

Metronomic Chemotherapy in the Treatment of Infantile Parotid Hemangioma – A Case Report

Asadbek Dadaboev^{1,*}, Malikakhon Shukurova^{1,*}, Makhmudjon Madrakhimov^{1,*}, Sedigheh Shakib Kotamjani^{2,*}

¹School of Medicine, Central Asian University, Tashkent, Uzbekistan; ²English Language Teaching and Educational Management, Central Asian University, Tashkent, Uzbekistan

*These authors contributed equally to this work

Correspondence: Asadbek Dadaboev, School of Medicine, Central Asian University, Tashkent, 111221, Uzbekistan, Email asadbekdadaboev23@gmail.com

Background: Infantile hemangiomas (IH) are the most common tumors in infancy and childhood. They are characterized by a fast proliferation phase followed by gradual involution. While most IHs follow a predictable course, those involving the parotid gland pose unique diagnostic and therapeutic challenges due to their location and potential for functional impairment. This case illustrates an unusual example of unilateral parotid hemangioma with prolonged growth, requiring alternative management strategies.

Case Presentation: A two-month-old girl presented with a large unilateral parotid hemangioma, first noted on the 15th day of life, which had been rapidly increasing in size. Oral propranolol was initially prescribed, but treatment was not started by the parents, and the patient was lost to follow-up. At 3.5 months of age, the patient underwent an unplanned cosmetic surgical excision at a rural hospital, which resulted in facial nerve paresis and functional facial asymmetry. She re-presented at 7 months with a markedly enlarged lesion. Propranolol (3 mg/kg/day) was reinitiated; however, despite dose escalation, the hemangioma remained unresponsive. Systemic corticosteroids (prednisolone, 1–3 mg/kg/day) at 8 months were added, but the lesion continued to progress. At 9 months of age, metronomic chemotherapy with vinblastine (1 mg/m² IV every 3 days) and cyclophosphamide (50 mg/m² orally for 10 days) was introduced under clinical supervision. This combination resulted in significant tumor regression, as confirmed by serial imaging and clinical examination.

Conclusion: This case reflects the challenges of managing IHs that do not respond to standard treatment guidelines. Early surgical intervention is contraindicated when other alternative medical treatment methods are available. Otherwise, it might result in significant complications, highlighting the importance of conservative management and adherence to treatment protocols. Metronomic chemotherapy has shown to be a useful option for patients who do not respond to standard beta-blockers and corticosteroids.

Keywords: infantile hemangioma, metronomic chemotherapy, parotid gland, propranolol, surgical excision

Introduction

Hemangiomas are developmental vascular anomalies that may be classified as hamartomas, true benign tumors, or malformations. They are the most common type of hamartoma affecting the orofacial region in infants and children.¹ Hemangiomas are broadly classified as infantile hemangiomas (IH) or congenital hemangiomas. IHs are GLUT1-positive, typically emerging within the first two months of life, showing rapid growth during the first year followed by slow involution. In contrast, congenital hemangiomas are fully formed at birth and may become symptomatic due to growth, infection, trauma, or hormonal changes. Infantile hemangiomas arise from vascular endothelium and are the most common vascular tumors in children.² Although IHs can develop anywhere in the body, the involvement of the parotid gland requires unique and accurate diagnostic and management methods.

The lesions follow a characteristic developmental pathway, marked by a rapid proliferative phase within the first 1–2 months of life. A secondary growth phase is frequently observed between 4 and 6 months of age, after which the tumors enter

a gradual involution phase. Although the majority of infantile hemangiomas regress spontaneously and are managed conservatively with regular monitoring, about 10–20% of cases with large, function-threatening, or cosmetically disfiguring lesions require more aggressive intervention. Available therapeutic options span a spectrum from continued observation to active measures, including oral β -blockers, intralesional or systemic corticosteroids, laser therapy, sclerotherapy, cryotherapy, surgical excision, radiation, and feeder-vessel embolization B.³ The present case is noteworthy because the lesion demonstrated prolonged growth and resistance to standard therapies, prompting further evaluation of its etiology and optimal management. In rare cases, hemangiomas with atypical growth or segmental involvement may be associated with syndromes such as PHACE or PROS, which should be considered during early diagnostic workup.^{4,5}

