

CASE REPORT

Unresectable angiosarcoma of the head and neck: A case report highlighting genomic alterations, targeted therapy, and clinical response

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Abstract

Angiosarcoma of the head and neck is an aggressive malignancy with limited therapeutic options when unresectable. We report the case of a 73-year-old male with advanced scalp and neck angiosarcoma characterized by *MYC* amplification and high tumor mutational burden. He received a multimodal treatment strategy including dual immune checkpoint blockade (nivolumab and ipilimumab) combined with cabozantinib, followed by paclitaxel and subsequent pazopanib. This approach achieved prolonged disease control exceeding 18 months, with manageable toxicities through dose adjustments and supportive care. Genomic profiling guided therapeutic decisions and highlighted the role of *MYC* amplification and tumor mutational burden as potential biomarkers for treatment response. This case emphasizes the importance of molecular characterization in guiding precision oncology for rare sarcomas and demonstrates the clinical utility of combining immunotherapy with antiangiogenic agents in the management of unresectable angiosarcoma.

Keywords: Angiosarcoma; Tumor mutational burden; *MYC* amplification; Immunotherapy; Cabozantinib; Case report

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1. Background

Angiosarcoma is a rare, aggressive malignancy of vascular endothelial origin with a poor prognosis, especially in the head and neck region. Angiosarcoma comprises <2% of all soft-tissue sarcomas and poses a significant clinical challenge due to its rapid progression, high metastatic potential, and limited responsiveness to conventional therapy. While standard treatment modalities include surgery, radiation, and chemotherapy, the advent of molecular profiling has begun to inform and personalize therapeutic strategies.^{1,2}

Angiosarcomas represent a heterogeneous group of soft-tissue sarcomas arising from endothelial cells, characterized by aggressive behavior and poor clinical outcomes. Predominantly affecting older adults, angiosarcoma of the head and neck region presents unique diagnostic and therapeutic challenges due to its rapid progression and difficulty in achieving clear surgical margins.^{1,2} Histologically, these tumors display a wide spectrum

of differentiation, often exhibiting hobnail endothelial morphology, and are typically positive for vascular markers such as ERG, CD31, and factor VIII.³ Recent studies have identified significant genomic alterations, such as *MYC* amplification, as potential therapeutic targets.^{3,4}

In recent years, next-generation sequencing (NGS) has elucidated the molecular underpinnings of angiosarcoma. *MYC* amplification is especially associated with radiation-induced or lymphedema-associated angiosarcomas, while a high tumor mutational burden has been identified as a potential biomarker for response to immune checkpoint inhibitors.^{4,5} The integration of molecular diagnostics into therapeutic decision-making marks a shift toward personalized oncology, particularly for rare malignancies with limited standard treatment options. Here, we describe a detailed case highlighting the diagnostic complexity, genomic insights, and evolving therapeutic approaches, integrating frontline and targeted therapies for improved patient management.

2. Case presentation

2.1. Initial presentation

A 73-year-old male with an unresectable angiosarcoma of the scalp and neck, characterized histologically by hobnail endothelial features and immunohistochemical positivity for ERG, CD31, and factor VIII, initially presented to Barnes–Jewish Hospital with facial and lower neck swelling causing significant pain. Biopsy of a left neck mass confirmed high-grade angiosarcoma. Initial positron emission tomography/computed tomography (PET/CT) scan imaging on initial presentation revealed patchy fluorodeoxyglucose (FDG) avidity and soft-tissue thickening involving the scalp, vertex, and upper back. Magnetic resonance imaging (MRI) of the neck confirmed diffuse subcutaneous infiltration in the posterior scalp. Molecular analysis revealed a *MYC* mutation and a high tumor mutational burden of 75%.^{4,5} Physical examination revealed extensive nodularity and ulceration with regional lymphadenopathy as well as progressive regional edema. In addition, physical examination revealed multifocal nodular lesions with irregular borders and purpuric discoloration extending across the posterior scalp and superior cervical region. Genomic profiling was performed using NGS via a comprehensive sarcoma panel (FoundationOne CDx), which assessed somatic mutations, copy number alterations, and tumor mutational burden. The panel identified *MYC* amplification as well as additional somatic alterations, including mutations in *TP53* and *KDR*, though these were not directly actionable for therapy selection in this case. This patient has not been previously described in the literature.

