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Current approach of juvenile nasopharyngeal angiofibroma: a case series

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Abstract

Juvenile nasopharyngeal angiofibroma (JNA) is a rare benign tumor that affects predominantly males and is known by its highly vascular character. We have performed a 3-year retrospective study of patients with JNA surgically treated within the third ENT Department of Prof. Dr. Dorin Hociotă Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania. In all the cases, the patients were investigated both clinically and through medical imaging before surgery and all tumors were embolized. Our study comprised of eight cases, of which seven were solved by endoscopic endonasal approach and one case was treated through a combined endonasal–external approach. JNA should always be managed through a multidisciplinary team (MDT) approach in centers with adequate experience, to gain favorable results.

Keywords: juvenile nasopharyngeal angiofibroma, epistaxis, embolization, endoscopic transnasal surgery.

Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a rare benign tumor that occurs in the nasopharynx, affecting mostly male adolescents and young adults and accounting for 0.05% of head and neck tumors [1–5].

This non-encapsulated tumor arises from mesenchymal tissue and is a highly vascular lesion with aggressive behavior and locally invasive growth patterns [6]. Localization, in most cases, is at the superior border of the sphenopalatine foramen, in the area of the pterygoid canal aperture [6–8].

Even though the microscopic structure is representative of a benign tumor, JNA frequently displays aggressive characteristics through its invasion of neighboring structures: the nasal turbinates, the nasal septum, the pterygopalatine fossa, the sphenoid, ethmoid and maxillary sinuses [9, 10]. In severe cases of JNA, when the tumor is neglected, it may invade the orbit or the neurocranium [11–13].

JNA etiopathogenesis remains currently unknown. Tumor development, predominantly (almost entirely) within the male population, can be explained through the elevated expression of androgen receptors within the tumor cells, multiple studies suggesting that JNA is an androgen-dependent disease [14].

The histopathological (HP) origin of JNA is a controversial issue, as well; most studies suggest that vascular endothelial cells or fibroblasts might be the cellular elements accountable for tumor proliferation and its growth process [15]. It is still unknown whether both cellular components proliferate and grow together, or if one cellular component is responsible for growth, while the other is a regular conjunctive partner. Immunohistochemical (IHC) and genetic studies conducted to date have not managed to clarify this problem [6].

The "gold standard" treatment remains surgery after endovascular embolization of the tumor.

Preoperative embolization is performed in all cases of JNA, with less intraoperative bleeding, decreased intraoperative time and improved surgical field [16, 17]. The development of endoscopic techniques makes the open approach relevant only in selected cases of JNA, with important extension to the infratemporal fossa (ITF) [3].

Aim

Our study aimed to evaluate the modern multidisciplinary approach of JNA.

Patients, Materials and Methods

We performed a retrospective study consisting in a series of eight patients surgically treated for JNA within the third ENT Department of Prof. Dr. Dorin Hociotă Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania, between 2019 and 2021.

Before surgery, each case was investigated clinically, endoscopically and through imaging: computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or arteriography to assess the Radkowski stage. Also, preoperative selective embolization was performed.

CT scans helped with the extent of the tumor, especially with assessment of sinus extension, bone erosion and invasion of the pterygopalatine and ITFs. On the other hand, MRI assessed the intracranial involvement of the tumor.

The same approach of endovascular embolization was

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performed for every patient, femoral access through right groin puncture and placement of 5F sheath, catheterization of external carotid artery (ECA) with angiographic study of their vascular regions, followed by Ver 5F guide catheter in proximal ECA and superselective catheterization of tumor feeding vessels. Also, angiographic study of internal carotid artery (ICA) was done. Given the possibility of massive bleeding, preoperative biopsy is contraindicated, therefore HP and IHC examination were performed after complete excision of the tumor [18].

All patients were operated in the Clinic after endovascular embolization, this being the "gold standard" in JNA.

Excised tumors were immediately placed in 10% neutral buffered formalin (pH 7.4) and then sent to the Laboratory of Pathology. After 48 hours of fixation time, fragments of approximately 1 mm thick were collected from the excised material and were then included in histological paraffin, in accordance with classical histopathology techniques. The HMB450 (Thermo Scientific) rotary microtome, equipped with a Peltier paraffin cooling module and a water bath system for histology sectioning helped obtain 4 μm thick sections, which were then collected on histology slides. Upon drying at a thermostat-controlled 37°C, the tumor sections were Hematoxylin–Eosin (HE) stained.