While IH can develop in any part of the body, those affecting the parotid gland bring in further diagnostic and therapeutic challenges due to their anatomical location and risk of cosmetic and functional consequences. Parotid hemangiomas are the most frequent salivary gland tumors in neonates; however, they remain relatively rare.⁶ Hemangiomas in the parotid gland can appear as localized, focal lesions or as part of a segmental structure, commonly involving areas like the mandibular region of the V3 dermatome.⁷ Segmental hemangiomas demonstrate unique biological characteristics compared to focal hemangiomas, marked by a more prolonged and aggressive growth phase, often lasting up to 18–24 months. In this case, the lesion was a large unilateral parotid hemangioma exhibiting prolonged growth, indicating potential segmental involvement.

Imaging is essential for diagnosis and differentiation from other vascular anomalies. Propranolol (marketed as Hemangiol), a nonselective beta-adrenergic antagonist, is considered the treatment of choice for hemangiomas that increase the risk of functional impairment or permanent disfigurement if there are no contraindications such as cardiac or neurovascular conditions.^{2,8} However, rebound growth of infantile hemangiomas (IH) has been documented in 6% to 25% of cases, often occurring well after the first year of life. As a result, propranolol therapy is now tapered gradually over several weeks to months to reduce this risk.⁹ In this case, the lesion displayed prolonged growth without the expected regression, creating differential diagnosis and treatment planning challenges. Elective surgical resection of IH during the proliferative phase is generally not recommended due to the increased risk of anesthesia-related complications, significant blood loss, and iatrogenic injuries, particularly because of the tumor's high vascularity and the young age of the affected patients.¹⁰

This case report describes a 3-year-old patient with unilateral parotid hemangioma with prolonged growth, who failed to respond to first-line treatments but showed a remarkable clinical response to metronomic chemotherapy. The report also emphasizes the importance of avoiding unnecessary surgical interventions that may result in irreversible complications.

Case Presentation

A two-month-old female infant, born at term via an uncomplicated delivery, was referred to the Center for Pediatric Hematology, Oncology, and Clinical Immunology due to progressive swelling in the left pre-auricular region. The mother noted the lesion appeared around the 15th day of life and gradually enlarged. On physical examination, a soft, pliable, noncompressible mass, approximately 6.5×6 cm in size, was measured. The mass was non-tender, firmly attached to the skin, and associated with flushed, bluish overlying skin marked by strawberry-like lesions. On examination, the mass extended into the neck region, and showed marked hyperemia and prominent vascularization (Figure 1A and B).

MRI with contrast revealed a 58×64×67 mm heterogeneous mass in the left parotid region with prominent vascularity, extending medially into the oropharyngeal space. No invasion into adjacent structures was seen (Figure 2A and B).

A biopsy confirmed congenital juvenile (infantile) hemangioma, with no cytologic atypia or malignant features. The mitotic index was low (3/10 HPF), and surgical margins could not be assessed due to tissue fragmentation. Based on clinical and histological findings, a diagnosis of infantile hemangioma involving the parotid gland and neck was made.

Initial treatment with oral propranolol (Hemangiol) was titrated to 3 mg/kg/day; however, the medication was not administered by the family. The patient was subsequently lost to follow-up, and tumor growth continued unchecked.

At seven months, the child returned with new-onset left-sided facial nerve paresis. Further history revealed that at 3.5 months of age, the lesion had been surgically excised at a rural facility. Postoperative imaging showed a residual cavity with regrowth of the lesion. On re-examination, the patient exhibited left facial droop and difficulty closing the eye. The tumor had enlarged significantly (Figure 3). This presentation was consistent with House–Brackmann Grade III facial



Figure 1 (A) Extension toward the periorbital region with superficial changes. (B) Prominent vascularization and hyperemia on close-up view.

