Annals of Clinical and Medical Case Reports

Case Report

ISSN 2639-8109 | Volume 14

A Case Study of a Rare Parameningeal Site as Middle-Ear: Highlighting an Overlooked Oncologic Rarity in the Pediatric Population

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Received: 16 July 2024

Accepted: 06 Aug 2024

Published: 12 Aug 2024

J Short Name: ACMCR

Keywords:

Pediatric angiosarcoma; Non-rhabdomyosarcoma soft tissue sarcoma; Head and neck cancer; Prognosis; Treatment challenges

Citation:

Beril Balci Topuz, A Case Study of a Rare Parameningeal Site as Middle-Ear: Highlighting an Overlooked Oncologic Rarity in the Pediatric Population. Ann Clin Med Case Rep. 2024; V14(1): 1-6

1. Abstract

1.1. Background: This article aims to underscore the rarity and complexity of pediatric angiosarcoma through a case study of a rare parameningeal site in the middle ear. Management is challenging due to the tumor's infiltrative nature, particularly in the head and neck region.

1.2. Case Presentation: A 4-year-old female presented with a 5 cm mass in her left posterior auricular area. Imaging revealed a 6x5 cm enhancing mass in the left mastoid region, causing bony destruction but no cranial extension. After a simple mastoidectomy and biopsy, pathology confirmed soft tissue angiosarcoma. Subsequent gross total resection and cranioplasty were performed, with surgical margins free. Postoperative PET-CT showed no distant metastasis. The patient was treated according to the ARST 0332 protocol, with chemotherapy and local radiotherapy (55.8 Gy). Despite treatment, recurrence was observed one month post-radiotherapy. The patient continued chemotherapy for 10 months but later presented with severe shortness of breath, pericardial and pleural effusion, and fungal lung infiltrations. She rapidly deteriorated and died 15 months after the initial diagnosis.

Conclusions: This case highlights the difficulties in achieving complete surgical resection (R0) and the significance of tumor location in treatment. Pediatric angiosarcoma has a particularly poor prognosis, with unfavorable factors such as deep tissue involvement and large tumor size complicating management. Currently, while soft tissue angiosarcoma is classified as a non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), the existing treatment protocols appears neither accurate nor sufficient for patients with angiosarcoma. Studies indicate a low 5-year overall survival rate, underscoring the need for tailored pediatric treatment strategies and further research into molecular characterization and targeted therapies. Advances in molecular characterization and targeted therapies hold promise for improving outcomes in this aggressive malignancy.

2. Introduction

Angiosarcoma, originating in lymphatic or vascular endothelial cells, is a highly aggressive cancer. It is known for rapid growth and invasiveness, classifying as a 'high-grade' tumor [1]. While more commonly observed in elderly individuals, pediatric cases are rare and exhibit distinct characteristics. Unlike adults, pediatric angiosarcoma often infiltrates deep tissues and visceral organs, including the head and neck, breast, spleen, bone, liver, and heart [2-5]. The 2020 World Health Organization Classification of Soft Tissue and Bone Tumors categorizes angiosarcoma into soft tissue and primary bone types [6]. In children, soft tissue angiosarcoma is classified as a non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), comprising about 7% of childhood cancers with angiosarcoma accounting for approximately 1% [7]. Despite its

rarity, angiosarcoma poses a significant oncological challenge due to its high mortality rates [8]. Historically, treatment strategies for pediatric angiosarcoma have mirrored those used in adults due to limited pediatric-specific studies. Recent progress in identifying prognostic factors and developing tailored treatment approaches has been driven by organizations such as the Children's Oncology Group (COG), Cooperative Weichteilsarkom Studiengruppe (CWS), and European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) [9]. Despite these advances, pediatric angiosarcoma remains a formidable challenge within NRSTS histologies. This article aims to underscore the rarity and complexity of pediatric angiosarcoma through a case study of a rare parameningeal site as middle-ear, offering insights into its management intricacies.