2.2. Initiation of therapy

Given the unresectable nature of the tumor, the patient was started on a combination of ipilimumab (Yervoy) and nivolumab (Opdivo) (CTLA-4 and PD-1 inhibitors, respectively) along with cabozantinib (a multi-target tyrosine kinase inhibitor (TKI) with VEGFR inhibition activity) at the Barnes–Jewish Hospital. This regimen was chosen based on the tumor's angiogenic profile and immunogenic potential.^{6,7}

2.3. Follow-up and first-line therapy

After one cycle, he developed worsening facial edema, prompting the administration of paclitaxel (Taxol), which led to symptomatic relief and improvement. PET imaging after 1 month showed decreased FDG uptake and reduced soft-tissue thickening in the scalp and face, though mild bilateral nodal reactivity and signs of treatment-related inflammatory pneumonitis were noted. After he completed three cycles of the triplet regimen (ipilimumab, nivolumab, and cabozantinib), imaging showed partial improvement in disease burden and reactive lymphadenopathy.

2.4. Ongoing care and transition

By June 2024, the patient transitioned to local care under Dr. Samir Dalia at the Mercy Hematology/Oncology Clinic to facilitate ongoing treatment closer to home. Laboratory workup at that time revealed thyroid-stimulating hormone elevation (8.64 μ IU/mL) with a normal free T4, normocytic anemia (hemoglobin 10.2 g/dL), stable liver enzymes, and a platelet count of 287×10^9 /L. PET scan imaging confirmed FDG-avid scalp and neck disease (SUV_{max} 4.9) and right hilar lymphadenopathy (SUV 5.2), without distant metastasis (Figure 1). MRI of the neck showed diffuse soft tissue enhancement; CT noted bladder wall thickening and renal nodularity without clear pathology.

The patient was transitioned to maintenance nivolumab and cabozantinib, where he reported intermittent facial

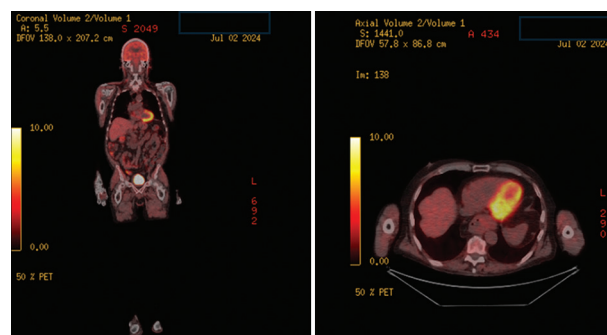


Figure 1. PET scan imaging demonstrating FDG uptake in the scalp and neck region during the initial therapy phase
Abbreviations: FDG: Fluorodeoxyglucose; PET: Positron emission tomography.

edema, hoarseness, persistent fatigue, and blistering. Liver function-related enzymes such as alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) remained mildly elevated during this time, and cabozantinib was dose-reduced to 20 mg. Despite temporary reductions in cabozantinib dosing to 20 mg, disease-related swelling persisted intermittently. 50 mg of prednisone was briefly introduced for symptomatic relief of swelling. Due to persistent progression and intolerance, treatment was modified.

2.5. Second-line therapy and toxicities

Due to progression, the patient was transitioned to second-line monotherapy with pazopanib (Votrient; a VEGFR inhibitor) at 400 mg daily. Initial response was stable; however, he developed grade 3 hepatotoxicity (bilirubin 7.7 mg/dL, ALP 416 U/L), necessitating drug discontinuation. After recovery, pazopanib was reintroduced at 200 mg daily, with subsequent alternation between 200 mg and 400 mg daily for tolerance, resulting in clinical improvement in pain and wound healing (Figure 2).

2.6. Subsequent management and supportive care

In January 2025, the patient reported improvement in swelling, headache, and wound healing. Pain was well-controlled

with extended-release morphine 30 mg BID and as-needed oxycodone. Appetite loss was managed with mirtazapine (Remeron) and supportive supplements. However, the level of ALP, AST, and ALT required ongoing monitoring, and transient elevations led to periodic dose holds.

