascular Surgery, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

ARTICLE INFO

Keywords:
Atypical angiofibroma
Endoscopic sinus surgery
Ethmoid sinus
Extranasopharyngeal angiofibroma
Sphenoid sinus

***Corresponding author:**
Dolly Irfandy

E-mail address:
dollyirfandy@med.unand.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i2.1500

A B S T R A C T

Background: Angiofibroma is a histologically benign but locally aggressive vascular neoplasm almost exclusively associated with the nasopharynx of adolescent males (Juvenile Nasopharyngeal Angiofibroma, JNA). Extranasopharyngeal angiofibroma (ENA) is an exceptionally rare variant that originates outside the sphenopalatine foramen, posing significant diagnostic and management challenges due to its atypical locations, age of presentation, and clinical mimicry of other sinonasal pathologies. **Case presentation:** We present two sophisticated cases of ENA managed at our tertiary center. Case 1: A 35-year-old male presented with unilateral nasal obstruction. Endoscopy and imaging revealed a hypervascular mass centered in the posterior ethmoid sinus, destroying the basal lamella and abutting the skull base. Histopathological analysis was initially confounded by features resembling a solitary fibrous tumor (SFT), requiring a comprehensive immunohistochemical panel (IHC) including STAT6 and nuclear beta-catenin to confirm the diagnosis of angiofibroma. Case 2: A 17-year-old male presented with symptoms and imaging (non-contrast CT) highly suggestive of a benign sphenochoanal polyp. An initial attempt at routine endoscopic removal was aborted due to unexpected, profuse hemorrhage. Subsequent advanced imaging (CTA/MRI) revealed a hypervascular sphenoid-based angiofibroma. Both patients underwent preoperative superselective embolization followed by successful, purely endoscopic tumor resection with no recurrence at 12 and 18-month follow-up, respectively. **Conclusion:** ENA is a critical, albeit rare, diagnostic consideration for any vascular sinonasal mass, regardless of patient age or tumor location. These cases underscore the unreliability of "classic" clinical and radiological signs, the diagnostic pitfalls of histopathological mimics like SFT and polyps, and the critical role of advanced IHC (nuclear beta-catenin) for definitive diagnosis. A modern, multidisciplinary approach combining preoperative embolization with endoscopic resection offers a safe and effective pathway to cure.

1. Introduction

Angiofibroma represents a clinicopathologically distinct, benign neoplasm of the head and neck, notorious for its intense vascularity, local aggressiveness, and high propensity for recurrence if incompletely excised.[1] The tumor accounts for a mere 0.05% to 0.5% of all head and neck neoplasms. Its classical presentation, so ingrained in otolaryngological literature as to be axiomatic, is that of juvenile nasopharyngeal angiofibroma (JNA).[2] This entity is defined by a rigid clinical triad: it occurs almost exclusively in adolescent males, originates from the vascular plexus at the posterolateral wall of the nasopharynx near the sphenopalatine foramen (SPF), and presents with a triad of progressive nasal obstruction, recurrent spontaneous epistaxis, and a

nasopharyngeal mass.[3]

The pathophysiology of JNA, while not entirely elucidated, is believed to be a complex interplay of hormonal, genetic, and vascular factors. The tumor's stromal cells, the true neoplastic component, express androgen receptors (AR), and tumor growth is often accelerated during puberty, suggesting a strong hormone-dependent mechanism.[4] More recent molecular investigations have uncovered a near-universal upregulation of the Wnt/beta-catenin signaling pathway, with somatic mutations in the CTNNB1 gene leading to aberrant nuclear accumulation of beta-catenin. This finding has become a cornerstone of modern histopathological diagnosis. Radiologically, JNA displays characteristic features, including a densely enhancing mass on contrast-enhanced CT and MRI, internal serpentine "flow voids" on T2-weighted MRI, and the pathognomonic Holman-Miller sign (anterior bowing of the posterior maxillary sinus wall) resulting from tumor extension from the SPF into the pterygopalatine fossa.[5]

However, a rare and enigmatic variant of this tumor exists: the Extranasopharyngeal Angiofibroma (ENA), also termed atypical angiofibroma. ENA is defined as an angiofibroma, histologically identical to its nasopharyngeal counterpart, but arising de novo from a primary site outside the nasopharynx and SPF. This entity severs the tumor from its classic demographic and anatomical anchors, creating a formidable diagnostic challenge. The true incidence of ENA is difficult to ascertain but is estimated to comprise less than 10% of all angiofibromas, with many publications limited to single case reports or small series.[6]

Unlike JNA, ENA demonstrates a much wider and more unpredictable demographic distribution. While a male predominance persists, cases have been reported in females and, significantly, in older adult males well beyond puberty, as seen in one of our patients. The clinical presentation is entirely dependent on the site of origin and is often nonspecific. The classic triad of epistaxis and obstruction is frequently absent. Instead, symptoms may include unilateral headache, facial pain, proptosis, cranial neuropathies, or, in many cases, simple, non-specific nasal congestion, leading to significant diagnostic delays.[7]

The sites of origin for ENA are varied and span the breadth of the sinonasal tract and beyond.[7] The most "common" atypical site is the nasal septum, followed by the maxillary sinus and the inferior turbinate. Far rarer, and representing the focus of this paper, are origins from the ethmoid and sphenoid sinuses. An ethmoid-based angiofibroma is an extreme rarity, with only a handful of cases documented in world literature. These tumors pose an immediate threat due to their proximity to the orbit and the anterior skull base (fovea ethmoidalis and cribriform plate). Similarly, primary sphenoid sinus angiofibromas are exceptionally rare. They present a profound diagnostic pitfall, as their clinical and initial radiological presentation can be indistinguishable from a benign sphenochoanal polyp, a routine finding for an otolaryngologist. This mimicry can lead to catastrophic intraoperative complications if a surgeon, anticipating a simple polypectomy, encounters a hypervascular angiofibroma.[8]