3. Case Presentation

A 4-year-old female presented with a 5 cm mass in her left posterior auricular area. Brain computed tomography (CT) (Figure 1) and magnetic resonance imaging (MRI) scans (Figure 2) revealed a 6x5 cm enhancing mass in the left mastoid region, extending from the external auditory canal to the cochlea, causing bony destruction in the temporal region. No cranial extension was evident at this stage. Following a simple mastoidectomy and ventilation tube surgery, a biopsy was taken. The tumor was observed microscopically to consist of solid sheets of cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei. Some cells exhibited lumen formation with the presence of erythrocytes within the cytoplasm. Immunohistochemically, the tumor cells stained positive for vimentin, CD31, CD34, Fli-1, D2-40, and Factor 8. Mitoses were frequent, and the Ki-67 index was 40-50%. Pathology confirmed angiosarcoma of soft tissue. Subsequent gross total resection and cranioplasty with titanium mesh were performed. Operation pathology was also consistent with angiosarcoma, and surgical margins were free. Postoperative positron emission tomography–computed tomography (PET-CT) revealed no distant metastasis, with evident surgical changes at the primary site (Figure 3). According to the ARST 0332 protocol, the patient was categorized in Treatment Arm C due to gross total resection, high-grade, >5 cm tumors, indicating intermediate risk, and chemotherapy (CHT) was initiated. By the 4th week, the patient underwent local radiotherapy. The treatment was delivered using intensity-modulated radiation therapy (IMRT) technique on a Linear Accelerator device, with a total dose of 55.8 Gy administered in fractions of 1.8 Gy each, using 6 MV energy, in accordance with the protocol (Figure 4). However, one month post-radiotherapy, at week 13 of the protocol, a 28x14 mm lesion consistent with recurrence was observed at the primary site. Chemotherapy with doxorubicin and paclitaxel was continued with interim assessments. Afterwards, a case with stable disease and no distant metastasis continued CHT for 10 months. Then, the patient presented to the emergency department with severe shortness of breath, where pericardial and bilateral pleural effusion were observed. Infiltrations possibly related to an infectious fungal process were seen in the left lung (21x18 mm). The patient's condition rapidly deteriorated, and she was intubated. The patient died approximately 15 months after the initial diagnosis.

Written informed consent was obtained from the patient in accordance with ethical guidelines.

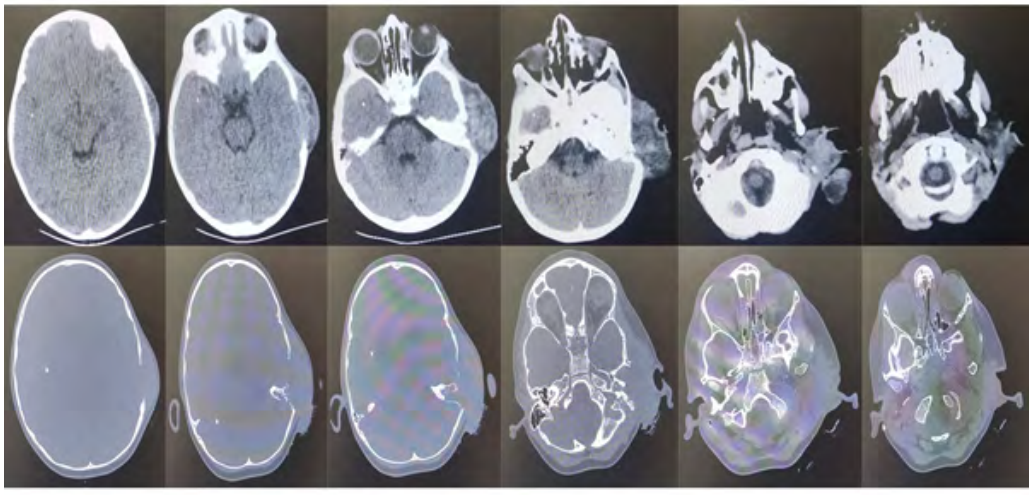

Figure 1: Axial brain computed tomography (CT) images at the time of diagnosis.

