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Outcome for Neoadjuvant Treatment of Parotid Gland Adamantinoma-Like Ewing Sarcoma: Case Report and Review of Literatures

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Abstract

Background. Adamantinoma-like Ewing sarcoma typically shows t(11;22) *EWSR1::FLI1* translocation and complex epithelial differentiation. It poses a diagnostic challenge, especially in the head and neck region, due to its under-recognition and significant histologic overlap with other malignancies. Neoadjuvant and adjuvant treatment information on head and neck Adamantinoma-like Ewing sarcoma is limited. *Case Presentation*. Herein, we report a case of a 78-year-old female with Adamantinoma-like Ewing sarcoma of the parotid gland, including the imaging findings and clinical response to neoadjuvant therapy followed by surgery. The efficacy of neoadjuvant therapy in the treatment of Adamantinoma-like Ewing sarcoma is discussed in the context of a review of pertinent literature. *Conclusion*. Adamantinoma-like Ewing sarcoma in the head and neck is frequently misdiagnosed as poorly differentiated squamous cell carcinoma or a basaloid salivary gland carcinoma. Adamantinoma-like Ewing sarcoma is a *EWS1::FLI1* translocation driven tumor; frequently misdiagnosed on head and neck biopsies as poorly differentiated carcinoma, or squamous cell carcinoma. Ewing sarcoma-specific chemoregimen appears effective for this entity. If diagnosed early, patient may be amenable to neoadjuvant therapy, which may improve surgical and cosmetic outcomes. This is especially important in head and neck regions.

Keywords

adamantinoma-like, ewing sarcoma, t(11;22), EWSR1::FLI1, head and neck, neoadjuvant therapy

Case Presentation

A 78-year-old female presented with a self-palpated, slowly growing left parotid mass over 7 months. Her past medical history was significant for stage III right breast cancer, status post lumpectomy about 14 years prior to current presentation. Her breast cancer was treated with surgery, followed by adjuvant doxorubicin-based chemotherapy and radiation, and was considered in remission. Family history is noncontributory. She was a nonsmoker, but has years of second-hand smoking from her husband's cigarette smoking. She did not consume alcohol. At the time of presentation, she was on aspirin, alendronate, simvastatin, and valsartan-hydrochlorothiazide.

Her physical exam was only remarkable for a 2 cm firm mass in the left preauricular region without overlying skin abnormalities and no cervical adenopathy. Her head and neck examination was otherwise unremarkable. Routine laboratory tests were noncontributory.

Diagnostic Assessment

Diagnostic Radiology

She underwent a computed tomography (CT) of the face without contrast which demonstrated an ill-defined, 15 mm superficial parotid gland mass, concordant with a solid mass on ultrasound. A baseline magnetic resonance imaging (MRI) study of the face and neck showed a 16 mm oval enhancing lesion in the superficial lobe of

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the left parotid gland with extension to the lateral cortex of the left mandibular ramus (Figure 1). There were several small, asymmetric left cervical and supraclavicular lymph nodes.

Diagnostic Pathology

The patient had a core needle biopsy of the parotid gland mass. The biopsy showed a hypercellular, basaloid neoplasm in a background of fibrous stroma (Figure 2). The tumor cells were basaloid to focally plasmacytoid, containing monomorphic nuclei with easily identified nucleoli and limited cytoplasm. Tumor necrosis, increased mitoses, and keratinization was not identified. The differential diagnoses included a poorly differentiated squamous cell carcinoma, basal cell adenocarcinoma, NUT carcinoma, *SMARCB1*-deficient carcinoma, poorly differentiated adenoid cystic carcinoma, Ewing sarcoma, adamantinoma-like Ewing sarcoma, and myoepithelial carcinoma. A pertinent, limited immunohistochemistry panel demonstrated immunoreactivity for multiple keratin markers (keratin AE1/AE3, keratin 19, keratin 5/6), p63, GATA3, INI1, CD99, and NKX2.2, while non-reactive for keratin 7, mammaglobin, ER, S100 protein, desmin, calponin, synaptophysin, and chromogranin (positive and negative controls appropriate). The Ki-67 proliferation index was 10-15%. The epithelial expression combined with the CD99 and NKX2.2 suggested adamantinoma-like Ewing sarcoma. A fluorescent in-situ hybridization (FISH) break-apart probe analysis showed the presence of the *EWSR1* gene rearrangement, confirmed by next generation sequencing (NGS) to be *EWSR1::FLI1* fusion. This aggregate of findings supported a diagnosis of adamantinoma-like Ewing sarcoma.