For the IHC study, tumor sections were collected upon special histology slides, coated in poly-L-lysine. A special IHC processing protocol was applied to these slides, in accordance with the revealed antigen. We have used the following IHC markers in our study: anti-cluster of differentiation (CD)34 (monoclonal mouse anti-human CD34 Class II, clone QBEnd 10, 1/50 dilution, Dako); anti-alpha-smooth muscle actin (anti-α-SMA) (monoclonal mouse anti-human SMA, clone 1A4, 1/100 dilution, Dako); anti-CD3 (monoclonal mouse anti-human CD3, clone F7.2.38, 1/25 dilution, Dako); anti-CD20 (monoclonal mouse anti-human CD20cy, clone L26, 1/50 dilution, Dako); anti-CD68 (monoclonal anti-human CD68, clone KP1, 1/100 dilution, Dako); anti-CD45RO (monoclonal mouse anti-human CD45RO, clone UCHL1, 1/50 dilution, Dako).

Results

Over a period of three years, eight patients who underwent surgery were identified, all male, and with an average age of 16.9 years, ranging from 11.1 years to 28.2 years. Out of the aforementioned eight patients, five came from a rural background, and three from an urban environment. A summary of their demographic, clinical and procedural characteristics is shown in Table 1.

All patients came to medical attention with long-term nasal obstruction and recurrent epistaxis, and only three had intermittent headache, while two others had facial pain. Mouth breathing was evident, patients specifically complaining of nighttime breathing difficulties. There was only one case with external facial deformity. The duration of symptoms ranged from five to 24 months.

The endoscopic examination (Figure 1) including white light endoscopy and narrow band imaging revealed a rubbery vascular mass which protruded at the level of the nasal space and nasopharynx with active serous discharge and bloody streaks.

Table 1 – ***Demographic, clinical and procedural characteristics***

Characteristics	Data
No. of patients (*n*)	8
Age, median [years]	16.9 (11.1–28.2)
Sex	All male
Preoperative CT scan (*n*)	5
Preoperative MRI (*n*)	7
Arteriography (*n*)	8
Preoperative embolization [%]	100
Median time between preoperative embolization and surgery [hours]	24
Endoscopic approach (*n*)	7
Combined approach (*n*)	1
Residual tumor (*n*)	0
Follow-up, median [months]	20.5 (3–37)
Other adjuvant therapies (*n*)	0
Postoperative MRI (*n*)	3

CT: Computed tomography; MRI: Magnetic resonance imaging.

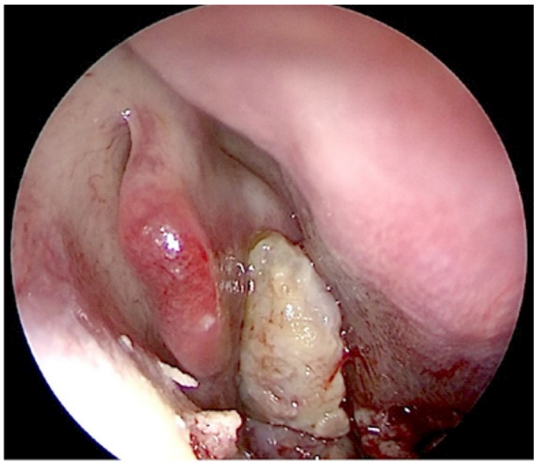

Figure 1 – ***Endoscopic aspect of a right juvenile nasopharyngeal angiofibroma (JNA).***

Routine hematological investigations were modified in a single case, revealing chronic anemia.

Diagnostic imaging raised a high suspicion of JNA. CT scan with contrast for five of the patients (Figure 2) and/or MRI with gadolinium (Figure 3, A and B) for seven of the patients were performed depending on each case, to assess the degree of tumor extension and the stage of JNA (Table 1). MRI examination revealed the specific salt and pepper sign, a common appearance of JNA.

