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Effectiveness of SQUID-12 in an Adult Patient with a Massive Right Pontocerebellar Angle Jugulotympanic Paraganglioma (Di2), Along with a Brief Review of New Embolization Materials

CASE REPORT

CORRESPONDING AUTHOR:
Vincenzo Colonna

Department of Neurosurgery, Sapienza University, Policlinico Umberto I, Viale del Policlinico, 155, 00161 Rome, Italy, E-mail:

v.colonna@uniroma1.it

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Vincenzo Colonna [1], Ignazio Divenuto [2], Daniele Ajello [2], Claudio Sicuso [2], Jad El Choueiri [3], and Nunzio Paolo Nuzzi [2]

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ABSTRACT

Endovascular embolization as adjuvant or stand-alone therapy has become an important part of the available tools for the treatment of head and neck paragangliomas; however, a thorough understanding of the angioarchitecture of the tumor and neurovascular anastomoses is an essential element for a proper diagnosis and treatment planning. Various copolymers (liquid embolization agents [LEAs]) are available on the market and are currently used. This clinical case study aims to demonstrate the efficacy and safety of the use of SQUID-12 (non-adhesive LEAs) as adjuvant therapy for highly vascularized intracranial lesions that are difficult to treat with surgery as a first-line treatment. SQUID-12, compared with some other LEAs, enables a better assessment of the tumor vasculature and the volume of injected LEA and is also able to shrink and reduce the vasculature of highly angiogenic lesions due to its properties of penetrating deeper and reaching the central microcirculation (nidus).

KEYWORDS

Head and Neck Paragangliomas, Endovascular Embolization, SQUID-12, Non-Adhesive Liquid Embolization Agents (LEAs) Adjuvant Therapy

INTRODUCTION

Paragangliomas

Paragangliomas (PGLs) are a group of rare highly vascularized neuroendocrine tumors that arise in the sympathetic or parasympathetic extra-adrenal autonomic paraganglia.[1,2] According to the 2017 WHO classification of tumors (fourth edition), these neuroendocrine tumors can be classified based on their location and origin.[3] In general, parasympathetic PGLs are non-chromaffin, non-secreting tumors mostly confining to the head and neck region (head and neck paragangliomas [HNPGLs]), along the glossopharyngeal and vagal nerves. Rarely, they can arise from the parasympathetic tissue in the thorax. In contrast, sympathetic PGLs are secreting tumors, mostly noradrenaline, that commonly arise from a collection of chromaffin tissue around the origin of the inferior mesenteric artery (the organ of Zuckerkandl) or the aortic bifurcation, and less frequently in the prevertebral and paravertebral sympathetic ganglia of the chest, abdomen, and pelvis. They make up 20% of chromaffin-secreting catecholamine tumors; the other 80% are located within the adrenal medulla and are referred to as pheochromocytomas[4–6] (Figure 1).

Head and Neck Paragangliomas

HNPGLs constitute approximately 65–70% of all PGLs, representing 0.6% of all head and neck malignancies.[7,9,10] The overall incidence of HNPGLs is estimated to be between 0.3 and 1 per 100 000 individuals with 90–95% coming from the parasympathetic chain and 5–10% originating in the sympathetic chain, that is, 95% of HNPGLs are non-secreting, non-chromaffin tumors. The age of onset varies widely, with hereditary cases typically presenting a decade earlier than sporadic ones.[11]

Although PGLs of the cervical sympathetic chain have been documented, most HNPGLs originate from the jugular bulb, glossopharyngeal nerve, vagus nerve, or carotid body.[7,10,12] Notably, carotid body PGLs account for up to 60% of all HNPGLs[9] (Figure 2).

Jugular-Tympanic Paraganglioma/ Tympano-Jugular Paraganglioma

Jugular-tympanic paragangliomas (previously known as glomus jugulo-tympanicum tumors) are usually parasympathetic slow-growing benign tumors that infiltrate the skull base and can be locally aggressive.[13] Considering these tumors'