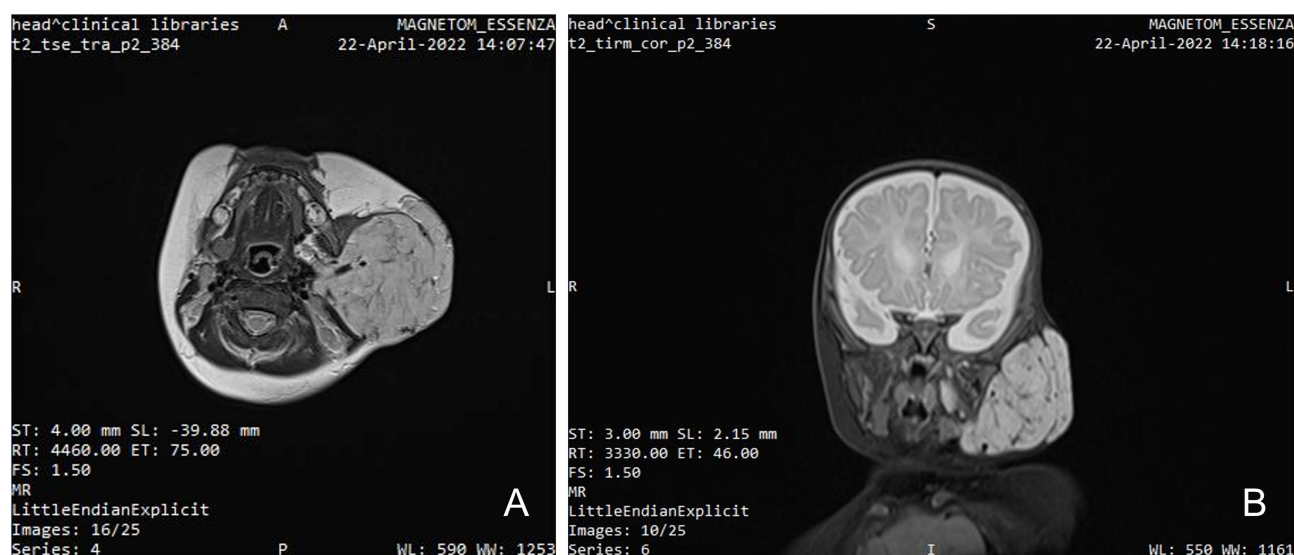


Figure 2 Axial (A) and coronal (B) T2-weighted MRI showing a large, heterogeneous left parotid mass compressing adjacent tissues.

nerve dysfunction, characterized by moderately severe weakness with obvious asymmetry at rest and noticeable synkinesis.¹¹ Propranolol was reinitiated at 3 mg/kg/day, but the response remained suboptimal. Systemic corticosteroids (prednisolone) were introduced in escalating doses (1–3 mg/kg/day) at 8 months, however, the lesion remained resistant to combination therapy. Due to limited access to targeted therapies like sirolimus in Uzbekistan, the care team consulted with specialists and opted for metronomic chemotherapy.

At nine months of age, metronomic chemotherapy was initiated alongside propranolol (3 mg/kg/day) under ECG monitoring. The regimen included:

- Vinblastine 1 mg/m² IV every three days (4 doses per cycle)
- Cyclophosphamide (Endoxan) 50 mg/m² orally for 10 days



Figure 3 Progressive left facial mass enlargement with asymmetry and facial nerve paresis, including incomplete eye closure and drooping.

Two cycles were administered, with a two-week interval in between. Supportive care included:

- Co-trimoxazole 5 mg/kg/day (trimethoprim content), 3 days/week for 2 months
- IV fluids 1.5–2 L/m²/day

CBC was monitored regularly to assess for toxicity.

Post-chemotherapy MRI showed a two-thirds reduction in tumor size (Figure 4A–C).

Propranolol was continued at the same dose for the next 20 months. Physiotherapy for facial nerve recovery was initiated, and the child showed gradual clinical improvement.

By three years of age, MRI demonstrated notable regression of the mass (Figure 5A and B), with corresponding clinical improvement (Figure 6A–C) but with residual hemangioma on ultrasound. No signs of relapse were noted. The patient was advised to continue propranolol therapy. Future plans include reconstructive interventions, such as laser therapy or fat grafting, after age five to address cosmetic and functional concerns. A chronological summary of key clinical events and therapeutic interventions is shown in Table 1.