This diagnostic ambiguity is further compounded at the microscopic level. While the H&E features of a biphasic tumor with a complex vascular network and stellate stromal cells are characteristic, they are not unique. ENA can be mimicked by other vascular sinonasal tumors, most notably solitary fibrous tumor (SFT), glomangiopericytoma, and sinonasal hemangiopericytoma. In the past, this overlap created significant confusion.[9] Today, a definitive diagnosis rests on a sophisticated immunohistochemical (IHC) panel. The pathognomonic finding for angiofibroma is strong nuclear positivity for beta-catenin, a feature absent in its mimics. Conversely, SFT is defined by diffuse CD34 positivity and pathognomonic nuclear positivity for STAT6, which is negative in angiofibroma.

The management of ENA, once confirmed, follows the principles established for JNA but must be adapted to the atypical location. The gold standard of

care is complete surgical resection. Historically, this required aggressive open approaches (lateral rhinotomy, midfacial degloving, or subcranial approaches). However, the last two decades have seen a paradigm shift. The combination of preoperative superselective embolization—a critical step to mitigate life-threatening intraoperative hemorrhage—and the advent of advanced endoscopic sinus surgery (ESS) techniques has revolutionized treatment. The endoscope, particularly when paired with neuronavigation, provides unparalleled visualization and access to recesses like the ethmoid and sphenoid sinuses, allowing for complete tumor removal with significantly reduced morbidity compared to traditional open craniotomy or facial-incising procedures. Despite this modern algorithm, the literature on ENA remains sparse, particularly concerning tumors of the ethmoid and sphenoid. Clinical decision-making is often guided by extrapolation from JNA principles rather than ENA-specific evidence.[10]

This study aims to report two exceptionally rare cases of extranasopharyngeal angiofibroma, one arising from the posterior ethmoid sinus in an adult male and the other from the sphenoid sinus in an adolescent, which perfectly mimicked a benign polyp. Through these two comprehensive cases, we seek to provide a detailed analysis of the profound diagnostic challenges and radiological and histopathological pitfalls inherent to ENA. We will provide a comprehensive discussion on the underlying pathophysiology, the differential diagnoses, and champion a modern, multidisciplinary management algorithm involving advanced diagnostics (IHC), preoperative embolization, and purely endoscopic resection. This report underscores the clinical imperative to include angiofibroma in the differential diagnosis of any vascular or atypical sinonasal mass, regardless of patient age, sex, or tumor origin, to prevent diagnostic error and surgical misadventure.

2. Case Presentation

Case 1: Ethmoid sinus angiofibroma in a 35-year-old male

A 35-year-old male, with an unremarkable medical history, presented to our Otorhinolaryngology-Head and Neck Surgery outpatient clinic with a five-month history of progressive, unilateral right-sided nasal obstruction and persistent hyposmia. He also reported intermittent, minor epistaxis, which he experienced primarily as a posterior, blood-streaked drip, especially upon waking. He denied facial pain, visual changes, or headaches. He had previously been treated by a general practitioner for "chronic sinusitis" with several courses of antibiotics and nasal steroids, which provided no relief. His occupation at a furniture factory was noted, but deemed non-contributory.

On anterior rhinoscopy, the right nasal cavity appeared occluded by a large, polypoid mass (Figure 1). Nasal endoscopy (0-degree) revealed a large, reddish-purple, firm, and rubbery mass, visibly distinct from typical edematous inflammatory polyps. The mass filled the right middle meatus, originated from the posterior-superior nasal cavity, and obscured visualization of the sphenoethmoidal recess. It was friable and bled moderately upon gentle palpation with a suction cannula, heightening suspicion of a neoplastic process. The left nasal cavity was unremarkable, save for a minor septal deviation. No other head and neck masses were noted (Table 1).

A contrast-enhanced Computed Tomography (CT) scan of the paranasal sinuses was performed. This revealed a 4.5 x 3.0 x 2.8 cm, avidly and heterogeneously enhancing soft tissue mass. The epicenter of the mass was clearly centered within the right posterior ethmoid sinus. It demonstrated aggressive local behavior, with bony destruction of the basal lamella of the middle turbinate, erosion of the medial orbital wall (lamina papyracea), and thinning and remodeling of the fovea ethmoidalis, signifying direct abutment against the anterior skull base. The nasopharynx and sphenopalatine foramen were clear (Figure 2).

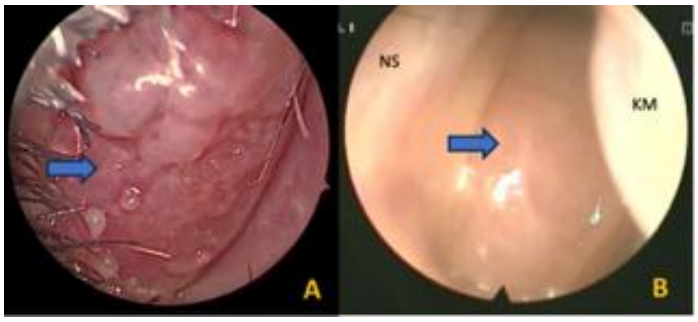


Figure 1. Preoperative nasoendoscopy. A) Mass filling the right nasal cavity (arrow). B) Mass from the right nasal cavity covering the choana of the left nasal cavity (arrow). KM: medial concha, NS: nasal septum.