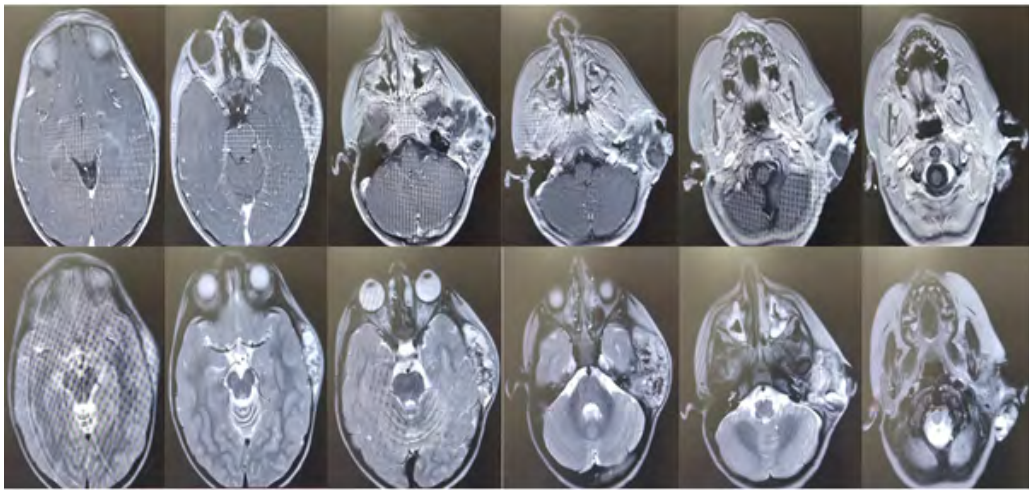

Figure 2: Axial magnetic resonance imaging (MRI) images at the time of diagnosis.

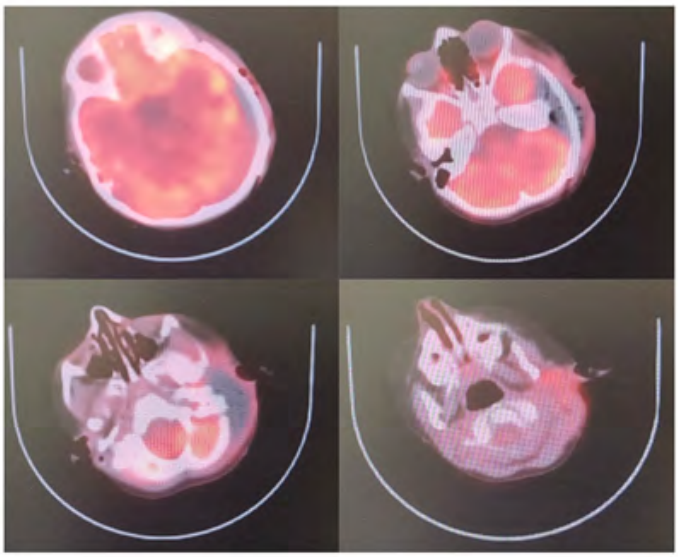

Figure 3: Postoperative positron emission tomography–computed tomography (PET-CT) images of the primary region and surgical changes.

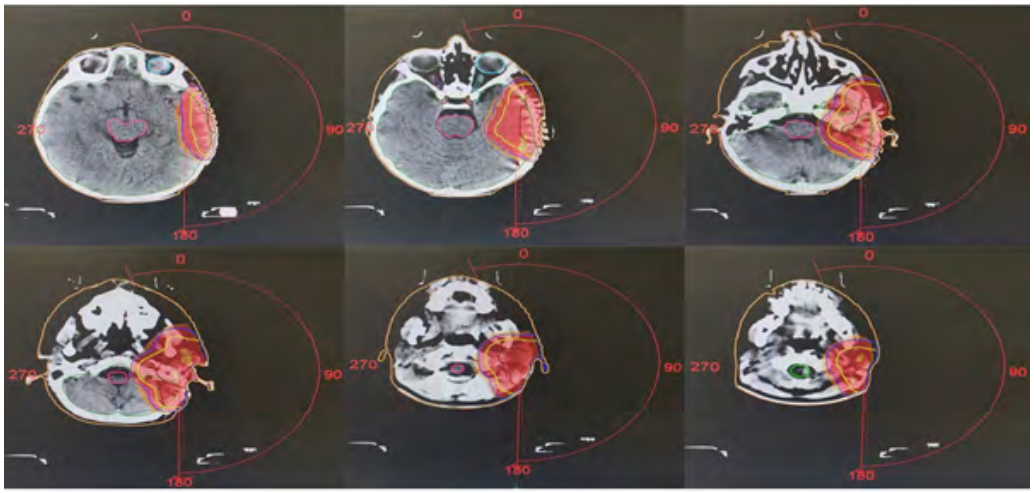

Figure 4: Gross tumor volume (GTV) (red) included all infiltrative disease detected at initial presentation. Clinical target volume (CTV) (yellow) is defined as GTV + 1.5 cm. Planning target volume (PTV) (blue) is defined as CTV with an additional margin of 0.5 cm. PTV is very well covered (100% of the volume is covered by 95% of the prescription dose). The dose prescription to the PTV was 55.8 Gy in 31 fractions. The red volume indicates a total dose of 55.8 Gy, while the orange volume represents 95% of the total dose. The intensity modulated radiotherapy (IMRT) plan utilized a single 180° partial arc, with the arc range chosen to minimize exposure to the contralateral organs at risk as much as possible.