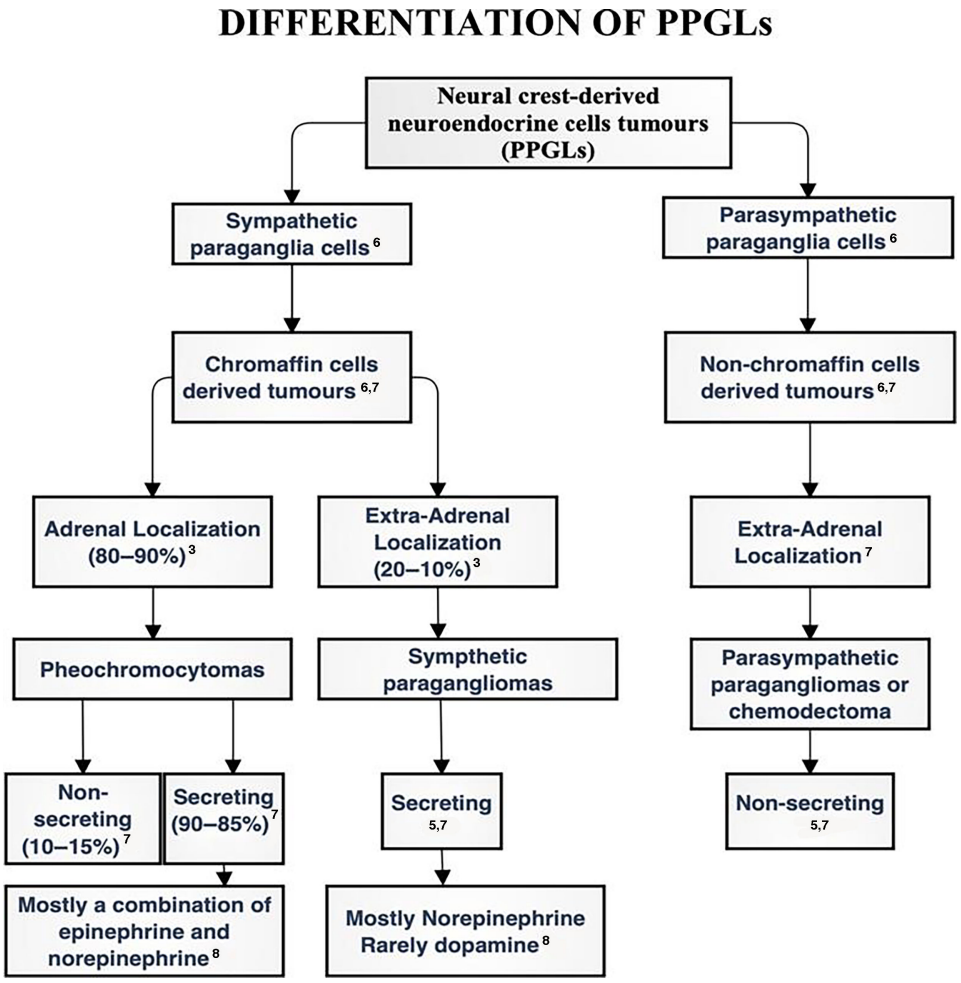

FIGURE 1. Flowchart summarizing the cellular origin, localization, and phenotype of pheochromocytomas and paragangliomas (PPGLs).[3,5–8]

vasculature and local aggressiveness, they present a challenge for the treating physician. A factor to consider is the involvement of important neurovascular structures, such as the internal carotid artery (ICA), the jugular bulb, the facial nerve, and the lower cranial nerves (CN IX, X, XI, XII). Tympano-jugular paragangliomas (TJPs) usually arise from paraganglia that can be found along the course of Jacobson's nerve, the nerve of Arnold, the adventitia of the jugular bulb, the osseous canal connecting the jugular fossa to the middle ear cavity, or within the middle ear[14] with most arising from the paraganglia situated in the wall of the jugular bulb, which is surrounded by the temporal bone and the occipital bone and connected to numerous venous channels.[15]

These tumors most commonly affect middle-aged adults, with a higher incidence in women (3:1). Peak incidence occurs between the ages of 40 and 60, and a portion of TJPs has been associated with mutations in the succinate dehydrogenase genes, which also happen to be implicated in other PGLs and pheochromocytomas.

As a result of their slow and silent growth, a delayed presentation is common, with cranio-temporal-cervical extensions.

The Fisch classification is important for planning treatment strategies and predicting outcomes; it usually correlates with the tumor's clinical behavior and degree of difficulty in tumor resection. The initial model classified them into classes A, B, C, and D based on the extent of ICA involvement and degree of intracranial extension, which was followed by a modification by Sanna to include sub-classifications and an additional class V, to comprise tumors that involve the vertebral artery.

The usual manifestation of a TJP is a pulsatile middle ear mass. In some cases, blanching of the middle ear component (Brown's sign) or also the 'rising sun' sign might appear. The most common presenting symptom is hearing loss, present in 60–80% of cases, with pulsatile tinnitus.

If the middle ear is invaded, sensorineural hearing loss and vestibular symptoms appear. Lower cranial nerve deficits develop secondary to the invasion of the jugular fossa, as palsies of the 9th and 10th cranial nerves are seen in 35–40% of cases, and those of the 6th and 7th are seen in approximately 20–30% of cases.[16]

Treatments of HNPGLs

Treatment plans for HNPGLs usually include observation and surveillance, surgery, radiotherapy, adjuvant chemotherapy, adjuvant embolization, or, in some cases, stand-alone embolization.[17]

Therapeutic embolization as a stand-alone treatment offers low-risk control of tumor growth, showing a significant reduction in tumor volume after treatment.[18] It has been shown to be a very safe and effective procedure even in conjunction with surgery where it may significantly reduce operative blood loss and associated morbidity. The distinct properties of each embolic