Tumor extension can overrun the pterygomaxillary fossa, paranasal sinuses with bone destruction, ITF, orbit, parasellar fossa, cavernous sinus, optic chiasmal region or pituitary fossa. For nasopharyngeal angiofibromas, there are different staging systems, most commonly used being the Radkowski system, which is based on tumoral extension.

According to the Radkowski staging system, there were two (25%) cases which involved the nose and nasopharynx (corresponding to stage IA), one case (12.5%) with minimal extension to the pterygopalatine fossa (stage IIA), three (37.5%) cases that involved the entire pterygopalatine fossa without erosion of the orbital apex (stage IIB), one case (12.5%) involving the ITF (stage IIC) and one case (12.5%) with erosion of the skull base and minimal intracranial extension (corresponding to Radkowski's stage IIIA).

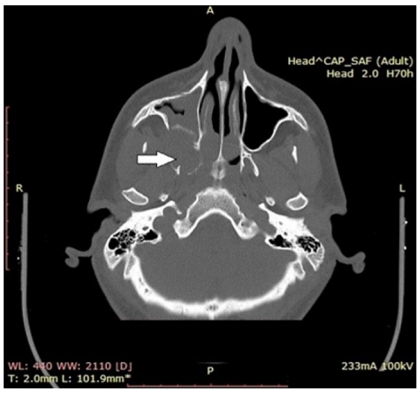

Figure 2 – ***Preprocedural CT scan axial view showing a right JNA with expansion of the pterygopalatine fossa and extension into the maxillary sinus. CT: Computed tomography; JNA: Juvenile nasopharyngeal angiofibroma.***

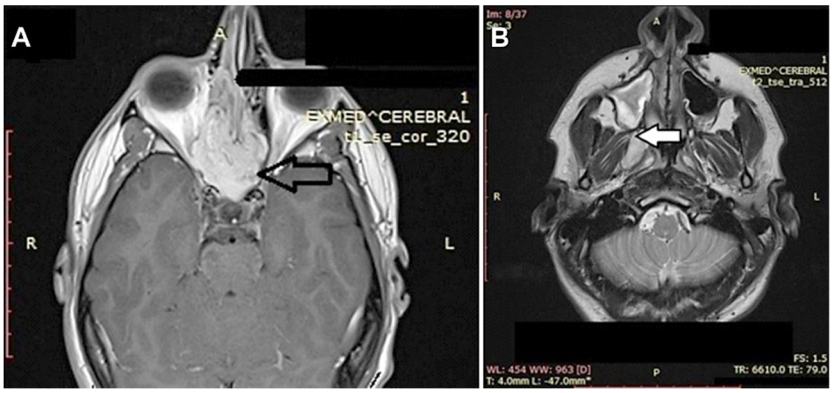

Figure 3 – ***Contrast-enhanced MRI in axial view illustrating a case of a right extended JNA: (A) The involvement of both ethmoid and sphenoid sinuses, as well as the tumor compressing the inferomedial wall of the right orbit, deforming through chronic compression the sella turcica wall; (B) The expansion of the pterygopalatine fossa and extension into the maxillary sinus. JNA: Juvenile nasopharyngeal angiofibroma; MRI: Magnetic resonance imaging.***

Arteriography of the bilateral carotid systems was routinely performed preoperatively in all cases.

Following arteriography, five cases had the tumors blood supply from left maxillary artery and three cases were from the right maxillary artery. None of the JNA cases had double vascularization in both carotid systems.

Embolization was performed using polyvinyl-alcohol (PVA) particle 500–710 μm in seven cases and Embozene microspheres 500 μm, 900 μm and 1300 μm in one case. Optimal final result, with postembolization loading and without periprocedural incidents.

Preoperative embolization was performed 24 hours before surgery in all cases (Table 1).

Surgery is the mainstay in the management of JNA. From this series, seven cases were solved by endoscopic endonasal approach (Figure 4, A–C), and one case was treated through a combined endonasal–external (Caldwell–Luc) approach.