Discussion

Infantile hemangiomas (IH) are the most common benign vascular tumors in infancy, characterized by a rapid proliferative phase followed by a gradual involution phase.² Hemangiomas comprise around 0.4% of all salivary gland tumors and are almost exclusively found in the parotid gland, accounting for roughly 50% of parotid tumors diagnosed during the first year of life.¹² Due to its anatomical location and vascularity, parotid hemangiomas may mimic other soft tissue tumors, complicating the diagnostic process. A characteristic clinical feature of parotid hemangiomas is the “turkey wattle sign”, where the lesion becomes more prominent during crying or straining, reflecting its vascular distensibility

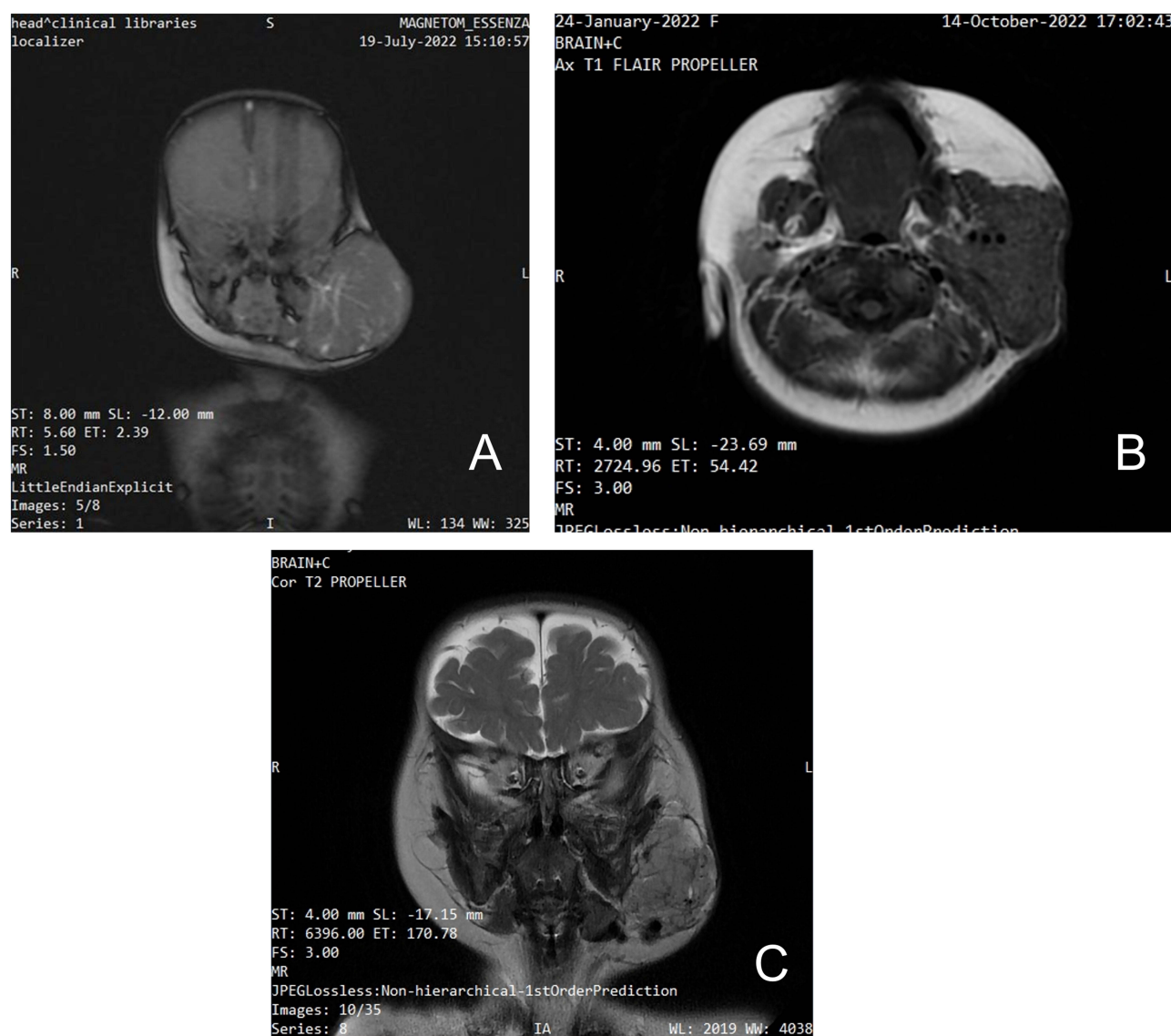


Figure 4 (A) Pre-chemotherapy contrast-enhanced MRI showing a large, hypervascular left parotid mass with compression of adjacent structures. (B and C) Post-chemotherapy MRI demonstrating significant tumor reduction, decreased vascularity, and improved soft tissue contours.

and aiding in clinical diagnosis. While many IH are uncomplicated and regress without intervention, a subset requires aggressive treatment due to their location, size, or impact on vital functions. The presented case highlights a rare parotid hemangioma with significant proliferation, requiring multimodal chemotherapy for disease control in case of refractory when access to Sirolimus is not available.

Treatment strategies are selected individually, taking into account the patient's general condition and the case's severity. Therapy is indicated if only there is a life-threatening situation, including bleeding, potential compromise of vital functions, or disfigurement. Propranolol, a nonselective beta blocker, is considered the first-line gold standard for treating infantile hemangiomas, and there are numerous cases of hemangiomas successfully treated with a single propranolol dose, which is generally enough to fully eradicate the disease.¹³ Despite its high efficacy, propranolol treatment requires careful monitoring for potential adverse effects, including bradycardia, hypotension, and hypoglycemia.¹⁴ In stark contrast, however, parotid hemangiomas have a lower response rate and are more likely to recur after the cessation of the drug.¹⁵ Additionally, systemic and local steroids are also one of the mainstays of pharmacological therapy.¹⁶

The medical literature reveals no report of unilateral parotid hemangiomas with prolonged growth that are resistant to first—and second-line treatments (propranolol and steroids, respectively) but are eliminated with chemotherapy. The