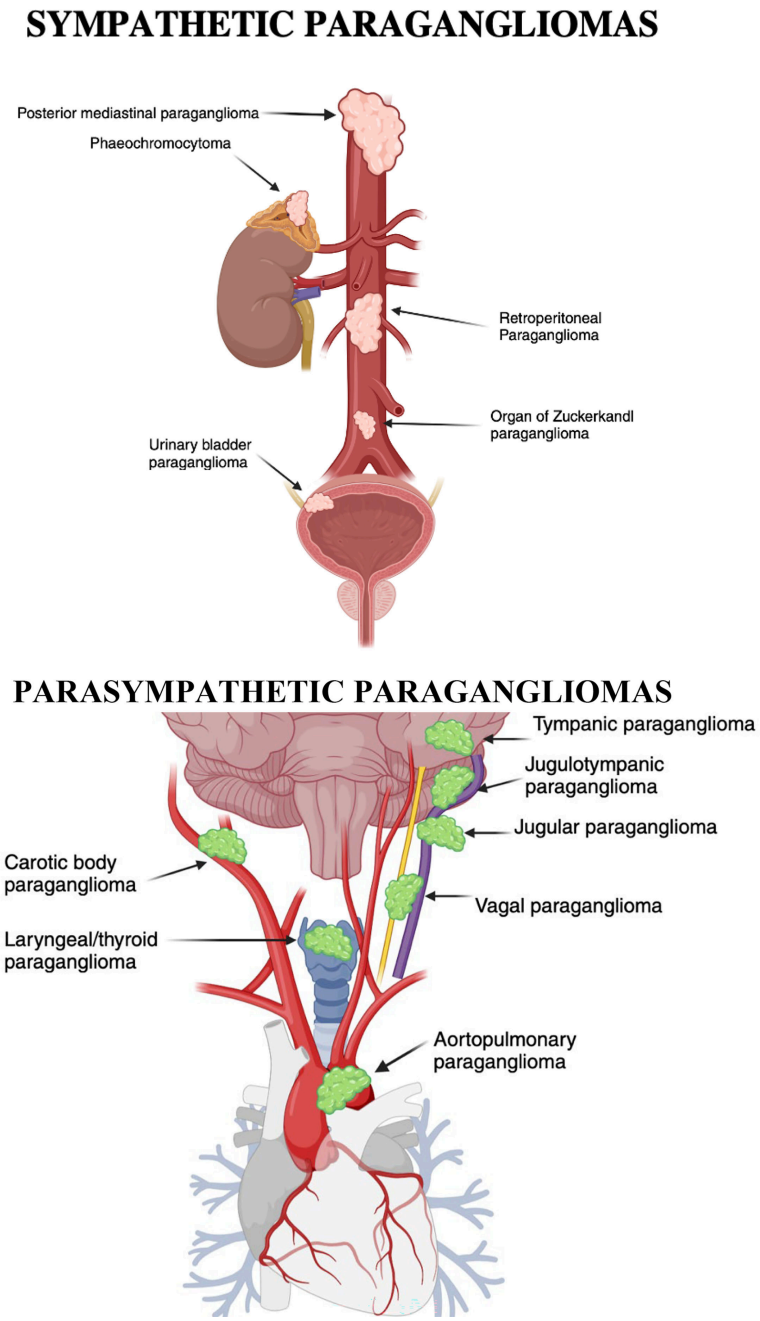

FIGURE 2. Graphical illustration of sympathetic and parasympathetic paragangliomas' most frequent locations.

material available provide multiple options for tumor devascularization.[19]

Embolization Materials

Embolization materials can be categorized into temporary and permanent agents based on the duration of the occlusion (Table 1). Temporary agents include Gelfoam, starch microsphere, and thrombin phase-change material-based nanoparticles. They usually are indicated as surgical peri-procedural adjuvants. On the other hand, arteriovenous malformations, dural arteriovenous fistulas, or vascularized lesions as PGLs indicate the use of permanent embolizing agents that can also be used pre-surgically. Permanent agents include coils, microparticles, and liquid embolization agents (LEAs), which are divided into adhesive types, such as glues (glubran, nBCA), and non-adhesive types, such as ONYX, SQUID, PHIL, and Easyx.[20]

Non-Adhesive Liquid Embolization Agents

Non-adhesive embolizing agents have several advantages over adhesive ones, including their excellent embolizing capacity and the ability to reach small vessels, with a reduced tendency to cause off-target embolization and a reduced risk of microcatheter entrapment. Furthermore, the embolization of a lesion in the days before definitive surgery minimizes the risk of intraoperative bleeding.[22] Conversely, the primary drawbacks include the necessity for compatible microcatheters, their elevated cost, and

TABLE 1 Advantages and limitations of temporary and permanent embolization agents[20] and the properties and compositions of different non-adhesive liquid embolization agents.[21]

Temporary	**Advantages**	**Limitations**
Microsphere	Deep microvasculature penetration Minimal clumping	Radiolucent Fragile
Gelfoam	Medium to large vessel occlusion Inexpensive Easy to use	Temporary
Permanent	**Advantages**	**Limitations**
PVA (polyvinyl alcohol)	Microvascular penetration Easy to use	Radiolucent Irregular shape may allow recanalization
Coils	Precise deployment Useful in high-flow vessels	Possible dislogment and embolization
Glues (nBCA)	Rapid solidification and occlusion Can flow into complex angioarchitecture	Catheter retainment
Copolymers (SQUID, ONYX, PHIL, and Easyx)	Usually slower solidification Can flow into complex angioarchitecture	Catheter retainment

Copolymers	**ONYX**	**SQUID**	**PHIL**	**Easyx**
Molecule	EVOH copolymer	EVOH copolymer	Hydroxethyl methacrylate copolymer	Iodinized Polyvinyl Alcohol Polymer Ether
Preparation	20-minute shaking	20-minute shaking	No needed	Ready to use (vial)
Radiopacity visibility	Excellent	Excellent	Good	Good
Radiopaque agent	Tantalum	Tantalum	Iodine	Iodine
Embolization power	Excellent	Excellent	Excellent	Excellent
Different viscosity	Yes	Yes	Yes	No
Texture	Chewy	Chewy	Chalky	Chewy
Injection time	Minutes (0.016 mL/min)	Minutes	Minutes	Minutes (0.025 mL/min)
CT-scan artifacts	Yes	Yes	No	No
Solidification process	Copolymerization	Copolymerization	Copolymerization	Copolymerization
Solvent needed	DMSO	DMSO	DMSO	DMSO
Staining	Yes (black)	Yes (black)	No (opaque-white color)	No (pearl-white color)

CT, computerized tomography; EVOH, ethylene vinyl alcohol.

the obligatory use of Dimethyl Sulfoxide. DMSO is required to maintain the embolic fluid in a dissolved state before injection, but it can lead to vasospasm, endothelial wall damage, and pain. Non-adhesive liquid embolization agents (NALEAs) also determine the contamination of the microcatheter that could not subsequently be used with other agents, despite a possible washing with DMSO.[23] NALEAs can be categorized according to their different molecular composition into ethylene vinyl alcohol (EVOH)-based (ONYX, SQUID), Hydroxyethyl Methacrylate-based (PHIL), and Iodinated Polyvinyl Alcohol Polymer-based (Easyx) LEAs (Table 1).