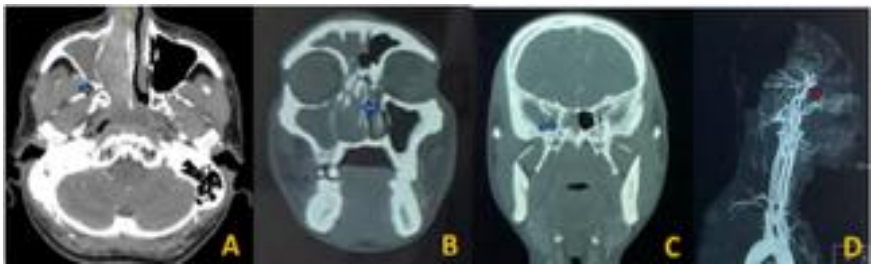


Figure 2. A. Axial slice of CT-Scan paranasal sinuses, there was a hyperdense lesion in the nasal cavity on the blue arrow and no erosion of the sphenopalatine foramen, B. Coronal slice, there was a hyperdense lesion in the frontal and maxillary sinus, C. Coronal slice there was a hyperdense lesion in the sphenoid sinus (blue arrow). D. Sagittal slice of CT-Scan angiography paranasal sinuses red arrow: right nasal cavity mass receiving blood supply from the right maxillary artery branch.

To better delineate the vascularity and relationship to the skull base, a Magnetic Resonance Imaging (MRI) scan with gadolinium contrast was obtained. The lesion was isointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. Critically, the T2-weighted sequences demonstrated multiple prominent, serpentine signal "flow voids" within the tumor matrix, a classic sign of a hypervascular neoplasm. Post-gadolinium, the mass showed intense, diffuse enhancement.

A subsequent formal CT-Angiography (CTA) identified the primary feeding vessel as the sphenopalatine artery, a terminal branch of the right internal maxillary artery. No significant contribution from the internal carotid artery (for instance, from the ethmoidal arteries) was identified, which was a critical preoperative finding.

Given the hypervascularity and skull base abutment, an incisional biopsy was performed in the operating room under controlled conditions. The initial hematoxylin and eosin (H&E) sections revealed a biphasic tumor composed of a prominent vascular component and a cellular stromal component. The vascular channels were variably sized, from small, slit-like "staghorn" vessels to larger, gaping thin-walled sinusoids, all lined by a single flat layer of endothelium (Figure 3). The stromal component, however, was highly cellular and composed of plump, spindle-to-stellate-shaped cells with bland, monomorphic nuclei, set in a dense collagenous matrix.

Table 1. Clinical summary findings of case 1.

Parameter	Finding
Patient Demographics	35-year-old male
Presenting Symptoms	• 5-month progressive right-sided nasal obstruction • Persistent hyposmia • Intermittent posterior blood-streaked drip (minor epistaxis) • No response to antibiotics or nasal steroids
Nasal Endoscopy	• Large, reddish-purple, firm, rubbery mass • Filled right middle meatus, originating posterior-superiorly • Bled moderately on gentle palpation • Clearly distinct from inflammatory polyps
Imaging (Contrast-CT)	• 4.5 × 3.0 x 2.8 cm avidly, heterogeneously enhancing mass • **Epicenter:** Right posterior ethmoid sinus • **Local Aggression:** - Bony destruction of basal lamella - Erosion of medial orbital wall (lamina papyracea) - Thinning/remodeling of fovea ethmoidalis (skull base abutment) • Nasopharynx and Sphenopalatine Foramen (SPF) were clear
Imaging (Contrast-MRI)	• T1-weighted: Isointense • T2-weighted: Heterogeneously hyperintense • **Key Sign:** Prominent serpentine signal "flow voids" on T2 • Intense, diffuse post-gadolinium enhancement
Imaging (CT-Angiography)	Primary feeding vessel identified as the sphenopalatine artery (from the right internal maxillary artery). No ICA contribution.
Histopathology (H&E)	• Biphasic tumor (vascular & stromal components) • Variable "staghorn" and slit-like vessels • Cellular stroma of plump, spindle/stellate cells • **Pitfall:** Appearance mimicked Solitary Fibrous Tumor (SFT)
Histopathology (IHC)	• **CD34: Negative** (in stromal cells) • **STAT6: Negative** (rules out SFT) • **Beta-catenin: Positive** (strong, diffuse nuclear staining) • Vimentin: Positive; SMA: Positive (perivascular)
Final Diagnosis	**Extranasopharyngeal Angiofibroma (Origin: Posterior Ethmoid Sinus)**
Therapeutic Intervention	• **Stage 1:** Preoperative superselective embolization (PVA particles, >90% devascularization) • **Stage 2:** Purely endoscopic resection with neuronavigation • **Intraoperative:** Middle turbinectomy for access, drilling of skull base attachment

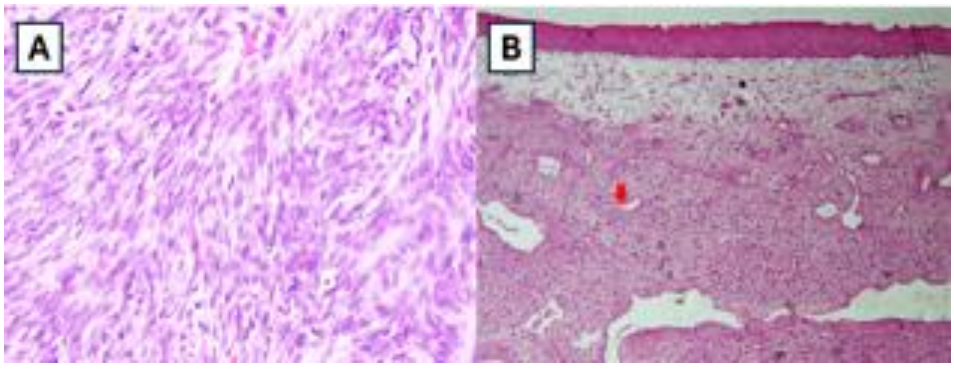


Figure 3. Angiofibroma histopathology. (A-B) The red arrow shows “slit-like” blood vessels.