After a few months of using pazopanib (Votrient), laboratory results revealed continued transaminitis (AST 181 U/L, ALT 268 U/L), elevated bilirubin (1.8 mg/dL), and profound ALP elevation (1,578 U/L), prompting another temporary cessation. Complete blood count showed persistent anemia (hemoglobin 10.6 g/dL), macrocytosis (mean cell volume [MCV] 103.3 fL), and neutrophilic predominance (absolute neutrophil count $7.54 \times 10^9/L$). Supportive care with intravenous (IV) fluids, dexamethasone for swelling, and Remeron for appetite stimulation was provided.

Despite these fluctuations, follow-up PET and MRI imaging demonstrated stable disease without new metastatic lesions. Most recent laboratory results indicated gradual hepatic improvement, and pazopanib was restarted at reduced dosing. As of April 2025, the patient continues on palliative therapy with the primary agent being pazopanib (Votrient) as well as pain control with long-acting morphine and intermittent oxycodone, maintaining stable functional status (ECOG 1) with supportive care interventions. Table 1 demonstrates the significant phases and therapies the patient underwent during the treatment regime.

3. Discussion

Angiosarcoma is a rare and aggressive endothelial malignancy, with cutaneous and soft-tissue variants presenting a significant therapeutic challenge due to high rates of local recurrence and distant metastasis.^{1,2} Head and neck angiosarcomas, in particular, are often unresectable at diagnosis due to their diffuse involvement and proximity to critical structures, necessitating multimodal approaches.

Based on expert consultation and the tumor's immunogenic potential, frontline treatment with nivolumab/ipilimumab and cabozantinib was initiated. This approach aligns with growing literature supporting the synergistic potential of checkpoint inhibitors and VEGFR-targeting tyrosine kinase inhibitors in sarcomas.⁷⁻⁹ In the SARC028 and Alliance A091401 trials, combination immunotherapy demonstrated clinical benefit in a subset of soft tissue sarcoma patients,⁹ and cabozantinib has been noted to normalize tumor vasculature, enhance immune infiltration, and potentially overcome resistance.¹⁰

This case of primary *de novo* unresectable angiosarcoma was genomically characterized by *MYC* amplification, a

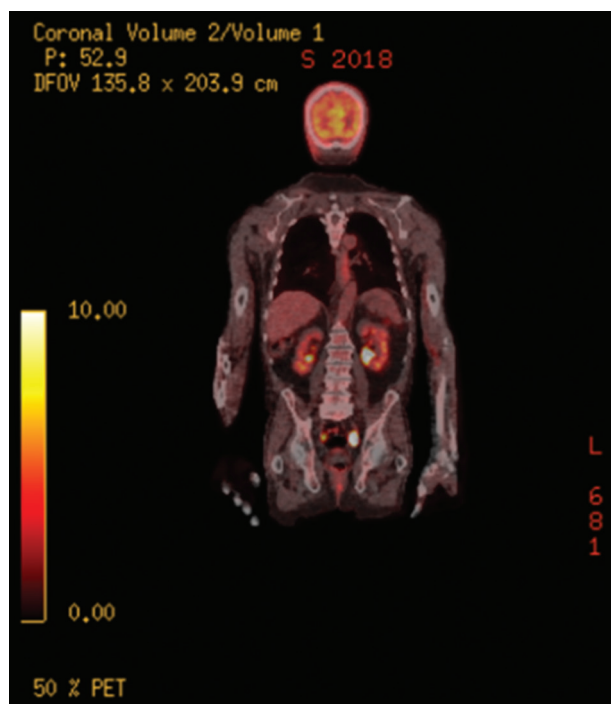


Figure 2. PET scan showing post-pazopanib disease status with decreased metabolic activity

Abbreviation: PET: Positron emission tomography.