ONYX is undoubtedly the longest-used NALEA, having first appeared in medical publications in the 1990s.[21] ONYX and SQUID share the same composition: EVOH copolymer, micronized tantalum powder, and DMSO, the difference being that the latter has a smaller tantalum grain size, making its precipitation and sedimentation twice as slow. This improves radiopacity homogeneity and enhances visibility during longer injection times.[22,24] Both are available in different compositions. ONYX 6.0%, 6.5%, and 8.0% have viscosities of 18, 20, and 34 centipoises (with the numbers representing the viscosity in cps at 40°C), respectively.[21] SQUID, indeed, is available in six formulations: SQUID-12, SQUID-12LD, SQUID-18, SQUID-18LD, SQUID-34, and SQUID-34LD. The key innovations of SQUID include the extra-low-viscosity versions (SQUID-12 and SQUID-12LD) and the low-density (LD) variants. The extra-low-viscosity types, with a lower concentration of EVOH, were created to allow deeper penetration of the liquid embolic agent (LEA) into the vascular nidus. The LD

variants have 30% less tantalum, making them less radiopaque while maintaining the same embolic properties as the standard versions.[24]

PHIL and Easyx (both from MicroVention, Tustin, CA, USA) are the newest liquid embolic agents on the market.[25,26] PHIL is composed of two copolymers, polylactide-co-glycolide, and poly-hydroxy-ethyl-methacrylate, along with DMSO and triiodophenol (an iodine compound) for radiopacity. Its ready-to-use formula offers a significant advantage by eliminating lengthy preparation times. Unlike ONYX and SQUID, PHIL does not contain tantalum, resulting in fewer computerized tomography (CT) artifacts. Additionally, PHIL does not cause a tattooing effect when the treated area is near the skin.[24] Easyx is the most recent LEA available on the market and, as PHIL, it is an embolic agent based on iodine used as a radiopaque agent and polyvinyl alcohol polymer ether as a polymer.[26]

Here, we show the safety and effectiveness of SQUID-12, in the treatment of an adult patient presenting with a voluminous right pontocerebellar angle jugular-tympanic PGL Di2 (40 mm × 45 mm × 65 mm).

ILLUSTRATIVE CASE

Clinical History

A patient in their fifties presented to the emergency department with a 3-month history of severe headache accompanied by blurred vision, worsening episodes of dizziness without rotational sensation, a tendency to fall, moderate dysarthria, dysphagia for both solids and liquids, and right retroauricular pain radiating to the right side of the face. The patient also reported progressive right-sided hearing loss over the past few months.

The patient's medical history includes hypertension and a previous stroke of unknown origin, for which they have been on aspirin therapy. There was no reported history of recent infections, nausea, or vomiting.

Physical Examination

The patient was admitted to our neurosurgery department, and she underwent a neurologist consultation. Upon physical examination, the patient showed moderate dysarthria, dysphonia, right tongue deviation, right lingual hypotrophy with spontaneous fasciculations, soft palate deviation to the right, ataxic gait, and a positive right Romberg sign.

Parameters and Laboratory Findings

The patient had normal vital parameters and blood laboratory results, as shown in Table 2.

TABLE 2 Laboratory findings and vital parameters at the emergency room.

Vital Parameters		**Normal Range**
Heart rate	78	60–100
Respiratory rate	18	10–18
Glasgow Coma Scale	15	15
Blood Pressure	118/78 mmHg	120/100 to 60/80 mmHg
Pulse	Rhythmic	—
SpO_2%	98%	>95%
Temperature	36	<37.3°C
Chemistry		**Normal Values**
Sodium	140	136–146 mmol/L
Potassium	4.2	3.5–5.3 mmol/L
Creatine kinase	**213**	15–145 U/L
Lipase	27	1–67 IU/L
Urea	28	17–43 mg/dL
Creatinine	0.66	0.7–1.5 mg/dL
Glucose	86	70–110 mg/dL
Total calcium	2.33	2.20–2.65 mmol/L
LDH	230	110–295 IU/L
CRP	0.16	0.01–0.50 mg/dL
Hemoglobin	13.4	14–17 gr/dL
Hematocrit	39.6	40–54%
Mean cell volume	86.8	85–95 FL
Erythrocytes	4.56	3.90–5.20 (10^6 /mm^3)
Leucocytes	8.16	4.00–10.00 (10^6 /mm^3)
PT	10.70	—
INR (PT)	0.97	0.9–1.18 s
a-PTT	32.50	—
INR (a-PTT)	1.08	0.81–1.20 s

Imaging

A brain CT scan was performed. A voluminous expansive formation at right pontocerebellar angle was detected, with erosive phenomena of the ipsilateral temporal bone, parietal obliteration of the bulb, and pontocerebellar cisterns on the right with a partial compression of the fourth ventricle, as shown in Figure 3.

The Magnetic Resonance Imaging (MRI) showed a voluminous expansive formation (40 mm × 45 mm × 65 mm) with its epicenter at the level of the right jugular foramen, extending both intracranially, occupying the cisternae of bulbo-cerebellar and pontocerebellar angle, and extracranially, reaching into the ipsilateral carotid space (Figure 4). This lesion appeared to be responsible for marked erosion of the jugular foramen and part of the carotid canal. At the intracranial level, this formation was responsible for a considerable mass effect on the brainstem, which was displaced to the left, and we had a compression of the fourth ventricle, which is also displaced with supratentorial hydrocephalus formation. The ipsilateral 9th, 10th, 11th, and 12th cranial nerves are not appreciable to the method.

Upon cerebral angiography, a voluminous and intense vascular blush with accelerated transit of the expansive lesion, fed by hypertrophic branches of the ipsilateral external carotid artery, was observed, as well as the occlusion of the right jugular vein gulf was observed (Figures 5 and 6).

The right ICA, immediately upstream to the entrance into the carotid canal, shows a reduction in caliber as imprinted by the lesion, with no obvious hemodynamic impact.

Given the high degree of vascularization, a jugular PGL was suspected.