Therapeutic Intervention

Neoadjuvant Therapy and Radiologic Response

The patient had advanced age and prior accumulated exposure of doxorubicin (240 mg/m^2; lifetime cap is 450 mg/m^2). Therefore, she did not receive a full dose Ewing sarcoma protocol. The patient was treated in accordance with the multi-disciplinary tumor board recommendation, and received 2 cycles of dose-reduced VDC chemotherapy (vincristine 1.4 mg/m^2; doxorubicin 60 mg/m^2; cyclophosphamide 920 mg/m^2), which was tolerated well. The tumor showed partial response by Response Evaluation Criteria in Solid Tumours (RECIST) criteria on her re-staging MRI of face and neck, from 16 mm (baseline) to 11 mm (post-therapy). One month following completion of chemotherapy, she underwent surgery.

Surgical Management and Final Pathology

Patient underwent a left superficial parotidectomy with facial nerve monitoring and left modified radical neck dissection. Intraoperatively, the tumor was adherent to the superior division of the facial nerve, but was successfully dissected with all facial nerve branches responsive to stimulation at the end of surgery.

Gross inspection showed a circumscribed 14×11 mm mass confined to the parotid gland, although present at the resection margin. The tumor was morphologically

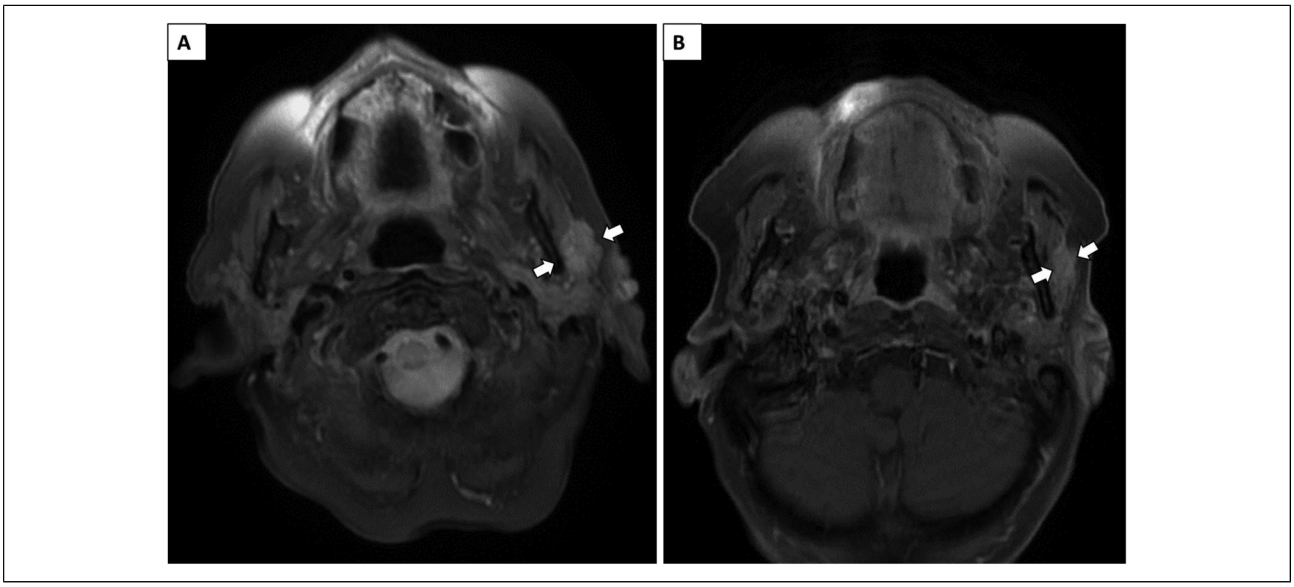

Figure 1. Magnetic resonance imaging (MRI) of face and neck showing the left parotid mass. A = Baseline imaging. B = Post-neoadjuvant therapy restaging scan. The tumor has decreased in size from 16 mm to 11 mm, meeting RECIST criteria of partial response (> 30% reduction in length of the longest axis).

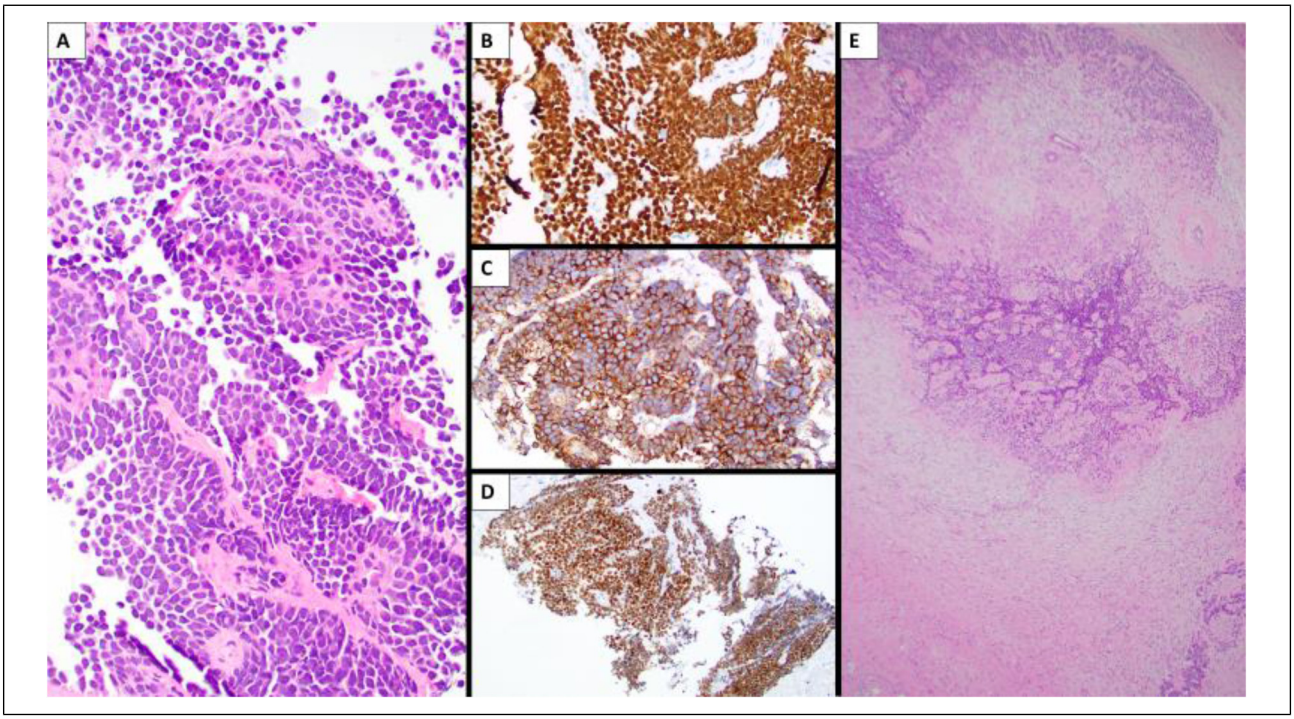

Figure 2. Histologic sections of adamantinoma-like ewing sarcoma of the parotid gland. A. Initial biopsy revealed hypercellular small round blue cells (40X). They are positive for p63 (B; 10x), CD99 (C; 10x) and NKX2.2 (D; 10x). E. Resection specimen demonstrating partial treatment effect following neoadjuvant therapy, where the viable tumor cells are embedded within edematous sclerotic scar tissue (2x).