This H&E appearance created a significant diagnostic dilemma, with the primary differential diagnoses being angiofibroma and a solitary fibrous tumor (SFT). An extensive immunohistochemical (IHC) panel was therefore initiated. The findings were as follows: (1) CD34: Diffusely negative in the neoplastic stromal cells; (2) STAT6: Completely negative in the tumor cell nuclei, effectively ruling out SFT; (3) Vimentin: Diffusely positive in stromal cells; (4) SMA (Smooth Muscle Actin): Positive in the perivascular cells, but negative in the neoplastic stromal cells; (5) S-100 & Desmin: Negative; (6) Beta-catenin: Strong, diffuse *nuclear* positivity was observed in the neoplastic stromal cells. This specific immunoprofile—STAT6 negative and nuclear beta-catenin positive—was pathognomonic. The final diagnosis was definitively established as extranasopharyngeal angiofibroma, arising from the posterior ethmoid sinus.

A multidisciplinary tumor board, including ENT, Vascular Surgery, and Radiology, planned a two-stage approach; (1) Stage 1 (Embolization): The patient was taken to the interventional radiology suite 48 hours prior to surgery. Under general anesthesia, a microcatheter was navigated into the right external carotid artery. Superselective catheterization of the right internal maxillary artery and, subsequently, the sphenopalatine artery was achieved. The tumor blush was confirmed. Embolization was performed using 300-500 μm Polyvinyl Alcohol (PVA) particles until stasis of flow was achieved. Post-embolic angiography confirmed >90% devascularization of the tumor; (2) Stage 2 (Surgical Resection): The patient was taken to the operating room for definitive endoscopic resection. The procedure was performed under general anesthesia with controlled hypotension. A 0-degree rigid endoscope and a high-definition camera system were used, with an electromagnetic neuronavigation system (Medtronic) registered to the preoperative CT/MRI fusion. A complete uncinectomy and maxillary antrostomy were performed for access. The middle turbinate was resected at its base to expose the tumor's origin. The tumor was identified and noted to be significantly less vascular than on initial endoscopy, appearing pale and firm—a direct result of successful embolization. Using a combination of endoscopic drills, microdebriders, and through-cutting instruments, the tumor was meticulously dissected. It was found to be densely adherent to the lamina papyracea and the fovea ethmoidalis. The involved bone of the skull base, which was thinned but not frankly breached, was drilled down with a 3mm diamond burr to ensure a clear margin. The dissection was carried posteriorly to the sphenoid face. The lamina papyracea was partially removed, but the periorbita was identified and preserved intact. The tumor was removed en bloc. Hemostasis was achieved with bipolar cautery. The total operative time was 180 minutes. The estimated blood loss (EBL) was approximately 350 mL, a remarkably low volume for a tumor of this nature, directly attributable to the preoperative embolization.

On follow-up, the patient had an uncomplicated postoperative course and was discharged on day 3. Postoperative nasal endoscopy at 7 days, 3 weeks, and 6 weeks showed a well-healing cavity with no crusting or signs of infection. At 6 months post-surgery, the cavity was fully mucosalized. A follow-up contrast-enhanced MRI at 12 months showed no evidence of residual or recurrent disease. The patient remains symptom-free with a normal sense of smell.

Case 2: Sphenoid sinus angiofibroma in a 17-year-old male

A 17-year-old male was referred to our clinic with a four-month history of complete and persistent right-sided nasal obstruction. He also reported thick, yellowish-green posterior nasal drip and a sensation of fullness in his throat. He denied epistaxis, facial pain, or visual changes. His symptoms had been worsening, and he was referred with a presumptive diagnosis of a "refractory sinonasal polyp" (Table 2).

Nasal endoscopy revealed a large, pale, glistening, and smoothly-surfaced polypoid mass. It completely filled the right nasal cavity, passed between the middle turbinate and the septum, and could be seen

extending into the nasopharynx, completely occluding the right choana. The mass was non-friable and did not bleed on gentle palpation. Its appearance was endoscopically indistinguishable from a large antrochoanal or sphenochoanal polyp (Figure 4).

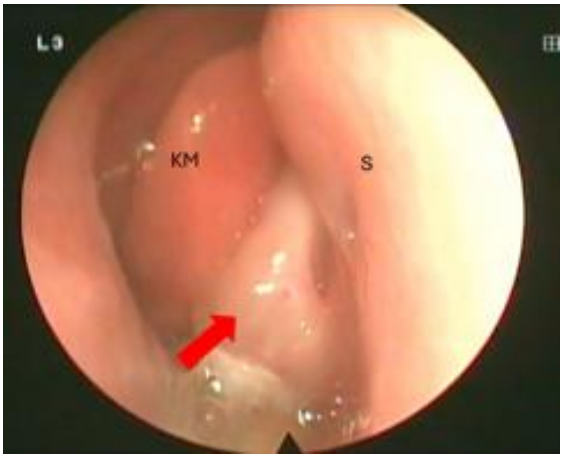


Figure 4. Right nasal cavity nasoendoscopy, a mass is visible with mucoid secretion (red arrow). (KM: *konka medial/*medial concha, S: septum).