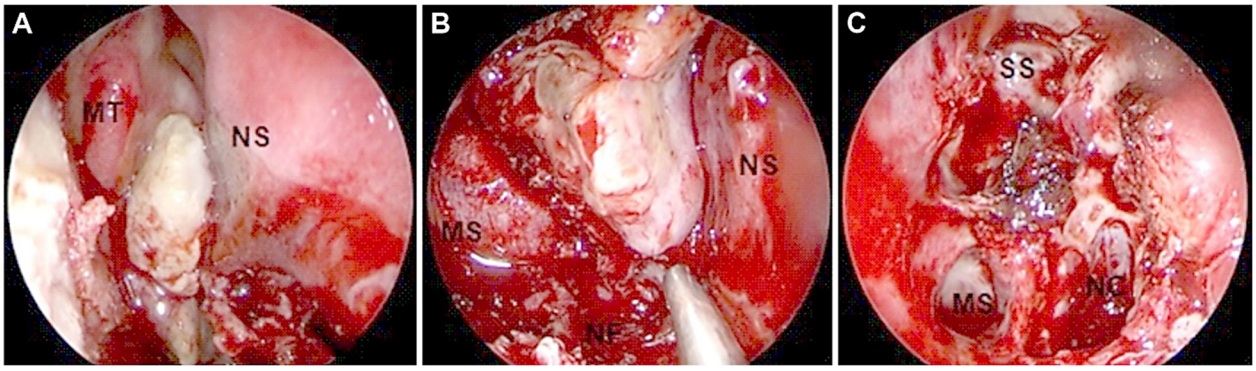

Figure 4 – ***Illustrative steps of JNA endoscopic transnasal resection: (A) Creating the intranasal operating field through endoscopic resection of a septal spur; in the center of the image, we can observe the anterior portion of a JNA intranasal extension; (B) Intraoperative view after right medial maxillectomy, which represents an intermediate step in approaching the tumor expansion within the pterygopalatine fossa, and its extension into the MS; (C) Final aspect after JNA excision; both the MS and SS are visible, as well as the right choana (posterior nasal aperture). JNA: Juvenile nasopharyngeal angiofibroma; MS: Maxillary sinus; MT: Middle turbinate; NC: Nasal cavity; NF: Nasal floor; NS: Nasal septum; SS: Sphenoid sinus.***

Complications were encountered in one case, a patient with chronic anemia who required blood transfusions. No mortality was observed.

Immediate postoperative imaging follow-up was performed in three selected cases through MRI, to assess if there is residual tumor.

Postoperative follow-up was based on periodic endoscopic and imaging examination (contrast-enhanced CT scan or MRI) for early detection of residual lesions, especially during the first year after surgery, with surveillance follow-up for a minimum of three years. At the time of this study, no patient had experienced a tumor recurrence. Median follow-up was 20.5 months (3–37 months). Only two patients have passed the 3-year surveillance period and two others are within the first postoperative year.

HP examination revealed the presence of polypoid tumoral masses, unencapsulated, made up of stromal connective tissue, highly vascularized, covered by a respiratory-type mucosa. Blood vessels were found having a multitude of shapes and dimensions, from a vascular-slit aspect to an arteriolar aspect. The vascular wall had uneven thickness, being made up of a layer of endothelial cells and a muscular tunic of varied thickness; among the muscular cells, some areas of hyaline and collagen deposits were identified. No elastic limitants or pericytes were identified as being present (Figure 5A). Some blood vessels had an empty lumen, caused by preoperative embolization, while others appeared to be congested, with erythrocytes in their lumen, caused by anastomosis with other blood vessels that haven't been embolized (Figure 5B). In certain

areas of the tumor, small blood vessels made up of endothelial cells of similar structure to angioblasts were identified, emphasizing an increased proliferation capacity of the tumors' vascular component (Figure 5C). In some patients, an abundant chronic inflammatory infiltrate made up predominantly of lymphocytes was identified around some of the blood vessels (Figure 5D).

It's been frequently noticed that the respiratory mucosa covering the tumor contained in its *lamina propria* a chronic inflammatory infiltrate that permeated the tumor stroma, with the surface epithelium exhibiting various modifications, from ulcerations to squamous metaplasia (Figure 5, E and F).