similar to the core. The tumor consisted of predominately monotonous-appearing basaloid cells, grew in cords and nests, showed an infiltrative pattern in a background of variably cellular fibrotic stroma with mild to moderate amount of lymphoplasmacytic infiltrates and occasional aggregates of histiocytes. The stromal appearance was consistent with partial treatment response. No tumor necrosis was identified. The modified radical neck dissection contained 14 benign lymph nodes.

Follow Up

She received follow-on radiation of 66 Gy in 33 fractions to the left parotid gland and neck over 3 months. There was no clinical or imaging evidence of recurrence at 3-, 6-, and 24- month follow-up.

Discussion

Ewing sarcoma belongs to a family of small round blue cell tumors with the characteristic t(11;22) *EWSR1::FLI1* translocation. Survival is improved with the addition of effective Ewing sarcoma-specific chemotherapy to surgery, radiation, or surgery and radiation. While Ewing sarcoma may be localized to an anatomic location (localized Ewing sarcoma) at presentation, subclinical systematic disease has already developed in many patients, explaining the high relapse rate. In adult Ewing sarcoma, neoadjuvant multiagent chemotherapy has proven to be just as effective as seen in pediatric patients, with survival greater than 70% and is now considered the standard treatment.[1–3] Approximately 20% of Ewing sarcoma show epithelial differentiation, either with squamous morules or abrupt keratinization, while demonstrating keratin 5/6 and p40 immunoreactivity.[4] In Ewing sarcoma, occasional focal to patchy keratin positivity can be seen. In contrast, in adamantinoma-like Ewing sarcoma, the tumor shows well-developed squamous differentiation by immunohistochemistry, with diffuse positivity for keratin and squamous markers such as p63 and p40. If unrecognized, adamantinoma-like Ewing sarcoma is commonly misdiagnosed as poorly differentiated squamous carcinoma or basaloid salivary gland tumors,[5,6] thereby subjecting the patients to wrong and potentially ineffective treatment algorithms.

Ewing sarcoma with t(11;22) *ESWR1-FLI1* translocation and epithelial differentiation has been called adamantinoma-like Ewing sarcoma.[7] Only a limited number of cases in the head and neck have been reported to date.[7–9] The majority of head and neck adamantinoma-like Ewing sarcoma occur in the salivary glands, followed by thyroid gland and sinonasal tract.[7] There appears to be

no sex predilection.[7] The clinical significance of epithelial differentiation in Ewing sarcoma, and efficacy of Ewing sarcoma-specific chemotherapy regimen in adamantinoma-like Ewing sarcoma tumors, has not been formally established. Tumors in the head and neck region frequently benefit from neoadjuvant therapy, which improves resectability and oncologic outcome.[10] This is especially true for the parotid gland, located in a cosmetically desirable location with facial nerve preservation a major consideration. Hence, accurate preoperative diagnosis of adamantinoma-like Ewing sarcoma may guide successful neoadjuvant therapy.

