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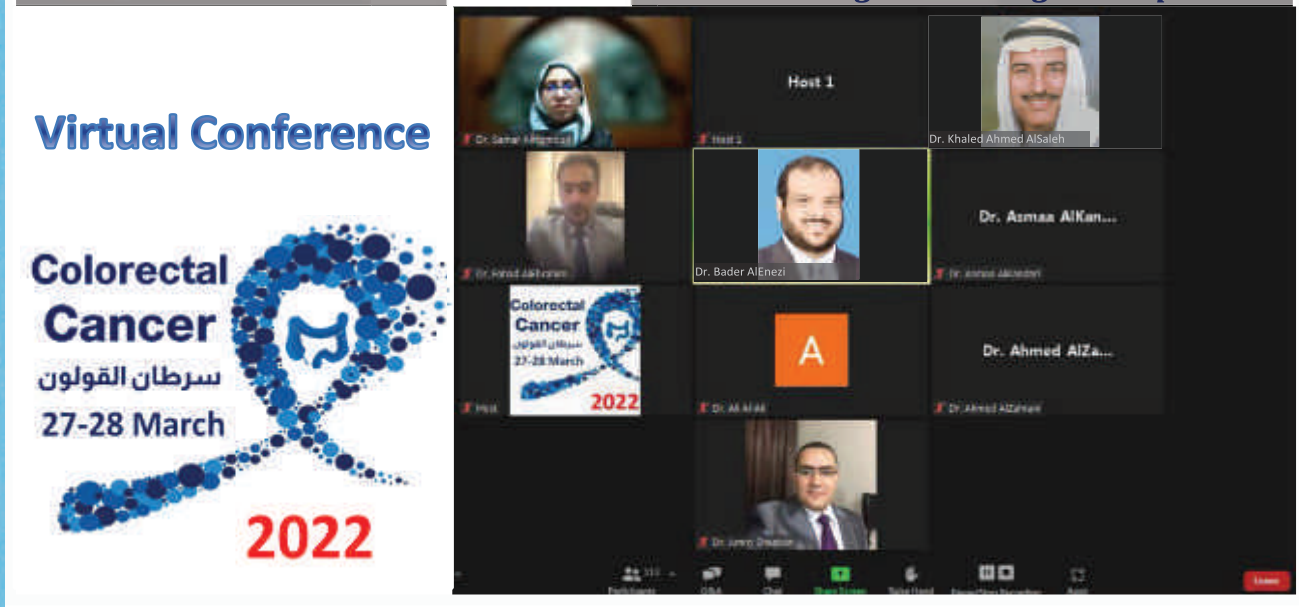

The Official Journal of the Gulf Federation For Cancer Control

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Review Article

Practical Approach in Management of Extraosseous Ewing's Sarcoma of Head and Neck: A Case Series and Review of literature

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Abstract

Extraosseous Ewing's Sarcoma (EES) is a high grade rare malignancy from Ewing's family tumors (EFTs) occurring in soft tissues. Diagnosis of EES relies on a constellation of features, including round cell morphology, characteristic immunohistochemistry (such as CD99, FLI–1 and NKX2.2 positivity), and pathognomic molecular abnormalities of t(11;22)(q24;q12). Multimodality treatment has improved the prognosis and clinical outcome in EFTs. Due to its rarity, the current recommendation to treat EES is based on Skeletal Ewing's Sarcoma (SES) guidelines. However, achieving clear surgical margins in the Head and Neck region is often challenging due to complex anatomy and close proximity to critical structures, placing patients at risk of loco–regional recurrence in the absence of adjuvant therapy. The literature on head and neck EES is scarce, consisting of a few retrospective case series and case reports. Herein, we describe the characteristic clinico–pathological features and treatment of three EES patients with primaries from Parotid, Nasal cavity/ Nasopharynx and Oropharynx, with a comprehensive review of the literature.

Keywords: Ewing's Family of tumors, Extraosseous Ewing's sarcoma of head and neck.