4. Discussion

The presented case report discusses the challenges in managing pediatric angisarcoma with poor prognosis. It also highlights the significance of tumor location on treatment, particularly in the head and neck region, even if achieving complete surgical resection (R0) management is challenging due to the tumor's infiltrative nature. Surgery remains the cornerstone of treatment for angisarcoma, involving en bloc resection with R0 margins [8,10]. Unfavorable prognostic factors, including deep soft tissue involvement, large tumor size, and invasion into surrounding structures, are seen in almost all cases consistent with its agressive nature [8]. These factors complicate surgery, especially in the head and neck parameningeal region. In preliminary studies, angisarcoma was evaluated in malignant vascular tumors. In Ferrari et al.'s study 4, 30% of 12 cases were head and neck tumors, all of which underwent incomplete excision or biopsy. Bien et al.5 found that 3 out of 10 cases were head and neck tumors, including one parameningeal site, all >5 cm in size and none achieving R0 resection. In another data8, 4 out of 14 cases were located in the head and neck region, and 3 of these were in the parameningeal area. Similarly, it was observed that R0 resection could not be achieved in all 14 cases. R2 resections were common in these cases unlike our case, which was the gross total resection. Yet, occuring recurrence in our case following radiotherapy was detected. In addition, there is another potential impact factor, which is age. In the study by Ferrari et al.4, three head and neck cases [T2BN0M0] within incomplete excision had a similar treatment plan, however, there were significant differences in their survival outcomes. Further support for this comes from a population-based study11 in 2015, indicating the poorest prognosis for malignant blood vessel tumors in the 0-9 age group. The importance of age groups should be studied further. Regarding survival outcomes, pediatric angiosarcoma had a particularly low 5-year overall survival (OS), Bien et al. 8 and Ferrari et al. 4 reported 14.3% and 29.2%, respectively. Deyrup et al [12]. Reported on 15 cases of deep soft tissue and visceral angiosarcomas, none of which were head and neck tumors, with an estimated 5-year disease-specific survival of 34.6%. Sixty-seven percent of patients died within 2 to 15 months. All these studies also underscore the aggressive nature and poor prognosis of angiosarcoma in pediatric cases. NRSTS is a diverse group of tumors, and angiosarcoma is just one subtype among many.13 Additionally, it is classified among chemosensitive sarcomas in studies [14,15]. Ferrari et al [16]. Have described a consensus suggesting that most adult-type NRSTS in pediatric cases, including angiosarcoma, should follow the same treatment approach. However, Ferrari et al.'s population-based study11 indicated that the prognosis and outcomes vary widely among different NRSTS subtypes. While the exact number of angiosarcoma cases in this study is unknown, blood vessel tumors in patients under 20 have a high rate of distant metastasis, second only to rhabdoid histology. The high metastasis rate suggests that a one-size-fits-all approach may not be effective. The optimal therapy for this tumor remains unclear, particularly in the pediatric population. Because angiosarcoma cases are relatively rare within NRSTS, studies often lack detailed, specific information about this subtype. Challenges also arise in determining the applicability and dosing of chemotherapeutic agents compared to adults. There is a need for tailored strategies and different approaches specifically for angisarcoma, rather than applying the same treatment protocols used for other NRSTS subtypes. Specific CHT protocols have been developed for certain sarcoma subtypes, but AS has often been overlooked in these guidelines [17]. The ARST 1321 study14 was designed to target a more specific subgroup, including chemosensitive adult-type NRSTS, and it investigates the efficacy of pazopanib. The study's results indicate that pazopanib combined with chemoradiation improved pathologic response in children and adults with large, unresected, intermediate- or high-grade chemosensitive sarcomas, suggesting better outcomes. However, due to the histological heterogeneity of the study, specific information regarding angiosarcoma is not available. Angiosarcoma is generally considered radioresistant, however, radiotherapy (RT) still plays a crucial role in the management of angiosarcoma, similar to other types of sarcomas. The importance of RT was shown, particularly in challenging localizations such as the head and neck [4]. It is also indicated for patients who are at a higher risk of local failure. This includes marginally-resected high-grade NRSTS, high-grade tumors larger than 5 cm, and initially unresectable disease [17]. Considering the clinical presentation at the time of diagnosis, RT is deemed necessary in most cases of angiosarcoma. Additionally, Ferrari et al.'s population based study11 identified that 42.1% of blood vessel tumor cases presented with localized disease. Relatively high radiation doses (more than 45–50 Gy) are often necessary to achieve therapeutic effects. In pediatric cases, protecting normal tissues during RT is critical to avoid long-term damage. Current radiation doses are deemed adequate for achieving this protection while still targeting the tumor effectively [18]. Angiosarcoma is also known to have a tendency for lymph node (LN) spread. Patients with isolated LN involvement have been observed to have better outcomes compared to those with extranodal metastases. Furthermore, the outcomes for patients with isolated LN involvement are similar to those with non-metastatic disease.7 This scenario has not yet influenced risk stratification for NRSTS. In current practice, regional LN involvement continues to be treated as metastatic disease, which is a logical approach given the aggressive behavior of angiosarcoma. Despite angiosarcomas commonly presenting in locally advanced and metastatic stages, there are instances of undertreatment in early-stage presentations according to NRSTS classification. Some studies suggest omitting RT and CHT for non-metastatic, low-grade, and completely resected tumors. This aligns with the broader trend in oncology to minimize overtreatment and reduce long-term side effects for patients in low-risk