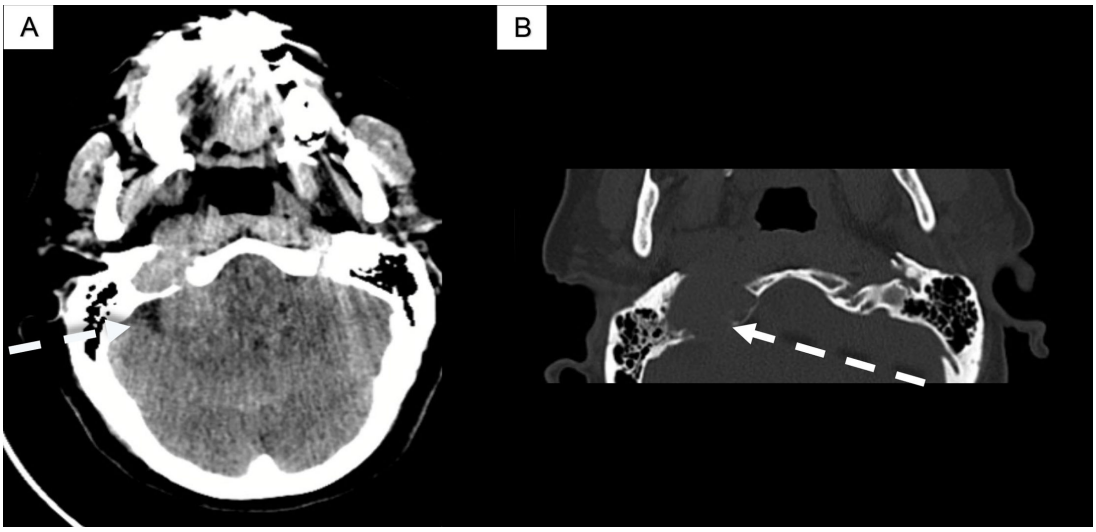

FIGURE 3. Patient axial brain computerized tomography (A) and axial bone window CT scan of the petrosal part of the right temporal bone with bone erosion (B). CT, computerized tomography.

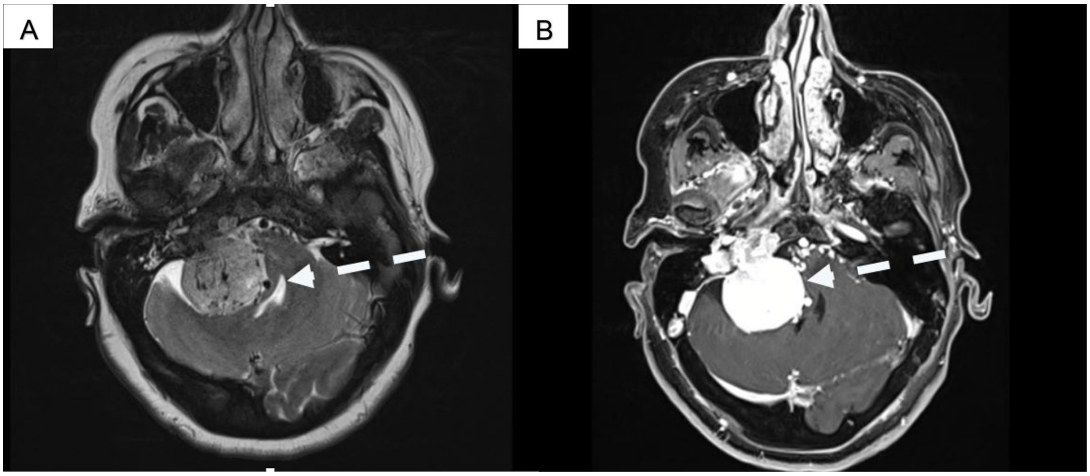

FIGURE 4. Patient axial brain MRI with T2-weighted (A) and T1-weighted with contrast (B) sequences.

Procedure

A benchmark-bearing catheter was placed in the right external carotid artery, and navigation with a double-lumen microcatheter with a 6–9 mm Eclipse balloon was performed, placed in the largest afferent artery of the lesion.

During occlusive inflation of the balloon through 'pressure cook' technique, approximately 4 ml of SQUID-12 material was injected (Figure 7).

An almost complete devascularization of the intracranial component of the lesion and a large part of the jugular and extracranial gulf components was performed (Figure 8).

Clinical Course

During the clinical course, the patient experienced episodes of increased inflammatory parameters and hyperpyrexia in the absence of clear organ recall in remission after antibiotic therapy. The patient started physiotherapy with gait and postural passage training and speech therapy rehabilitation. The patient had a dysphagic diet.

The patient experienced no new-onset neurological deficits and achieved autonomous mobilization.

A month after embolization, a new brain MRI scan was performed. The MRI showed a significant size reduction of the right jugular PGL, showing necrotic-colliquative phenomena within it (LL × AP × CC 40 × 45 × 65 mm vs. 30 × 35 × 50 mm approximately). Consensual re-expansion of the fourth ventricle, disappearance of the supratentorial hydrocephalus, and reduction of mass effect on the brainstem were observed. No recent onset ischemic areas on the brain parenchyma were seen (Figure 9).

Moreover, the patient showed slight symptoms of improvement, especially regarding dysphagia and dysarthria.

DISCUSSION

The present case reported a successful example of a massive and very vascularized intracranial jugular-tympanic PGL approach and outcome using an NALEA. Our singular case stands out not only because of the tumor's rarity but also due to the chosen treatment modality: adjuvant endovascular embolization using