The IHC study we performed has demonstrated that vascular structures (whatever the caliber) are covered in a continuous layer of endothelial cells (Figure 6A), and the muscular tunic consists of smooth muscular cells (intense positive for anti-α-SMA antibody), unevenly distributed, which makes the blood vessel wall exhibit areas of varying thickness (Figure 6B). The assessment of the inflammatory reaction revealed numerous T-lymphocytes within the stroma, as well as memory T-cells (Figures 6, C and D), rare B-lymphocytes (Figure 6E) and rare macrophages (Figure 6F). In comparison to locally malignant tumors or rhinopharyngeal polypoid structures, we find that the inflammatory response in angiofibromas is much more diminished and has no role in this type of tumor pathogeny.

The stromal component comprised of an increased number of fibroblasts of various shapes (oval, fusiform, star-shaped, filiform cells, etc.), with large nuclei, hypochromic, with basophilic cytoplasm, and without cellular atypia, as well as rare mitoses. The stromal connective tissue contained numerous collagen fibers with a tendency to assemble in fascicles.

Discussions

Even though JNA is diagnosed in teenagers and young males between the ages of 10 and 25, in professional literature, there are case reports of female patients and also of male patients older than 25 years of age [19, 20]. In our cases series, there is one patient of 28 years old, with symptoms present for several years, but ignored [21].

Presenting symptoms are inconspicuous and may be easily ignored without proper endoscopic or imagistic exploration. Frequent symptoms are represented by nasal obstruction, followed by epistaxis, headache, and facial swelling. Other inconsistent symptoms are present depending on the extent of the tumor.

Occasionally, the symptomatology is similar to that of an inflammatory rhinopharyngeal condition; in other cases, it mimics a tumoral nasal congestion, entailing a thorough clinical examination and urgent diagnostic imaging [22–24].

CT imaging provides detailed information regarding bone structures, especially regarding the sphenoid bone. CT is essential for tumor staging and evaluation of the extension and peritumoral anatomy. For detecting intra-cranial or orbital extension of JNA, MRI is superior to CT.

The major benefit of tumor staging is to provide prognostic information for case management and patient counseling. It is useful to maintain uniform reporting within the literature, allowing results analogy and establishing standards of care. We used the Radkowski staging system for JNA, but there are more than 10 JNA staging systems [3].