categories [9]. However, non-metastatic, high-grade, ≤5 cm, and completely resected tumors are also classified as low-risk. This classification underscores the need for careful consideration of histological subtypes and potential risks even in low-risk categories. The study of COG ARST033213 evaluated this issue, finding that 92% of patients with non-metastatic, ≤5 cm, high-grade tumors undergoing R0 resection were free of local recurrence, suggesting the potential omission of RT. However, it is important to note that even low-risk cases may experience local recurrence to an undeniable extent. Moreover, 9% of low-risk patients with high-grade tumors developed metastases, a non-negligible rate, indicating significant variability in outcomes based on the tumor's histological characteristics. When comparing angiosarcoma outcomes with high-risk NRSTS patients, where the estimated 5-year event-free survival (EFS) is 21.2% and OS is 35.5%, angiosarcoma outcomes align with these rates.13 This underscores the importance for healthcare providers to remain vigilant and adopt aggressive management strategies, even in early-stage cases.

Integrating histological diagnosis with molecular characterization has become essential for understanding the biological mechanisms of NRSTS and developing effective treatment strategies [17]. Angiosarcomas exhibit distinct genetic alterations, indicating a complex biology that requires further exploration [19]. These tumors often overexpress genes associated with vascular receptor tyrosine kinases such as TIE1, KDR, TEK, and FLT1 (VEGFR1). Some angiosarcomas also harbor mutations in KDR and FLT4. Targeting this hyperactive axis using tyrosine kinase inhibitors (such as taxanes, pazopanib, sorafenib, sunitinib, and regorafenib) or antiangiogenic/antivascular therapies (like bevacizumab and propranolol) holds promise as potential treatment options [20]. Understanding primary resistance mechanisms to VEGF/VEGFR inhibitors is also crucial. These include mutations in VEGFR2 (KDR), PLCG1, loss-of-function mutations in PTPRB, and amplification of c-MYC and VEGFR3 (FLT4) [21]. Vascular permeability factor (VPF), which induces microvascular hyperpermeability and acts as a mitogen for endothelial cells, plays a significant role in angiosarcoma progression. It interacts with high-affinity receptor tyrosine kinases FLT1 and KDR. Additionally, high expression levels of HIF1 alpha and HIF2 beta, regulators of VEGF, are commonly observed in angiosarcomas [22]. Moreover, oncogenic pathways such as RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and p16(INK4A) are also implicated in these tumors. Targeting these pathways could offer therapeutic benefits in selected cases in the future, potentially improving treatment outcomes for this aggressive malignancy [20]. In conclusion, the prognosis for angiosarcoma patients remains bleak, underscoring the urgent need for enhanced treatment options. The rarity and heterogeneity of angiosarcomas have posed significant challenges, limiting advancements in therapeutic strategies. It is crucial for physicians to assess whether specific subtypes of soft tissue sarcomas exhibit consistent biological and clinical characteristics across different age groups. Future research should prioritize gaining a deeper understanding of promising preclinical targets and leveraging insights from comprehensive clinical, genetic, and immunological datasets of angiosarcomas.

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