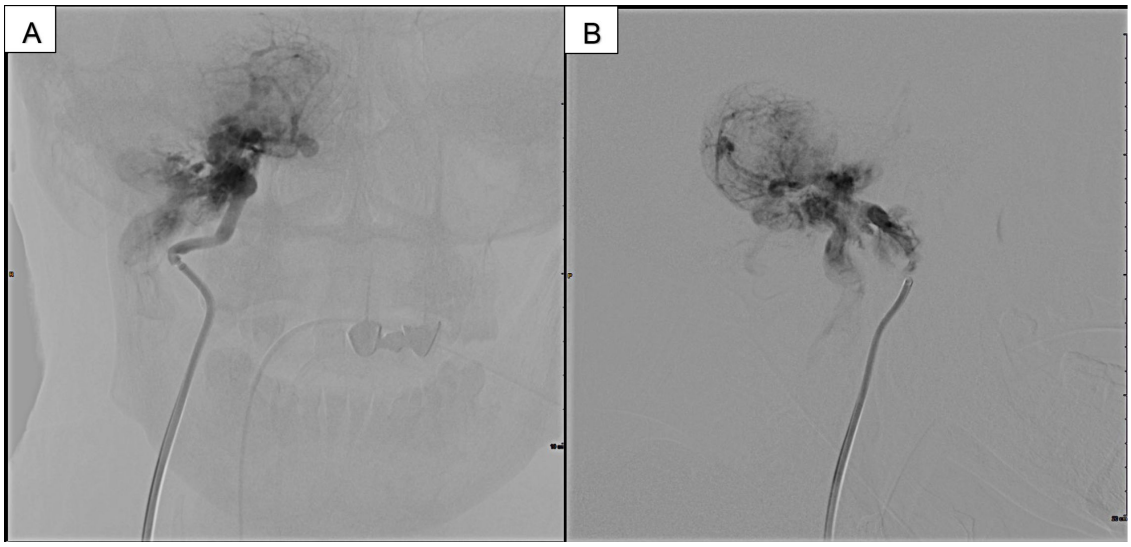

FIGURE 5. Frontal (A) and lateral (B) cerebral angiography views demonstrate an intense vascular blush originating from a right-sided expansive intra-extracranial lesion. This was observed following selective injections into the hypertrophied posterior branch of the right ascending pharyngeal artery, supplying the lesion.

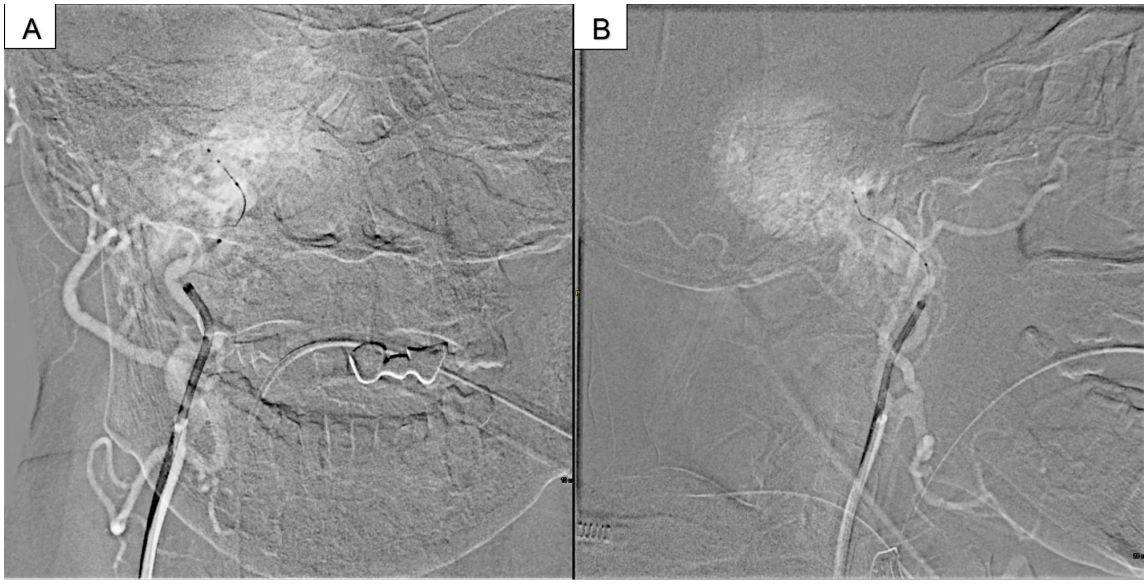

FIGURE 6. Frontal (A) and lateral (B) cerebral angiography projections of our patient demonstrate super-selective navigation using a double-lumen microcatheter, with a 6–9 mm Eclipse balloon positioned within the primary vessel supplying the lesion.

SQUID-12. The decision to use SQUID-12 specifically, instead of other embolizing agents, comes down to its favorable properties as its extra-low-viscosity versions with a lower concentration of EVOH, allowing deeper penetration into vascular nidus and a more comfortable and better assessment of the vascularity of the lesion.

Hereafter we elaborate on the uniqueness of the case, the rationale behind the choice of SQUID-12, and its demonstrated effectiveness.

HNPGLs being typically uncommon, slow-growing tumors, are usually treated with surgery, radiotherapy, and embolization. Surgical resection carries significant risks due to the tumor's vascular nature, and radiotherapy is associated with delayed tumor response and potential long-term side effects. Embolization reduces the tumor's vascularity, shrinking the tumor, and it has been proposed as either an adjuvant to operations or a stand-alone treatment. HNPGLs can benefit greatly from endovascular embolization, but its impact remains a matter of ongoing debate.[27] In a single-center study, evaluating the efficacy and feasibility of pre-operative embolization of HNP, it has been observed that pre-operative embolization was indeed effective;[28] this came in line with other studies done on the same topic.[29] In comparing methods of embolization, a meta-analysis by Schartz et al. found a higher success rate with direct puncture compared

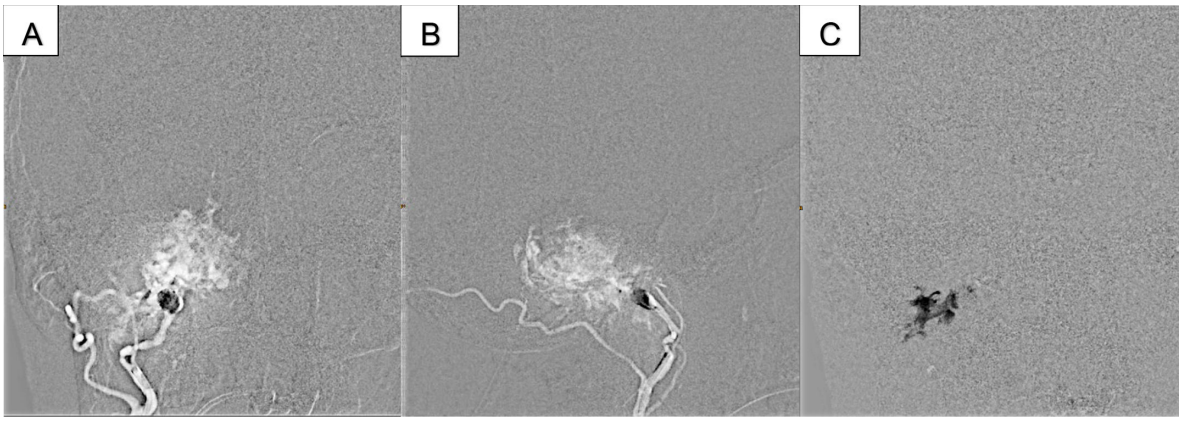

FIGURE 7. Frontal (A) and lateral (B,C) cerebral angiography projections. During occlusive balloon inflation ('pressure cook' technique), approximately 4 ml of SQUID-12 non-adhesive embolizing material was injected.