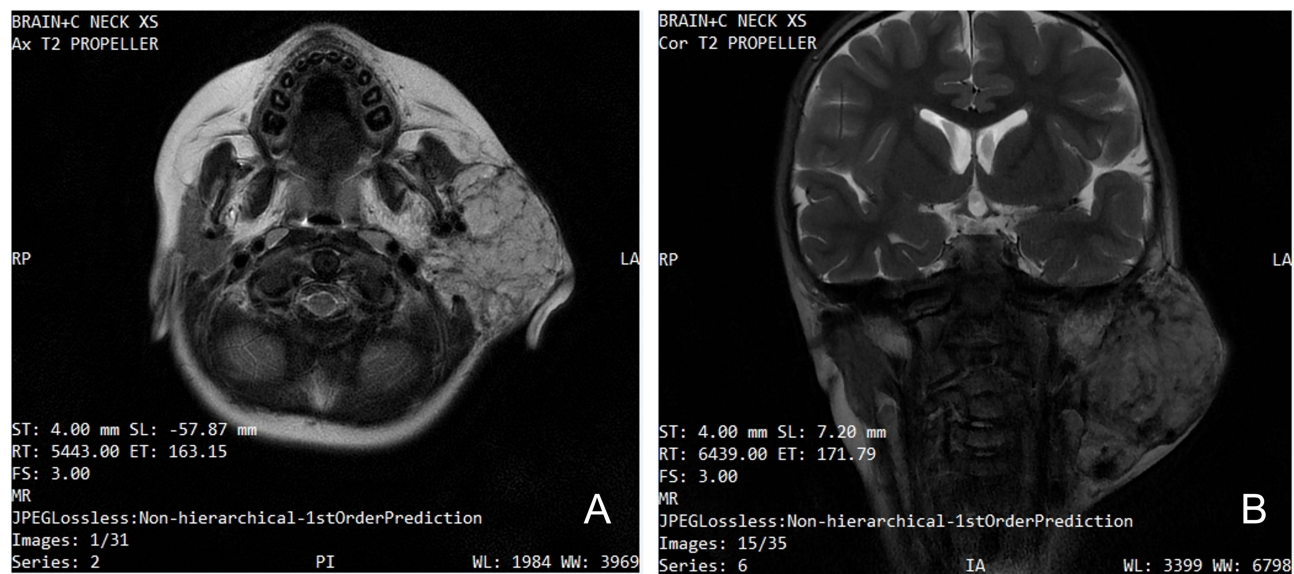


Figure 5 (A) Axial and (B) coronal T2-weighted MRI showing marked lesion regression, reduced hyperintensity, and improved symmetry with minimal mass effect.

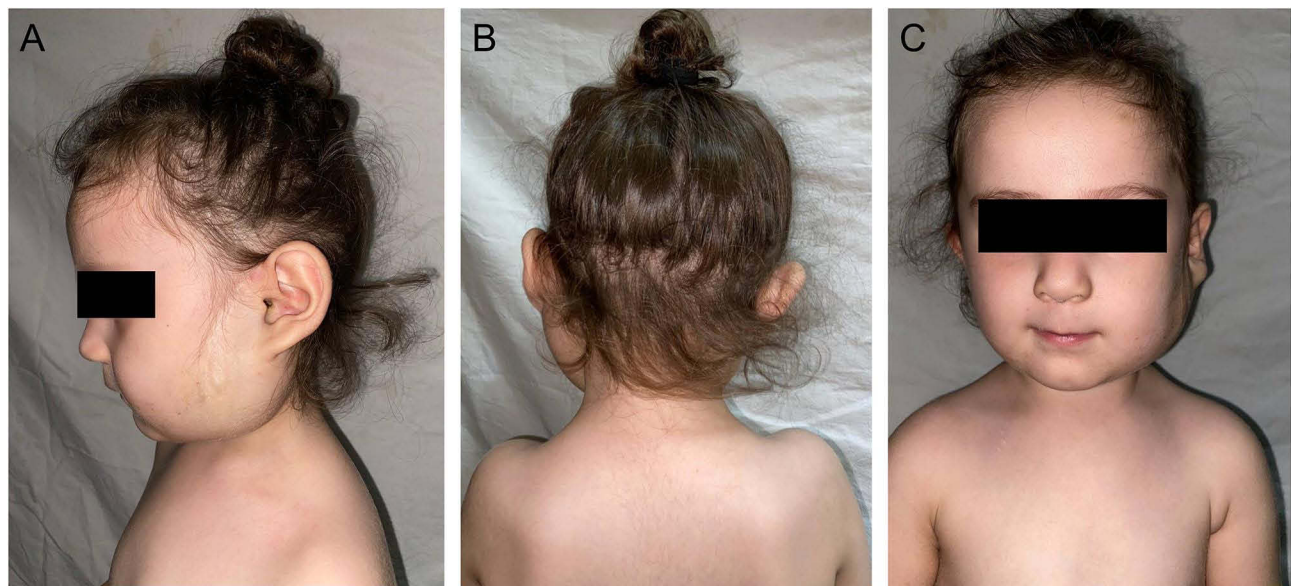


Figure 6 (A) Lateral, (B) posterior, and (C) frontal views at three years showing reduced swelling, restored symmetry, and minimal residual fullness.

chemotherapy regimen used in this case fits the definition of metronomic chemotherapy, characterized by frequent, low-dose administration without extended drug-free breaks. Its aim is anti-angiogenic control of tumor vasculature rather than direct cytotoxicity, making it suitable for pediatric vascular tumors.¹⁷

While vincristine and vinblastine have been previously used in the management of complicated or multifocal hemangiomas,^{18,19} to the best of our knowledge, there are no prior reports describing the successful use of a metronomic chemotherapy regimen specifically in a case of unilateral parotid infantile hemangioma. This case thereby expands the therapeutic scope of metronomic protocols to localized, treatment-resistant hemangiomas.