A non-contrast paranasal sinus CT scan was obtained, as is standard for presumed polypoid sinusitis (Figure 5). The scan showed a large, isodense (31 Hounsfield Units) soft tissue mass completely opacifying the right nasal cavity and the sphenoid sinus. The mass caused smooth, non-erosive expansion of the sphenoid sinus walls and widened the spheno-ethmoidal recess, bowing the nasal septum to the left. The orbital walls and pterygoid plates were intact. These radiological findings—a non-enhancing, isodense mass causing smooth bony remodeling without destruction—were all highly characteristic of, and consistent with, a sphenochoanal polyp.

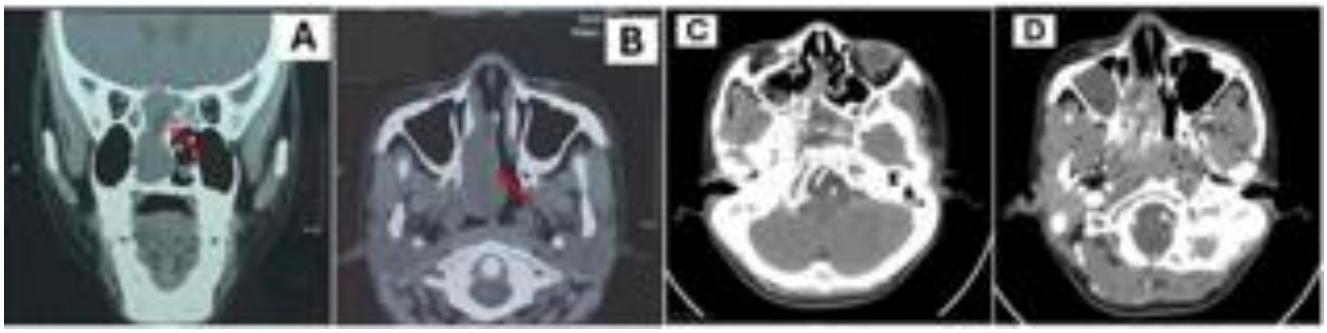


Figure 5. Non-contrast paranasal sinus CT scan. A) Coronal slice showing hyperdense at the right nasal cavity up to the posterior ethmoid (red arrow). B) Axial slice showing hyperdensity in the right nasal cavity and deviation of the septum contralaterally (red arrow). C) and D) Head CT angiography showing mass in the right nasopharynx, right nasal cavity, up to the sphenoid sinus, suggesting juvenile angiofibroma.

Based on the unanimous clinical and radiological diagnosis of a sphenochoanal polyp, the patient was scheduled for a routine functional endoscopic sinus surgery (FESS) and polypectomy. Under general anesthesia, the endoscope was introduced. An initial incision was made into the mass with a microdebrider, anticipating avascular, edematous polyp tissue. Instead, this was met with immediate, pulsatile, and profuse arterial hemorrhage, which quickly obscured the endoscopic field. The procedure was immediately aborted. The nasal cavity was rapidly packed with adrenaline-soaked packing to achieve tamponade. The patient remained hemodynamically stable. The patient was emergently transferred for a CTA and an MRI. This new, advanced imaging painted a completely different picture. The mass, which was isodense on non-contrast CT, now showed intense, heterogeneous enhancement on both CTA and post-gadolinium MRI sequences. The CTA identified a prominent feeding artery arising from the external carotid artery branch, specifically the vidian artery (a branch of the internal maxillary artery) at the base of the pterygoid canal. The mass was centered in the sphenoid sinus, confirming its origin. The diagnosis was revised to a suspected hypervascular neoplasm, with angiofibroma being the primary differential. A biopsy was taken and confirmed the diagnosis of angiofibroma.

A new, definitive multidisciplinary plan was formulated; (1) Stage 1 (Embolization): One month after the first aborted procedure, the patient was brought to the interventional radiology suite. A microcatheter was advanced into the right internal maxillary artery. Superselective embolization of the vidian artery and posterior nasal branches was performed, this time using micro-coils to occlude the main feeding vessel, supplemented with PVA particles. Post-embolization angiography showed complete cessation of tumor blush; (2) Stage 2 (Surgical Resection): Two days after embolization, the patient returned to the operating room for definitive endoscopic resection under general anesthesia and neuronavigation guidance. The right nasal cavity was entered, and the previous packing was removed. The tumor was pale and significantly reduced in turgor. A wide right-sided sphenoidotomy was performed, removing the sphenoid rostrum and its anterior wall. The mass was found to be originating from the lateral wall of the sphenoid sinus, near the exit of the vidian canal. The tumor was dissected from the sphenoid walls. To achieve adequate access and margins, a posterior ethmoidectomy and a partial medial maxillectomy (removing the posterior aspect of the medial maxillary wall) were performed. The tumor, which extended into the nasopharynx, was dissected free from the choana and delivered *en bloc* through the nasal cavity. The origin site on the lateral sphenoid wall was drilled down with a diamond burr to eradicate any microscopic disease. The total operative time was 150 minutes. The EBL was a controlled 250 mL. The patient's postoperative course was complicated by a transient, transfusion-requiring anemia (post-op Hb 4.2 g/dL from the initial aborted surgery's blood loss, which was significant), which was managed with 4 units of PRC. He was discharged 4 days post-operatively.

Postoperative follow-up at 1, 2, and 4 weeks showed a rapidly healing cavity. Endoscopy at 3 months revealed a wide-open, epithelialized sphenoid sinus with no evidence of residual tumor. The patient did not attend his 2-month follow-up but returned at 18 months, at which time he remained completely asymptomatic with a clear endoscopic examination.

3. Discussion

The presentation of these two cases—a middle-aged adult with an ethmoid-based, SFT-mimicking neoplasm, and an adolescent with a sphenoid-based, polyp-mimicking lesion—encapsulates the profound diagnostic and therapeutic challenges posed by extranasopharyngeal angiofibroma (ENA). These cases shatter the classic axioms of angiofibroma management, forcing clinicians to rely on a high index of suspicion and advanced molecular diagnostics rather than on traditional clinical and radiological signs.[11]

Table 2. Summary of clinical findings in case 2.