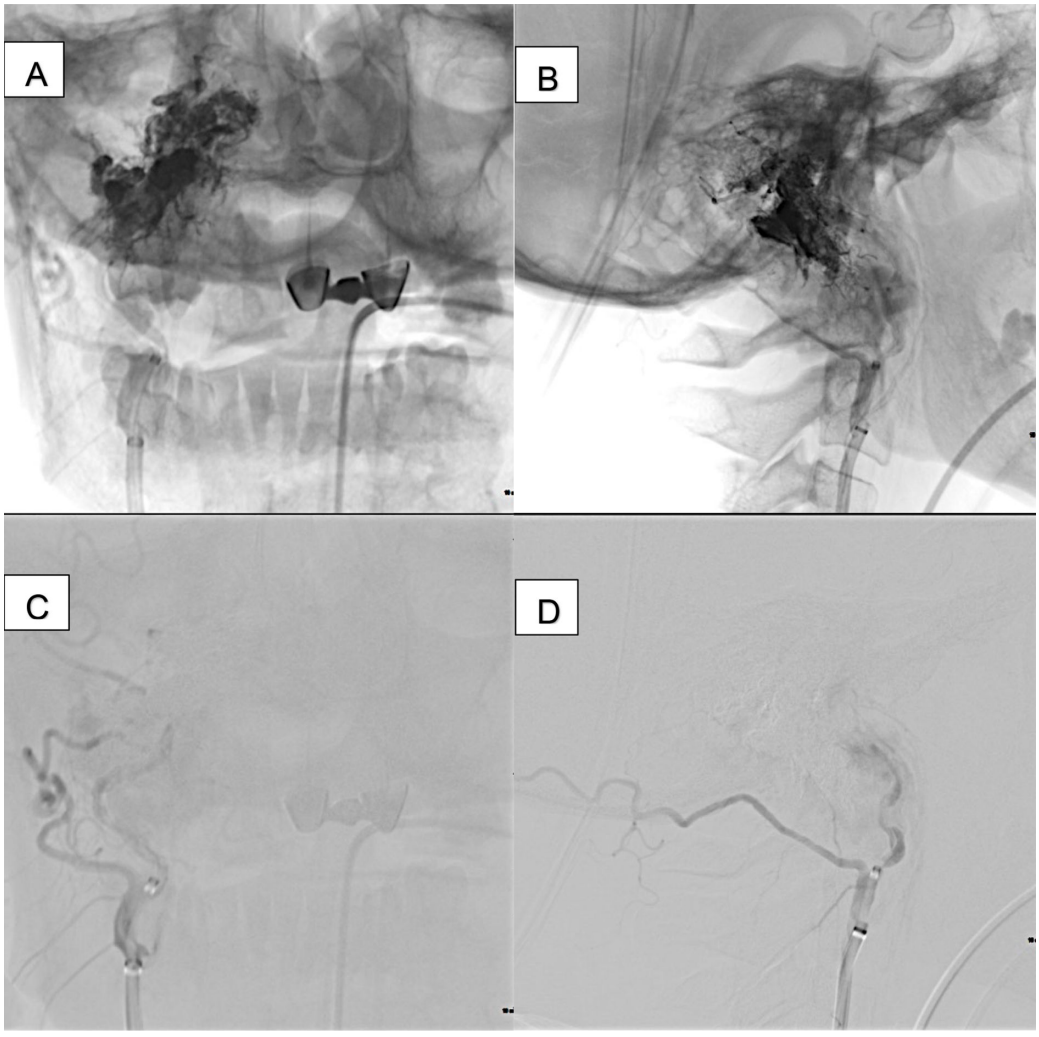

FIGURE 8. Frontal cerebral angiography projection without (A) and with subtraction (C) and lateral cerebral angiography projection without (B) and with subtraction (D) after complete deafferentation of the lesion.

with trans-arterial embolization; however, the preferred method for the management of HNPGLs is still trans-arterial embolization[30] mainly due to the possibility of using a wide variety of embolic materials.