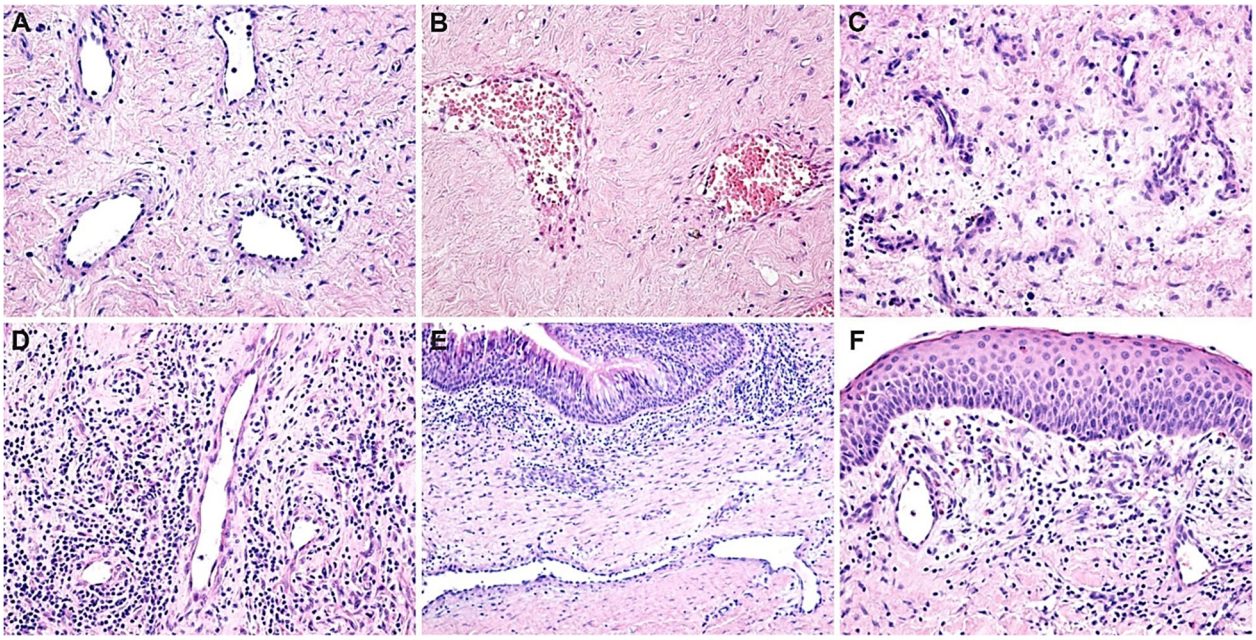

Figure 5 – ***Histopathological images of angiofibromas: (A) Microscopy image of a juvenile nasal angiofibroma revealing the presence of empty tumor blood vessels (belonging to the network of embolized blood vessels), with walls of varying thickness, laid out in a connective stroma that is rich in fibroblasts and collagen fibers; (B) Tumor blood vessels of varying shape, congested, full of figurative elements; (C) Tumoral area with angiogenic vessels; (D) Tumor vessels disposed in a stroma strongly infiltrated by inflammatory cells; (E) Tumor area developed as far as the lamina propria belonging to the nasal mucosa; (F) Tumor area covered by squamous metaplastic epithelium. Hematoxylin–Eosin (HE) staining: (A–D and F) ×200; (E) ×100.***