In this case the patient showed partial response to only 2 cycles of dose-reduced VDC chemotherapy, suggesting that adamantinoma-like Ewing sarcoma is highly sensitive to an Ewing sarcoma-specific chemotherapy regimen. Indeed, complete radiologic resolution of locally advanced sinonasal adamantinoma-like Ewing sarcoma following an Ewing sarcoma-specific chemotherapy regimen has been previously reported.[9] In our case, the tumor mass demonstrates stromal changes consistent with treatment effect, even though no tumor cell necrosis was identified. Even though the final margin was focally positive (< 5 mm linear extent), local control can be achieved with adjuvant chemoradiation.[11,12] The tradeoff of microscopic residual tumor is a medical equipoise considering the significant morbidity of facial nerve paralysis. Indeed, in this current case, while our patient had microscopic positive surgical margin, she remains alive with no evidence of disease 2 years following Ewing sarcoma-specific neoadjuvant and adjuvant regimens. Induction chemotherapy-induced tumor necrosis is a prognostic factor for 5-year disease survival rate and relapse rate in localized Ewing sarcoma of the extremities.[13,14] At this time, there are insufficient cases to establish tissue-based disease prognostic factors, such as histologic response to neoadjuvant chemotherapy in head and neck adamantinoma-like Ewing sarcoma. This underscores the importance of increasing the awareness and diagnosis of adamantinoma-like Ewing sarcoma in the head and neck region on diagnostic biopsies, so that more patients could benefit from neoadjuvant therapy. In a review of the pertinent literature (Table 1), only 2 head and neck adamantinoma-like Ewing sarcoma patients (3 patients total including the current case) received induction chemotherapy. They all have either stable disease or are disease free with a follow-up period between 12 to 36 months. Long term follow-up information is accruing.

A PUBMED search and review of all reported head and neck adamantinoma-like Ewing sarcoma cases was undertaken with specific attention to chemotherapy, radiation, and neoadjuvant therapy response (Tables 1 and 2). Inclusion criteria were: (1) histologic characteristic (small round blue cell tumors, positivity for CD99, keratin, and squamous markers such as p63 or p40); (2) molecular confirmation of *EWSR1::FLI1* translocation, either by in situ hybridization or next generation sequencing; and (3) availability of treatment and follow-up data $\geq$ 6 months. Only 17 patients reported in the literature met these criteria (18 patients total when including the patient in this case report). Six patients received the correct diagnosis of adamantinoma-like Ewing sarcoma at diagnosis (Table 1). Of these, 3 patients (2 from the literature and 1 from this current case report) were treated with neoadjuvant chemotherapy.[6,9,15] All of these patients have favorable outcomes and are alive with either no disease or stable disease at follow-up (Table 1). In patients who received the correct diagnosis of adamantinoma-like Ewing sarcoma at diagnosis and underwent upfront surgery (no neoadjuvant therapy), these patients also

Table 1. Clinicopathologic Features and Outcomes of Three Adamantinoma-Like Ewing Sarcoma (ALES) Patients with Diagnosis Prior to Induction Chemotherapy.

Author	Age	Sex	Tumor site	Tumor size (cm)	Preoperative diagnosis	Therapy received	Follow-up (mo)	Outcome
Bishop et al[6]	21	M	Sinonasal tract (ethmoid sinus with intracranial and orbit extension)	N/R	ALES	XRT and chemotherapy (VDC/IE)	12	Alive with stable disease
Li et al[9]	39	F	Sinonasal tract (ethmoid sinus with intracranial and orbit extension)	6.5	ALES	XRT and chemotherapy (VDC/IE)	32	Alive with no evidence of disease
Current case	78	F	Parotid gland	1.6	ALES	Reduced dose chemotherapy (VDC) $\times$ 2 cycles + surgery; postoperative XRT (66 Gy in 33 fractions over 3 mo)	24	Alive with no evidence of disease

Abbreviations: mo, months; N/R, not reported; M, male; F, female; XRT, radiation; VDC/IE, vincristine, doxorubicin, cyclophosphamide/ifosamide, etoposide.

Table 2. Clinicopathologic Features and Outcomes of 12 Adamantinoma-Like Ewing Sarcoma (ALES) Patients with Incomplete Diagnosis Prior to Initiating Therapy and 3 ALES Patients with Correct Diagnosis but no Neoadjuvant Therapy.