Introduction

Ewing's Family of tumors (EFTs) include Skeletal Ewing's Sarcoma (SES), Extraosseous Ewing's Sarcoma (EES), and Primitive neuroectodermal tumor (PNET).[1] EES was first described by Tefft et al. in 1969 in paravertebral soft tissue tumors histologically resembling Ewing's Sarcoma (ES).[2] EES accounts for 20–30 % of all soft tissue ES. Compared to SES having male to female ratio is 2:1; EES occurs in similar frequency in males and females.[3] The sites commonly involved are soft tissues of the trunk (particularly paravertebral region), pelvis or lower extremities with rare occurrence in the head and neck.[4] Owing to the paucity of literature: herein, we report clinicopathological characteristics and treatment outcome of three patients with EES of head and neck, along with a comprehensive review of the literature.

Case Series

Case 1: Parotid Adamantinoma like Ewing's sarcoma

Twelve–year–old female child presented in pediatric outpatient clinic with the chief complaint of slow–growing painless swelling in the right preauricular area of 6 months duration. Initial evaluation with fine needle aspiration cytology (FNAC) revealed a malignant tumor with epithelioid morphology. Computed tomography scan (CT) findings revealed well–defined heterogeneously enhancing soft tissue density lesion in the superficial lobe of the right parotid gland. It was extending for a distance of ~ 0.5 cm medial to the retromandibular vein into the deep gland of parotid. Laterally the lesion was reaching upto skin surface in retro–auricular region. Lesion was confined to the parotid gland with no infiltration into the adjacent structures. On wide local excision – macroscopic examination showed encapsulated, well–circumscribed lesion breaching the capsule at places, and microscopic examination showed a biphasic appearance of epithelial and mesenchymal areas with areas of necrosis and brisk

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mitosis. Immunohistochemistry studies (IHC) studies revealed CD99, FLI–1 and pancytokeratin strong positivity as shown in figure1A–1F. Subsequent Fluorescent in–situ hybridization (FISH) analysis for EWSR1 rearrangement turned out positive resulting in a final diagnosis of Adamantinoma–like Ewing's sarcoma, a rare entity – more so in this age group and at this site. She was managed with adjuvant radiotherapy and chemotherapy as per standard SES guidelines. IHC, molecular testing details and adjuvant treatment details are mentioned in Table 1.

Case 2: Nasal cavity/Nasopharyngeal Ewing's Sarcoma/PNET

Five–year–old female presented with a three–week history of bilateral nasal stuffiness, epistaxis, swelling around the eyes (more on left), and intermittent headache in ENT clinic in her native place. Nasal endoscopy revealed a diffuse nasal mass. CECT of paranasal sinuses showed heterogeneously enhancing mass in the nasal cavity extending to the nasopharynx, orbital apex, left parasellar and left medial temporal fossa region. She underwent debulking surgery and diagnosed with Ewing sarcoma. She was referred to our institute for further treatment. Histopathology review of slides and blocks revealed sheets of small round blue cells with extensive areas of necrosis in alternate light and dark patterns. IHC Positivity for CD99 & FLI–1 confirmed the diagnosis of Ewing's Sarcoma as shown in figure 2A–2D and she received adjuvant treatment as per standard SES guidelines. (Table 1)