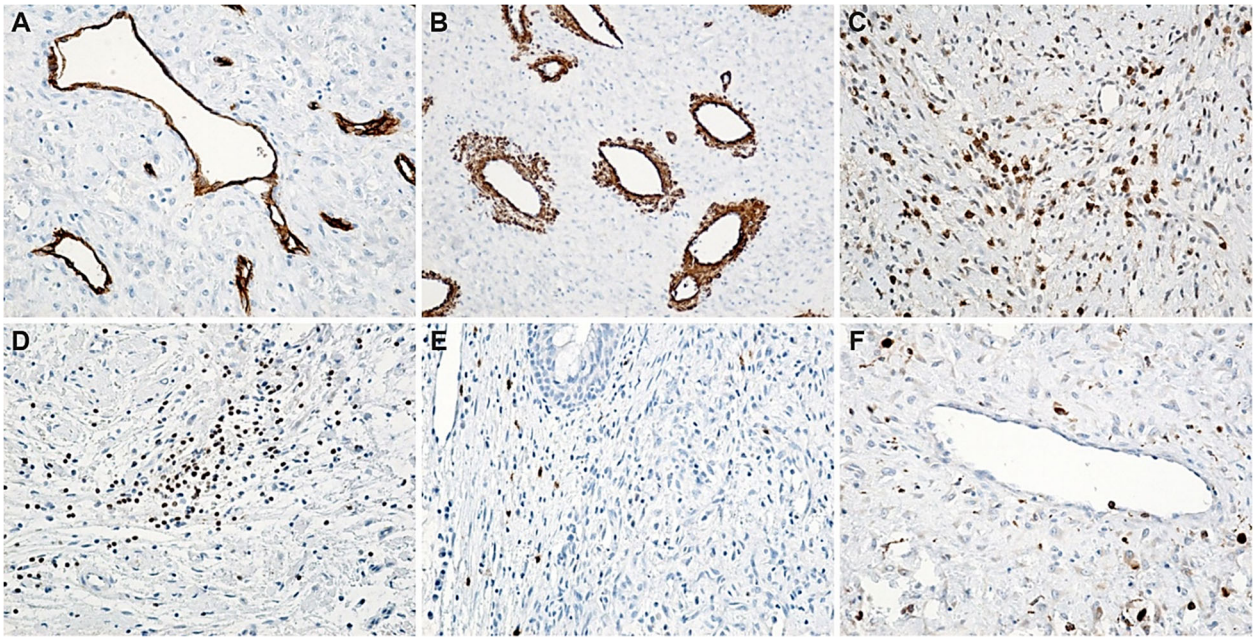

Figure 6 – ***Immunohistochemical aspects of nasopharyngeal angiofibroma: (A) Tumoral vessels of varying caliber and shape, bounded by an uninterrupted row of endothelial cells; (B) Smooth muscle cells irregularly disposed within the tumor vessel wall; (C) Moderate inflammatory infiltrate present within the tumor stroma; (D) Tumor stroma infiltrated by numerous T-lymphocytes; (E) Tumor stroma with a low B-lymphocytes content; (F) Tumor stroma with a low macrophages count. Anti-CD34 antibody immunomarking: (A) ×200. Anti-α-SMA antibody immunomarking: (B) ×100. Anti-CD45RO antibody immunomarking: (C) ×200. Anti-CD3 antibody immunomarking: (D) ×200. Anti-CD20 antibody immuno-marking: (E) ×200. Anti-CD68 antibody immunomarking: (F) ×200. α-SMA: Alpha-smooth muscle actin; CD: Cluster of differentiation.***

Arteriography revealed that all tumors were fed from the ECA territory, from the distal internal maxillary artery branches, mainly the sphenopalatine, descending palatine and posterior superior alveolar branches [25]. Also, ascending pharyngeal or vidian arteries can contribute to the tumor blood supply, although in our cases it did not happen. Besides, it is necessary to detect existing anastomoses between ECA and ICA, to avoid intra-procedural iatrogenic embolic complications, such as optic nerve ischemia [26]. Arteriography is also needed to evaluate the contralateral carotid branches as to exclude contribution to tumor bloody supply, mainly when the JNA extends beyond the midline [27–29].

Nowadays, preoperative embolization and endoscopic surgery represent the standard of care [17, 30].

Preoperative embolization provides excellent devascularization of feeding arteries of the tumor and is commonly performed 48 hours before surgery. In our case series, it was performed 24 hours before surgery, with timing between embolization and surgery being crucial. This preoperative preparation has revolutionized the surgical approach by dramatically decreasing intraoperative bleeding and therefore making the assessment of tumor borders during dissection more accurate. Not all surgeons agree on routinely performing preoperative embolization because the peripheral tumor transformation induced by the procedure can increase the possibility of leaving residual tissue behind.

Endoscopic endonasal surgery is a viable alternative to external approach in the management of JNA, from small tumors up to tumors involving different regions (Table 2) owing to expanded endonasal endoscopic approach for resection. External surgical approach, such as transpalatal, Le Fort I, medial maxillectomy, ITF or facial translocation are exemplified in Table 2, depending on JNA extension. In those advanced tumors involving the cavernous sinus or closely related to the ICA, a mixed approach is used. Endoscopic endonasal surgery approach has the advantage of shorter mean operative time, lower rate of postoperative complications and lower risk of recurrence [31, 32]. For sizeable intracranial extension, the otorhinolaryngology surgeon will usually cooperate with a neurosurgeon to select the best surgical management [33].

Table 2 – ***Examples of surgical approach techniques depending on JNA extension***

	Endoscopic	Transpalatal	Le Fort I	Medial maxillectomy	ITF	Facial translocation
Nasopharynx	■	■	■	■	■	■
Intranasal	■	■	■	■		■
Ethmoid	■		■	■		■
Sphenoid	■	■	■	■	■	■
Pterygopalatine fossa	■		■	■	■	■
Medial ITF	■		■	■	■	■
Lateral ITF					■	■
Medial cavernous sinus			■	■		■
Lateral cavernous sinus					■	■
Middle cranial fossa					■	■

ITF: Infratemporal fossa; JNA: Juvenile nasopharyngeal angiofibroma.

The advantage of medical imaging through MRI in the immediate postoperative period, especially in cases of extensive JNA, is owed to the absence of any inflammatory changes, making any residual tumor tissue easily identified.

In our study, the postoperative period was uneventful except for the patient with chronic anemia who needed two units of blood transfusion. Fortunately, none of the cases had complications related to endoscopic surgery [34, 35].

Radiation therapy was taken into consideration only as a treatment reserved for recurrences, for inoperable cases or for patients who refuse surgery.

In literature, the recurrence rate for endoscopic approach for JNA is 13% compared to 28% in open approaches [36, 37].

Conclusions

JNA is a rare and difficult tumor affecting predominantly males, which should always be managed by a multidisciplinary team (MDT) approach in centers with adequate experience, to gain favorable results.

Conflict of interests

The authors declare that they have no conflict of interests.

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