Author	Age	Sex	Tumor site	Tumor size (cm)	Preoperative diagnosis	Therapy received	Follow-up (mo)	Outcome
Cruz et al[18]	42	F	Thyroid gland	2.5	Small cell carcinoma	Surgery	38	Alive with no evidence of disease
Kikuchi et al[19]	11	F	Neck soft tissue	4.8	Highly malignant tumor with unknown histologic classification	Surgery, chemotherapy (VDC/VC + IE) and radiation (whole neck; 50.45Gy)	42	Dead of disease. Relapsed at 5 months and 2.8 years after initial diagnosis. Died of widely metastatic disease at 3.5 years after initial diagnosis
Morlote et al[20]	20	F	Thyroid gland	4	Suspicious for carcinoma on FNA; *PTEN* loss by ThyroSeq	Total thyroidectomy, chemotherapy (VDC/IE × 14 cycles), and XRT (50.4 Gy × 28 fractions)	7	Alive with no evidence of disease
Eloy et al[21]	24	M	Thyroid gland	5.3	Poorly differentiated carcinoma	Completion thyroidectomy, left cervical lymphadenectomy and radioactive iodine	156	Alive with no evidence of disease
Maldi et al[22]	66	M	Thyroid gland	4.5	Malignant tumor of possible neuroectodermal origin	Total thyroidectomy. No chemoradiation due to patient co-morbidities	8	Alive with metastatic disease
Bishop et al[6]	37	F	Sinonasal tract (ethmoid sinus)	N/R	Poorly differentiated squamous cell carcinoma	Primary disease: Surgery. Recurrence: Surgery, XRT, and chemotherapy (docetaxel, carboplatin, capecitabine, methotrexate)	52	Dead of disease. Relapsed at 24th and 46th month
Bishop et al[6] Rooper & Bishop[7]	7	F	Orbital soft tissue	N/R	Myoepithelial carcinoma	Surgery, XRT, and chemotherapy (I/CE, then I/VE)	61	Alive with no evidence of disease
Ongkeko et al[23]	36	M	Thyroid gland	N/R	Poorly differentiated carcinoma	Primary disease: Surgery ad XRT. Metastatic disease: chemotherapy (VDC/IE)	24	Alive with distant metastasis at 2 months. No evidence of disease following VCD/IE
Rooper et al[5]	77	M	Submandibular gland	3.6	Poorly differentiated carcinoma with basaloid features	Surgery, XRT, and chemotherapy (doxorubicin)	13	Alive with no evidence of disease
Rooper et al[5]	32	M	Parotid gland	3.9	Poorly differentiated	Surgery, XRT, and chemotherapy (VDC/IE)	19	Alive with no evidence of disease

(continued)

Table 2. (continued)

Author	Age	Sex	Tumor site	Tumor size (cm)	Preoperative diagnosis	Therapy received	Follow-up (mo)	Outcome
					carcinoma with basaloid features			
Rooper et al[5]	41	M	Parotid gland	3.6	Poorly differentiated carcinoma with basaloid features	Surgery, XRT, and chemotherapy (initially carboplatin paclitaxel then VDC/IE)	24	Alive with no evidence of disease
Alnuaim et al[24]	29	M	Parotid gland	8.5	Poorly differentiated carcinoma	Superficial parotidectomy, chemotherapy (5 cycles), radical parotidectomy, chemotherapy, and XRT	22	Alive with local recurrence, multiple pelvic-abdominal deposits, and spinal bone metastatic lesions
Rekhi et al[16]	36	M	Neck soft tissue	3	ALES	Surgery, chemotherapy, and XRT	17	Alive with disease
Torres et al[17]	40	F	Parotid gland	2.4	ALES	Surgery, chemotherapy, XRT	96	Alive with no evidence of disease
Torres et al[17]	79	F	Parotid gland	2	ALES	Surgery	16	Alive with no evidence of disease