Table 1. Clinical treatment timeline

Phase	Therapy	Duration/notes	Outcome/imaging
Initial therapy	Ipilimumab/nivolumab+cabozantinib	3 cycles	Partial response, improved swelling
Intervening	Weekly paclitaxel	1 month	Symptom control
Maintenance	Nivolumab+cabozantinib	Ongoing for 2 months	Stable disease on PET
Second-line	Pazopanib 200–400 mg (alternate dosing)	Ongoing (dose adjustments for ALP, AST, and ALT)	Stable disease, improved pain

Abbreviation: PET: Positron emission tomography.

hallmark in certain radiation-associated angiosarcomas but also seen in primary subtypes, and an elevated tumor mutational burden of 7.4 mutations/Mb.⁴ Although this tumor mutational burden does not meet the ≥ 10 mutations/Mb threshold used by the FDA for tumor-agnostic pembrolizumab approval, emerging evidence suggests that tumors with moderately elevated tumor mutational burden may still respond to immunotherapy, particularly when combined with angiogenesis inhibitors.^{9–11} Furthermore, microsatellite stability (stable) was confirmed, which is consistent with the majority of soft-tissue sarcomas and underscores the importance of additional biomarkers.

While toxicities such as hepatotoxicity and edema necessitated dose interruptions and eventual treatment switches, disease control was sustained for several months. Toxicity management, including temporary cabozantinib holds and corticosteroid use, played a pivotal role in maintaining functional status and delaying progression. This reflects findings from pazopanib and cabozantinib studies in sarcoma, where toxicity burden can be mitigated through personalized dose titration.^{6,12}

The immunotherapy response observed, albeit difficult to isolate due to concurrent therapies, suggests potential benefit in select angiosarcoma cases with genomic and clinical features indicative of immune responsiveness. PD-L1 testing was not performed, but previous studies have shown PD-L1 expression in approximately 30–40% of angiosarcomas, and such expression may correlate with immunotherapy benefit.^{5,8} Comparative data are limited, but in previously published cases, monotherapy with taxanes or TKIs yielded only modest survival benefit in advanced angiosarcoma.^{13,14} The use of immunotherapy in our case provided prolonged disease stabilization beyond expected benchmarks for chemotherapy alone. This aligns with emerging data on biomarker-directed approaches in rare sarcomas.⁹

Although radiotherapy was not employed in this case, it warrants brief mention as a potential adjunct in select angiosarcoma cases for palliation or microenvironmental modulation. Some studies suggest that low-dose radiotherapy may enhance immunogenicity and sensitize tumors to checkpoint blockade, though this remains

largely theoretical in sarcomas.^{9,15} This case confirms that molecular typing, including *MYC* amplification and tumor mutational burden, can critically inform therapeutic selection. By employing a combined immunotherapy and targeted antiangiogenic strategy, durable disease control exceeding 18 months was achieved. These findings provide a practical reference for similar rare cases and highlight the need for further research into biomarker-treatment correlations in angiosarcoma.

4. Conclusion

This case underscores the evolving paradigm in angiosarcoma management—where histopathologic confirmation is supplemented by genomic and molecular data to personalize therapy. The use of combined immunotherapy, antiangiogenic TKIs, and cytotoxic chemotherapy achieved disease control and improved patient quality of life. Vigilant monitoring of lab parameters and flexible dose modification were critical in maintaining treatment continuity. High tumor mutational burden and *MYC* amplification may serve as predictive biomarkers for immunotherapy responsiveness in angiosarcoma. Future research should continue to explore integrated treatment strategies and biomarker-driven approaches for this rare and lethal malignancy.

Incorporating molecular profiling into clinical management significantly influences treatment strategies for angiosarcoma, enabling targeted therapeutic approaches and improved patient outcomes, particularly for those harboring high tumor mutational burden and *MYC* mutations. A multidisciplinary, personalized approach remains essential in managing this complex malignancy.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors

Investigation: Vasisht Karri

Supervision: Samir Dalia

Writing–original draft: Vasisht Karri

Writing–review & editing: Samir Dalia

Ethics approval and consent to participate

This study reports a single-patient case based on retrospective clinical data and does not involve experimental intervention. Institutional review board approval was not required for this type of case report. The case was reviewed and deemed exempt by the IRB at Mercy Hospital, Joplin, Missouri.

Consent for publication

Written informed consent was obtained from the patient for the publication of all clinical details and accompanying images included in this manuscript. The signed consent form is retained by the authors and is available for audit if requested.

Availability of data

All data supporting the findings of this case report are contained within the manuscript. No additional datasets were generated or analyzed for this report.

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