Parameter	Finding
Patient Demographics	17-year-old male
Presenting Symptoms	• 4-month complete right-sided nasal obstruction • Thick, yellowish-green posterior nasal drip • Sensation of fullness in the throat • Key Negative: Denied epistaxis or facial pain
Nasal Endoscopy	• Large, pale, glistening, smoothly-surfaced mass • Completely filled right nasal cavity and choana • Did not bleed on gentle palpation • Diagnostic Pitfall: Appearance was indistinguishable from a benign sphenochoanal polyp
Imaging (Non-Contrast CT)	• Isodense mass (31 Hounsfield Units) • Opacified right nasal cavity and sphenoid sinus • Smooth, non-erosive bony expansion of sphenoid • Diagnostic Pitfall: Findings were highly characteristic of a sphenochoanal polyp
Initial Procedure	• Routine FESS / Polypectomy was planned • Complication: Incision met with immediate, profuse, pulsatile arterial hemorrhage • **Outcome: PROCEDURE ABORTED**
Revised Diagnostic Workup	• True Nature Revealed: Intense, heterogeneous enhancement on CTA/MRI • **Feeding Vessel:** Vidian artery (from internal maxillary) • **Epicenter:** Confirmed in the sphenoid sinus
Final Diagnosis	**Extranasopharyngeal Angiofibroma (Origin: Lateral Sphenoid Sinus)**
Definitive Intervention	• **Stage 1:** Preoperative superselective embolization (micro-coils + PVA) of vidian artery • **Stage 2:** Purely endoscopic resection with neuronavigation • **Intraoperative:** Wide sphenoidotomy, posterior ethmoidectomy, partial medial maxillectomy; drilling of origin site
Surgical Outcome	• **EBL:** ~250 mL (for definitive surgery) • Post-op anemia (Hb 4.2) requiring 4 units PRC (related to *initial* aborted procedure) • **Follow-up:** No evidence of recurrence at 18 months • **Status:** Asymptomatic

To understand ENA, one must first understand the fundamental biology of angiofibroma itself. The tumor is not a true hemangioma or a simple fibroma; it is a complex, biphasic neoplasm. The true neoplastic component is the stellate and spindle-shaped stromal cell, which, in turn, orchestrates the development of the striking, abnormal vascular component.[12] The pathophysiology is best understood as a convergence of hormonal, genetic, and vascular growth factor pathways.

The classic restriction of JNA to pubertal males is the strongest evidence for a hormonal driver. The stromal cells of angiofibroma have been consistently shown to express high levels of androgen receptors (AR). It is hypothesized that circulating androgens, particularly testosterone and dihydrotestosterone (DHT), bind to these receptors and promote tumor proliferation. This theory is further supported by observations of tumor regression with anti-androgen therapy (such as flutamide) and rare reports of JNA in postmenopausal females undergoing androgen supplementation.[13] However, the hormonal theory is incomplete. It does not fully explain the tumor's origin in pre-pubertal males, in females, or in older adults like our 35-year-old patient. This suggests that while androgens may be potent promoters of tumor growth, they are likely not the initiators of tumorigenesis.

The most significant breakthrough in angiofibroma pathophysiology has been the identification of the Wnt/beta-catenin signaling pathway as the primary oncogenic driver. In a healthy cell, beta-catenin is a cytoplasmic protein targeted for destruction by a complex (including APC, axin, and GSK-3β). Upon Wnt signaling, this destruction is inhibited, allowing beta-catenin to translocate to the nucleus, where it acts as a transcription factor for cell proliferation genes, such as MYC and CCND1. In nearly all angiofibromas (both JNA and ENA), this pathway is constitutively activated, most commonly via somatic, gain-of-function mutations in the CTNNB1 gene, which codes for beta-catenin itself. These mutations make the beta-catenin protein resistant to degradation, leading to its massive, aberrant accumulation and subsequent translocation into the nucleus.[14]

This discovery has two profound implications: (1) Diagnosis: As demonstrated in our first case, this molecular event provides a pathognomonic diagnostic marker. The nuclear accumulation of beta-catenin on IHC is now the gold standard for diagnosing angiofibroma, distinguishing it from all its histopathological mimics; (2) Pathogenesis: This finding redefines angiofibroma. It is not just a "vascular tumor" but a beta-catenin-driven neoplasm, analogous to other tumors with Wnt pathway mutations (such as desmoid fibromatosis and medulloblastoma). This molecular uniformity strongly suggests that ENA and JNA are not different diseases. They are the same disease, defined by Wnt/beta-catenin pathway activation, presenting in different anatomical locations. The "classic" SPF origin may simply be a "hotspot" for this mutation, perhaps due to a unique embryonic vascular plexus, but it is not the sine qua non of the disease itself.

The intense vascularity is a secondary, non-neoplastic proliferation driven by the neoplastic stromal cells. These stromal cells have been shown to overexpress a potent cocktail of angiogenic growth factors, including Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor-beta (TGF-β), and Platelet-Derived Growth Factor (PDGF). These factors act in a paracrine fashion on nearby endothelial cells, stimulating the formation of the abnormal, thin-walled, and poorly contractile vascular channels that are the hallmark of the tumor and the source of its dangerous hemorrhage.[15] This is why anti-angiogenic therapies (like bevacizumab) have been trialed as a neoadjuvant treatment, though their efficacy remains unproven compared to embolization.