Abbreviations: M, male; F, female; N/R, not reported; FNA, fine needle aspiration; XRT, radiation; VDC/IE, vincristine, doxorubicin, cyclophosphamide/ifosamide, etoposide.

experienced favorable clinical outcomes (Table 2).[16,17] In cases where the initial diagnosis was not adamantinoma-like Ewing sarcoma (12 cases; 67%; Table 2), surgery was the initial therapy.[5–7,18–24] Of them, metastatic disease occurred in 5 patients (5/12; 42%).[6,19,22–24] Of them, two patients had no adjuvant therapy following surgery due to underlying comorbidities or old age.[17,18] One patient developed two recurrences, neither of which were treated with ES-specific chemotherapy and she eventually died from her disease.[6] One patient was initially treated with surgery and radiation, but when he developed pancreatic metastasis 2 months later, the correct diagnosis of adamantinoma-like Ewing sarcoma was rendered and he was treated with Ewing sarcoma-specific regimen consists of vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE). After receiving Ewing sarcoma-specific regimen, he remains in remission at two years follow-up.[23] This underscores the importance of making the correct diagnosis in order for the patient to receive Ewing sarcoma-specific chemoregimen which appears effective in the treatment of adamantinoma-like Ewing sarcoma. The composition of the adjuvant chemotherapy regimen was not reported in three reports.[16,17,24] Of these, two of the three patients were alive with metastatic disease. Among them, one presented with suboptimal resection.[24] He was treated with chemotherapy, followed by completion radical parotidectomy and neck dissection. This case was unique in that the tumor was the largest size reported to date (8.5 cm), and displayed focal chondro-osseous differentiation. Unfortunately, his post-operative course was aggressive with widely metastatic disease twenty-two months following his definitive surgical intervention, and was eventually referred to palliative care. Tumors with heterologous metaplastic differentiation, such as metaplastic breast cancer or carcinosarcoma of the gynecologic tract, are associated with aggressive clinical course and poor outcomes. Heterologous metaplastic differentiation in adamantinoma-like Ewing sarcoma may be a harbinger of aggressive feature.

In conclusion, optimal therapy is predicated on an accurate diagnosis of adamantinoma-like Ewing sarcoma. Ewing sarcoma-specific chemotherapy regimen seems to be effective in adamantinoma-like Ewing sarcoma, and has led to complete remission in isolated cases *without* surgical intervention. This tumor entity is frequently confused with other more common neoplasms in the head and neck region, such as basaloid squamous cell carcinoma, poorly differentiated squamous cell carcinoma, adenoid cystic carcinoma, basal cell adenocarcinoma, and others. With the emergence of targeted therapies for treating Ewing sarcoma,[25] accurate diagnosis will lead to increased treatment options and clinical trial eligibility, when immunohistochemistry results can

inform appropriate molecular testing to reach an actionable diagnosis. The benefit of neoadjuvant therapy for allowing resectability is important in the head and neck region, further underscoring the importance of making accurate diagnosis of adamantinoma-like Ewing sarcoma on pre-treatment diagnostic biopsies. While small, this report shows the potential promise of Ewing sarcoma-specific chemoregimen in managing salivary gland adamantinoma-like Ewing sarcoma, even at reduced dose regimen as used in our current case where the patient still experienced a good response. Our understanding will continue to evolve with increased awareness and additional publications on this unique tumor.

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Ethical Approval

All activities performed in this retrospective analysis involving a human participant were in accordance with the ethical standards, with patient consent obtained for publication of anonymized clinical data and images. This study was approved by Institutional review board (IRB# 215254). The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of City of Hope or Southern California Permanente Medical Group.

Declaration of Conflicting Interests

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Informed Consent

Informed consent was obtained from the patient, who has graciously allowed us to report this case for educational/research purposes.

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Trial Registration

N/A

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