If the patient has large facial hemangiomas with prolonged growth, some alternative differential diagnoses should be considered, such as PHACE syndrome. PHACE syndrome includes a range of disorders, such as arterial abnormalities, cardiac defects, posterior fossa malformations, eye abnormalities, and hemangiomas. Magnetic Resonance Angiography is needed to evaluate any abnormality in the cerebrovascular system.²⁰

Table 1 Timeline of Clinical Events, Treatments, and Outcomes

Age	Event	Treatment	Response
Day 15	Lesion appeared	—	—
2 months	Diagnosed	Propranolol prescribed at 3 mg/kg/day (not given)	Lost to follow-up
3.5 months	Surgery in rural hospital	Excision (unplanned)	Facial nerve paresis
7 months	Re-evaluated	Propranolol reintroduced at 3 mg/kg/day	No response
8 months	Corticosteroids added	Prednisolone 1–3 mg/kg/day	Still no response
9 months	Started chemo	Vinblastine + Cyclophosphamide+ Propranolol at 3 mg/kg/day	Tumor regression
3 years	Follow-up	—	Facial symmetry improving, no relapse

Note: — indicates no treatment given during this period.

Moreover, the PI3K/Akt/mTOR signaling pathway also plays an important role in developing hemangiomas. PI3K produces 3-phosphorylated inositol lipids, which trigger downstream signaling and activate protein kinase B (PKB; aka c-Akt). Activation of PKB leads to downstream modulation of key regulators such as mTOR, whose hyperactivation drives cellular growth and has been implicated in various tumor pathogenesis, making it a potential therapeutic target.^{21–23}

It is evident from the scientific literature that PROS syndrome, also known as PIK3CA-Related Overgrowth Spectrum disorders, is also associated with the mutation in the PI3K/Akt/mTOR signaling pathway.⁵ Considering the positive effect of the drug on hemangiomas with prolonged growth, physicians should also consider the possible diagnosis of this syndrome. Surgical treatment is restricted only to those with life-threatening complications including airway and visual obstructions, persistent or residual lesions, non-responsiveness to medical treatments, or failure of medical therapy.²⁴

Take-Home Message

This case underscores the importance of considering metronomic chemotherapy as a feasible and effective third-line treatment in infantile parotid hemangiomas that are resistant to beta-blockers and corticosteroids. It also emphasizes the risks of premature surgical intervention, particularly in resource-limited settings where standard follow-up or targeted agents like sirolimus may not be available.

Patient Perspective

The patient's family expressed relief and gratitude following visible tumor regression and functional improvement. They acknowledged the importance of adherence to treatment and regular follow-up, which was initially missed, and appreciated the multidisciplinary care that ultimately improved the child's appearance and functional outcomes.

For patients with parotid hemangiomas causing persistent asymmetry or residual soft-tissue deformities, plastic and reconstructive interventions can play a vital role in restoring facial contour and symmetry. Speech and feeding assessments should also be incorporated into follow-up care to adequately address functional impairments. Long-term follow-up is necessary to monitor tumor regression, nerve recovery, and potential recurrence, as well as to plan for reconstructive interventions if needed.

Conclusion

This case highlights a rare instance of a unilateral parotid hemangioma exhibiting prolonged growth and resistance to both first- and second-line therapies. The remarkable clinical response to metronomic chemotherapy underscores its potential as an effective, accessible alternative in resource-limited settings. It also emphasizes the need for long-term follow-up, multidisciplinary management, and early consideration of alternative diagnoses such as PROS or PHACE syndromes in atypical cases. Future efforts should focus on expanding treatment accessibility and individualized care strategies.

Ethical Approval

Ethical approval was not required for this case report.

Consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Hasan S, Khan A, Banerjee A, Ramalingam K. Infantile hemangioma of the upper lip: report of a rare case with a brief review of literature. *Cureus*. 2023;15(7):e42556. doi:10.7759/cureus.42556
- Darrow DH, Greene AK, Mancini AJ, Nopper AJ. Section on dermatology, section on otolaryngology-head and neck surgery, and section on plastic surgery. Diagnosis and management of infantile hemangioma. *Pediatrics*. 2015;136(4):e1060–e1104. doi:10.1542/peds.2015-2485
- Hasan S, Arif S. Hemangioma of the buccal mucosa treated with sclerotherapy: a rare case report. *IP Int J Periodontol Implantol*. 2024;9(1):46–50. doi:10.18231/j.ijpi.2024.010
- Garzon MC, Epstein LG, Heyer GL, et al. PHACE syndrome: consensus-derived diagnosis and care recommendations. *J Pediatr*. 2016;178:24–33. e2. doi:10.1016/j.jpeds.2016.07.054
- Kepler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A*. 2015;167A(2):287–295. doi:10.1002/ajmg.a.36836
- Toscano F, Versace P. Unilateral parotid gland double hemangiomas in an infant: a rare case report. *Radiol Case Rep*. 2024;19(12):6587–6590. doi:10.1016/j.radcr.2024.09.089
- Waner M, Suen JY. *Hemangiomas and Vascular Malformations of the Head and Neck*. New York: Wiley; 1999.
- Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics*. 2013;131(1):128–140. doi:10.1542/peds.2012-1691
- Bagazgoitia L, Hernández-Martín Á, Torrelo A. Recurrence of infantile hemangiomas treated with propranolol. *Pediatr Dermatol*. 2011;28(6):658–662. doi:10.1111/j.1525-1470.2011.01644.x
- Greene AK. Management of hemangiomas and other vascular tumors. *Clin Plast Surg*. 2011;38(1):45–63. doi:10.1016/j.cps.2010.08.001
- House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg*. 1985;93(2):146–147. doi:10.1177/019459988509300202
- Barnes L, Eveson JW, Reichart P, Sidransky D. *Pathology and Genetics of Head and Neck Tumors*. Lyon: IARC Press; 2005.
- Fuchsmann C, Quintal M, Giguere C, et al. Propranolol as first-line treatment of head and neck hemangiomas. *Arch Otolaryngol Head Neck Surg*. 2011;137(5):471–478. doi:10.1001/archoto.2011.55
- Shahrokhi M, Gupta V. Propranolol. In: *StatPearls*. Treasure Island (FL): StatPearls; 2025.
- Harris J, Phillips JD. Evaluating the clinical outcomes of parotid hemangiomas in the pediatric patient population. *Ear Nose Throat J*. 2021;100(5):NP242–5. doi:10.1177/0145561319877760
- Khachatryan LA. In cases of drug resistance. *Pediatr Hematol Oncol Immunopathol*. 2021;20(2):156–167. doi:10.24287/1726-1708-2021-20-2-156-167
- Simsek C, Esin E, Yalcin S. Metronomic chemotherapy: a systematic review of the literature and clinical experience. *J Oncol*. 2019;2019:5483791. doi:10.1155/2019/5483791
- Wasserman JD, Mahant S, Carcao M, Perlman K, Pope E. Vincristine for successful treatment of steroid-dependent infantile hemangiomas. *Pediatrics*. 2015;135(6):e1501–5. doi:10.1542/peds.2014-2542
- Glade RS, Vinson K, Becton D, Bhutta S, Buckmiller LM. Management of complicated hemangiomas with vincristine/vinblastine: quantitative response to therapy using MRI. *Int J Pediatr Otorhinolaryngol*. 2010;74(11):1221–1225. doi:10.1016/j.ijporl.2010.07.014
- Keith L. PHACE syndrome: a review. *Semin Pediatr Neurol*. 2024;51:101152. doi:10.1016/j.spen.2024.101152
- Lamming DW, Ye L, Sabatini DM, Baur JA. Rapalogs and mTOR inhibitors as anti-aging therapeutics. *J Clin Invest*. 2013;123(3):980–989. doi:10.1172/JCI64099
- Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. *Nat Rev Drug Discov*. 2011;10(11):868–880. doi:10.1038/nrd3531
- Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. *Clin Cancer Res*. 2012;18(21):5856–5864. doi:10.1158/1078-0432.CCR-12-0662
- Boyd VC, Bui D, Naik B, Levy ML, Hicks MJ, Hollier L Jr. Surgery: the treatment of choice for hemangiomas. *Semin Plast Surg*. 2006;20(3):163–168. doi:10.1055/s-2006-949118

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