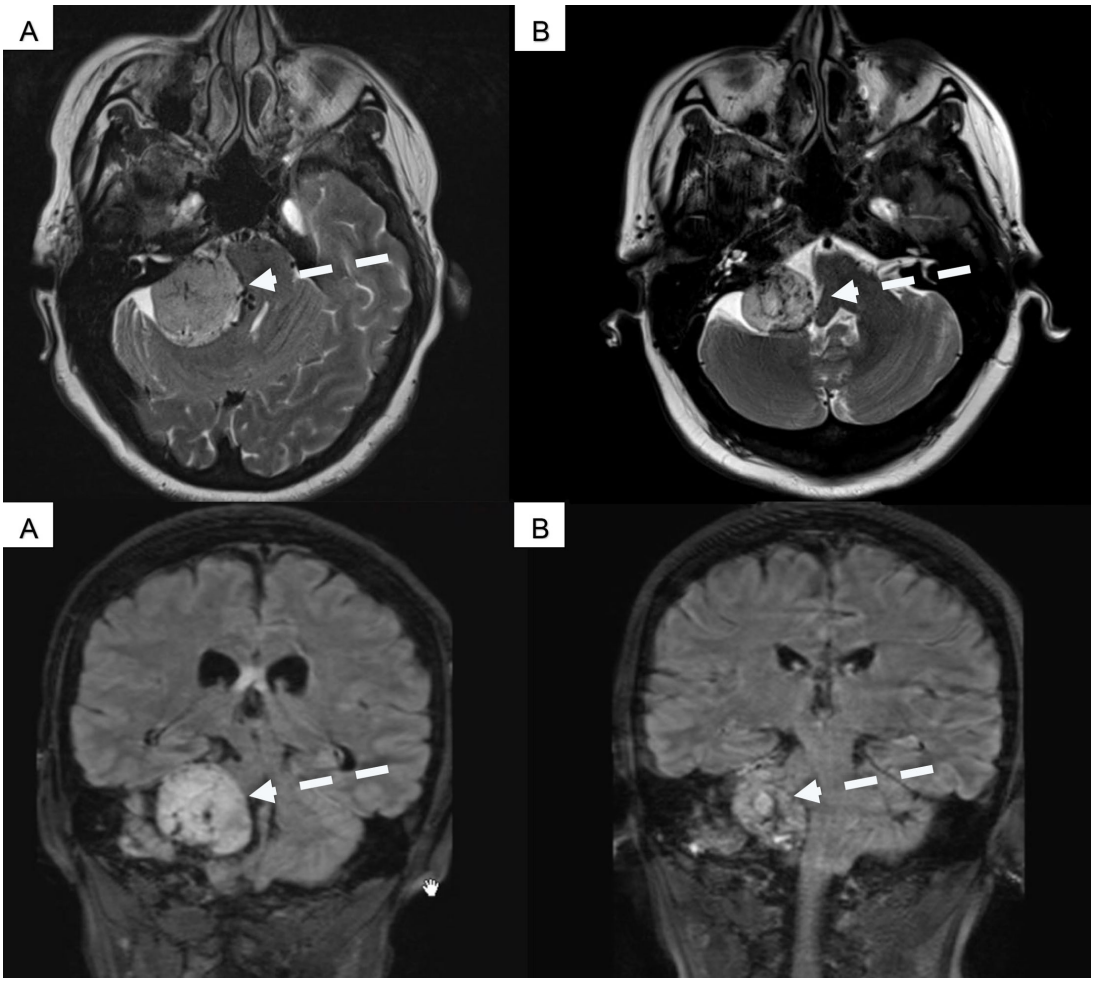

FIGURE 9. Upper pre-embolization (A) and post-embolization (B) axial brain MR T2-weighted sequences and lower pre-embolization (A) and post-embolization (B) coronal MR T1 sequences of our patient showing around a reduction of the size lesion of approximately 25–30% 1 month after endovascular embolization.

Concerning the use of SQUID-12, most studies in the literature have demonstrated its efficacy and safety in the direct puncture of hypervascular tumors of the head and neck, but few focused on its use and effectiveness through the endovascular route, especially in intracranial lesions.

In the study by Paweł Szmygin et al., a total of 27 patients underwent selective HNP embolization. SQUID was used in three cases (all with carotid PGL) by direct puncture. The other cases were treated with endovascular embolization using liquid adhesive embolizing agents, including coils and microspheres. Patients treated with SQUID observed a higher successful outcome (91.5%).[28]

A retrospective study by Pedicelli et al. examined 12 cases of hypervascular tumors of the head and neck using the SQUID direct puncture technique, of which near-total devascularization was achieved in 11, and complete en-bloc removal of the tumor in surgery was achieved in all cases.[31] Another study by Garcià et al. retrospectively looked at their experience using SQUID in direct puncture glomus embolization, concluding that this method of carotid PGLs only using SQUID is safe and relatively simple.[32] In a similar fashion, Paolucci et al. also assessed retrospectively their cases of carotid body PGLs that underwent pre-surgical embolization with the use of SQUID-12 as the sole embolizing agent. Their findings aligned with the other studies, establishing this type of embolization as safe, efficient, and with few complications.[33] The stand-alone role of SQUID was suggested in a study by Rustemi et al. in which they totally embolized, using direct puncture of SQUID as the sole treatment. They completely excluded the lesion in the two selected cases.[34] On the other hand, a paper by Moreno-Paredes et al. reports permanent facial palsy after embolization with SQUID-12;[35] therefore, the overall effectiveness should include further studies preferably including longer follow-ups.

As already emphasized above an interesting note to be made is the lack of literature and evidence surrounding the endovascular use of SQUID-12, especially in highly vascularized intracranial tumors like PGLs.

Further studies and clinical trials should validate these findings and explore the role of endovascular SQUID-12 embolization in highly vascularized intracranial tumor management. Moreover, it cannot be excluded that newer NALEAs such as Easy and PHIL may be as effective, if not superior, as an additional endovascular embolization tool for this type of lesion. Given the scarcity of data in the literature, further studies will be necessary.

CONCLUSIONS

Endovascular embolization with SQUID-12 for TJP (Di2) provided an effective adjunctive endovascular treatment to surgical resection or even a stand-alone solution, with an approximately 25% size reduction of the original tumor, within 31 days after the procedure. This case shows its effectiveness in achieving significant tumor shrinking with minimal complications and it thus can offer a viable treatment option for patients with similar presentations.

Affiliations

[1]Department of Neurosurgery, Humanitas University Hospital, Milan, Italy
[2]Department of Neuroradiology, Humanitas University Hospital, Milan, Italy
[3]Humanitas Medical School, Humanitas University, Milan, Italy

Patient consent

Informed consent was obtained from the patient for participation in this case report and for the publication of their case details, including any relevant medical images.

Contributors

Vincenzo Colonna was responsible for the clinical management of the patient, data collection, and writing the initial draft of the case report. Ignazio Divenuto contributed to the clinical assessment and management, reviewed the manuscript for important intellectual content, and provided critical revisions. Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of interest

None.

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ORCID iD

Vincenzo Colonna http://orcid.org/0009-0008-9929-8973

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