Our two cases serve as exemplars of the diagnostic traps ENA sets for the unwary clinician. Case 2 is a striking example of a critical radiological pitfall. The patient's initial non-contrast CT (NCCT) showed an isodense mass causing smooth, expansile remodeling of the sphenoid sinus. These are the exact features of a benign sphenochoanal polyp, which is a common, avascular inflammatory mass arising from the

sphenoid sinus mucosa and prolapsing into the choana.[16]

This mimicry highlights a crucial teaching point: non-contrast CT is insufficient and potentially dangerous for evaluating any atypical or large sinonasal mass. While NCCT is the standard for routine inflammatory sinusitis, it cannot differentiate between protein-rich mucus (as in a polyp) and a cellular, isodense neoplasm. For any mass that is atypical in size, location, or behavior, a contrast-enhanced study (CT or MRI) is mandatory. On our patient's subsequent contrast-enhanced studies, the intense, avid enhancement immediately unmasked the tumor's true vascular nature and ruled out a polyp, preventing a surgical catastrophe during the definitive procedure. The Holman-Miller sign (antral bowing) is also absent in ENA, as the tumor does not originate in the pterygopalatine fossa, further reducing the utility of classic radiological signs.

Case 1 demonstrates the challenge at the microscopic level. The H&E findings of a cellular, spindle-cell tumor with prominent "staghorn" or hemangiopericytoma-like vessels are shared by several entities. The primary differential in this case, Solitary Fibrous Tumor (SFT), is a ubiquitous soft tissue tumor that can also occur in the sinonasal tract and shares many features with angiofibroma. An SFT is also a vascular, spindle-cell tumor. Historically, SFT and "hemangiopericytoma" were considered separate entities, but are now known to be the same, defined by a NAB2-STAT6 gene fusion. This fusion leads to the pathognomonic nuclear expression of STAT6, which has become the definitive IHC marker for SFT.[17]

Therefore, when a pathologist is faced with a tumor like our Case 1, a specific IHC panel is non-negotiable. The diagnostic logic is as follows: (1) Angiofibroma: Nuclear Beta-catenin (+), STAT6 (-), CD34 (variable stroma + vessels); (2) Solitary Fibrous Tumor: Nuclear Beta-catenin (-), STAT6 (+), CD34 (+ strong stroma); (3) Glomangiopericytoma: Nuclear Beta-catenin (-), STAT6 (-), CD34 (-), SMA (+). Our pathologist's comprehensive panel was critical. The negative CD34 and STAT6 results in the stroma effectively ruled out solitary fibrous tumor, which is classically defined by strong and diffuse positivity for both markers. This left angiofibroma as the primary consideration. The diagnosis was then definitively confirmed by the strong, diffuse nuclear positivity for beta-catenin. This case demonstrates how this specific immunoprofile (CD34-negative, STAT6-negative, nuclear beta-catenin-positive) is essential to confidently distinguish angiofibroma from its mimics.[18]

The treatment of ENA, particularly in challenging locations like the ethmoid and sphenoid, requires a seamless, multidisciplinary approach. Angiofibroma bleeds not because of a single large vessel, but from thousands of abnormal, thin-walled, non-contractile sinusoids. Surgical resection without devascularization is not heroic; it is dangerous and risks incomplete resection due to an obscured field, as well as life-threatening hemorrhage. Our aborted first attempt in Case 2 is a testament to this fact. Preoperative embolization, performed 24-72 hours before surgery, is the standard of care. This window is large enough for the tumor to become ischemic and fibrotic, but not so long as to allow for re-vascularization from collateral vessels. The goal is to occlude the tumor's primary feeding vessels, which, for most sinonasal angiofibromas (JNA and ENA), arise from the terminal branches of the internal maxillary artery (including the sphenopalatine, descending palatine, and vidian arteries).

The choice of embolic agent depends on the vessel. In Case 1, PVA particles were used to flow distally and occlude the small-vessel tumor bed. In Case 2, micro-coils were used to occlude the main, identifiable feeding trunk (vidian artery) before it could branch. Both techniques are effective in achieving the primary goal: transforming a "bleeding-to-death" operation into a controlled, precise dissection with minimal blood loss. Our EBL of 250-350 mL for such large tumors is directly attributable to this step.[19]

The evolution from open, facial-incising approaches (such as lateral rhinotomy, midfacial degloving, or subcranial approaches) to a purely endoscopic technique is one of the great success

stories of modern rhinology. For ENA of the ethmoid and sphenoid, the endoscope is not just an option; it is the superior tool. The 0, 30, and 45-degree endoscopes provide a magnified, high-definition view of critical anatomy that is impossible to achieve with the naked eye or a microscope through an open approach. This allows for precise dissection of the tumor off the skull base (Case 1) and the lateral sphenoid wall (Case 2). As used in both our cases, image-guidance systems are essential. They provide a real-time "GPS" that allows the surgeon to know their precise location relative to the orbit, the optic nerve, the internal carotid artery, and the skull base, especially when normal anatomical landmarks have been destroyed by the tumor. The endoscopic approach avoids all external incisions, significantly reduces hospital stay, minimizes pain, and preserves facial cosmesis and function.[20]

The surgical strategy itself must be aggressive. It is not a "FESS" procedure. It is an endoscopic oncologic resection. This often requires the planned sacrifice of normal structures to achieve a wide field and clear margins, as demonstrated by the medial maxillectomy in Case 2 and the middle turbinectomy in Case 1. The tumor's origin must be identified and drilled down with a diamond burr to eradicate the "root" of the disease and prevent recurrence.

4. Conclusion

Extranasopharyngeal angiofibroma is a rare but critical entity that represents a significant diagnostic and therapeutic challenge. Our two cases—one in an adult male originating from the ethmoid sinus and mimicking a solitary fibrous tumor, and the other in an adolescent originating from the sphenoid sinus and mimicking a benign polyp—perfectly illustrate the treacherous nature of this disease. These cases demonstrate that the classic clinical and radiological presentation of angiofibroma is unreliable and absent in ENA. A high index of suspicion must be maintained for any atypical or hypervascular sinonasal mass, regardless of patient age or tumor location. Advanced imaging with contrast-enhanced CT and MRI is mandatory to prevent surgical misadventure. Furthermore, modern histopathological diagnosis is not complete without a definitive immunohistochemical panel, where nuclear beta-catenin positivity has emerged as the pathognomonic gold standard to differentiate ENA from its mimics. Once diagnosed, a modern, multidisciplinary management algorithm provides a clear and safe path to a cure. Preoperative superselective embolization is an indispensable tool that transforms a hemorrhagic and dangerous procedure into a controlled, precise dissection. This, combined with a purely endoscopic, navigation-guided resection, represents the current gold standard of care, offering maximal tumor clearance with minimal patient morbidity.

5. References

1. Nandhini J, Ramasamy S, Kaul R, Austin R. Juvenile primary extranasopharyngeal angiofibroma, presenting as cheek swelling. J Oral Maxillofac Pathol. 2018; 22(4): 73.
2. Ghazizadeh M, Mokhtarifar F. Endoscopic removal of a rare case of extranasopharyngeal angiofibroma: a case report and review article. J Minim Invasive Surg Sci. 2018; 7(1).
3. Tyagi BS. Extranasopharyngeal angiofibroma of the nasal septum in an elderly postmenopausal female: a very rare presentation. Otorhinolaryngol Clin - Int J. 2018; 10(1): 39–41.
4. Gupta N, Dass A, Saini V, Anil Pol S, Mittal L. Extranasopharyngeal angiofibroma: a diagnostic dilemma. Philipp J Otolaryngol Head Neck Surg. 2018; 33(1): 39–42.
5. Türk B, Ünsal Ö, Akpınar M, Başak ŞT, Coşkun BU. Extranasopharyngeal angiofibroma localized in the nasal dorsum: a rare location for this tumor. SiSli Etfal Hastan Tip Bul/Med Bull Sisli Hosp. 2018; 52(3): 229–31.
6. Lee G-E, Kim TG, Bae K-E, Cho KR, Sohn JH, Kim BY, et al. Extranasopharyngeal angiofibroma of the nasal septum: a case

report. J Korean Soc Radiol. 2019; 80(4): 750.
7. Kim HD, Choi IS. Extranasopharyngeal angiofibroma mimicking choanal polyp in patients with chronic paranasal sinusitis. Auris Nasus Larynx. 2019; 46(2): 302–5.
8. Kujundžić T, Perić A, Đurđević BV. Extranasopharyngeal angiofibroma arising from the anterior nasal septum in a 35-year-old woman. Craniomaxillofac Trauma Reconstr. 2019; 12(2): 141–5.
9. Arulappan LAS. Extranasopharyngeal angiofibroma in an adolescent male: a case report. Int J Otorhinolaryngol Head Neck Surg. 2019; 5(5): 1416.
10. Capodiferro S, Limongelli L, D'Agostino S, Tempesta A, Dolci M, Maiorano E, et al. Diode laser management of primary extranasopharyngeal angiofibroma presenting as maxillary epulis: report of a case and literature review. Healthcare (Basel). 2021; 9(1): 33.
11. Vemagiri CT, Pamidi C, Damera S, Atluri SN, Kallukuri M. An extranasopharyngeal angiofibroma of mandibular ramus in a preschool child - an extremely rare case report. J Evol Med Dent Sci. 2021; 10(28): 2128–30.
12. Wan MH, Govindaraju R, Narayanan P. Maxillary extranasopharyngeal angiofibroma: A case report and a review of similar cases. Egypt J Ear Nose Throat Allied Sci. 2022; 23(23): 1–7.
13. Kurien R, Mehan R, Varghese L, Telugu RB, Thomas M, Rupa V. Frontoethmoidal extranasopharyngeal angiofibroma with orbital pyocele. Ear Nose Throat J. 2022; 101(9): 575–7.
14. Windyaningrum R, Permana AD, Saifuddin OM. Extranasopharyngeal angiofibroma from hypopharynx: a rare case report. J Med Health. 2022; 4(1): 8.
15. Yeon ER, Park C, Jeong SJ, Park SK. Extranasopharyngeal angiofibroma of the natural ostium of maxillary sinus. J Craniofac Surg. 2022; 33(3): e298–300.
16. Chandra J, K V, Dhabaria H, Abdulla R. Unusually large extranasopharyngeal angiofibroma of the infratemporal fossa: a rare case report. J Maxillofac Oral Surg. 2022; 21(2): 705–8.
17. Yan Y-Y, Lai C, Wu L, Fu Y. Extranasopharyngeal angiofibroma in children: a case report. World J Clin Cases. 2022; 10(21): 7429–37.
18. Hernando M, Lowy A, Agra C, Souvirón R, Pasamontes JA, Fernández-Fernández M. Recurrent pediatric extranasopharyngeal angiofibroma of the epiglottis: case report. Turk Arch Otorhinolaryngol. 2023; 61(2): 99–102.
19. Kim T-G, Whangbo C-H, Ye MK, Shin S-H. A case of extranasopharyngeal angiofibroma arising from nasal dorsum. Braz J Otorhinolaryngol. 2025; 91(1): 101508.
20. Alkheder A, Yousfan A. Extranasopharyngeal angiofibroma in the tongue: a case report with literature review. Ear Nose Throat J. 2025; 1455613251336869.