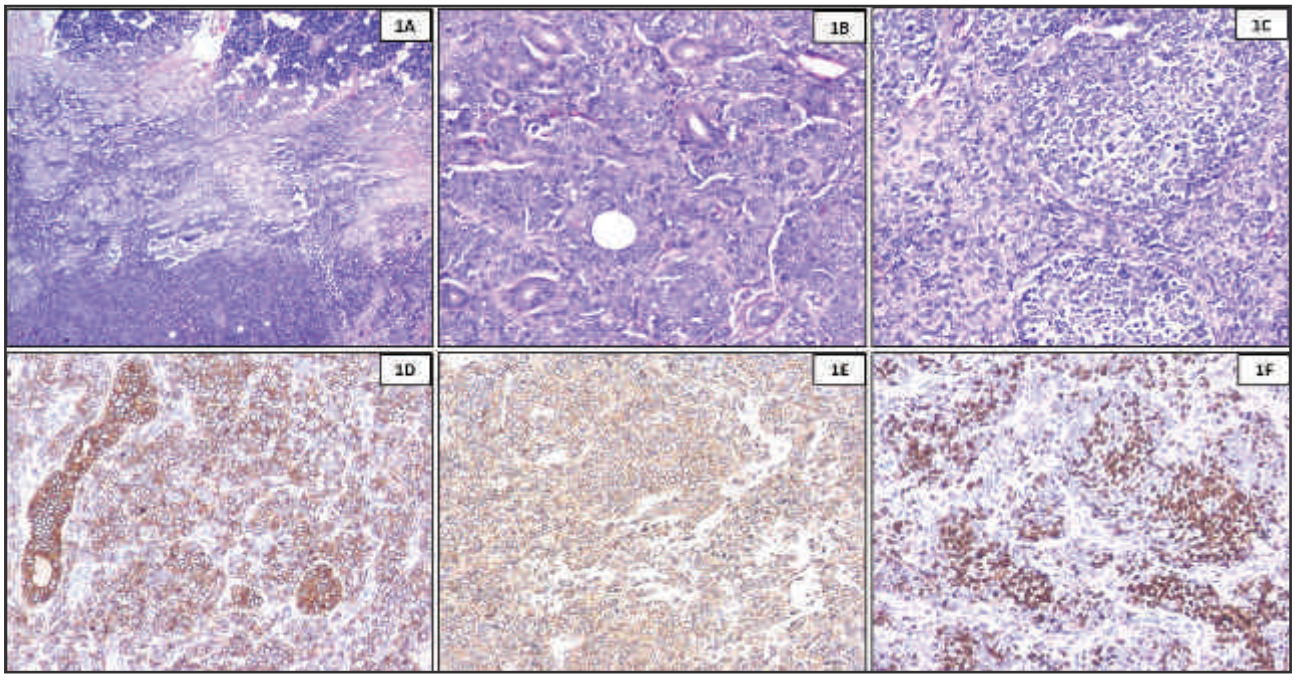
Case 3: Oropharyngeal Ewing's Sarcoma

Twenty eight–year–old married female, non–smoker, non–alcoholic presented with a history of progressively increasing dysphagia for solids associated with change in voice for one month. Direct laryngoscopy revealed mucosa covered bulge involving base of tongue and bilateral vallecula. Contrast enhanced CT (CECT) scan

Parameters	Case 1	Case 2	Case 3
Age (years)/ Gender	12/ Female	5/ Female	28/ Female
Site	Parotid	Nasal cavity/Nasopharynx	Oropharynx
Presentation	Painless parotid mass x 6 months	Nasal stuffiness, epistaxis, intermittent headache, Eye swelling x 3 weeks	Dysphagia to solids x 4 weeks
PET–CT	Non metastatic	Non metastatic	Non metastatic
Bone marrow Aspiration and Biopsy	Not Involved	Not Involved	Not Involved
IHC –Positive	Strongly positive – CD99, NSE, p63, AE1/AE3, synaptophysin, Cytokeratin; Focally positive –FLI 1, p40 ki67 index– 30%	CD99, FLI–1, NSE	CD99, FLI–1, PAS
IHC– Negative	Heppar 1, Alpha fetoprotein, NUT, nuclear B catenin, desmin, S100, EMA ,SMA,CD117 and CK7. (CK7 highlighted the entrapped ducts)	LCA, Synaptophysin	Synaptophysin, NSE & PanCK; CD3 and CD20–highlighted the reactive B and T cells
FISH (Fluorescent in situ hybridization)	EWSR1 rearrangement	Not done	Not done
Pathological Diagnosis	Adamantinoma–like Ewing's sarcoma	EES/PNET	EES
Surgery	WLE	Debulking	Biopsy
Resection Margin	R1	R2	–
Chemotherapy (Compressed chemotherapy q 2weeks with filgrastim support)	VAC/IE x 11 cycles	VAC/IE x 16 cycles	VAC/IE x 4 cycles
Radiotherapy (Sandwiched)	50.4Gy/28#	55.8 Gy/31#	55.8 Gy/31#
Status	CR	CR	Defaulted treatment, Alive, Asymptomatic Disease status unknown (Post RT no imaging available)

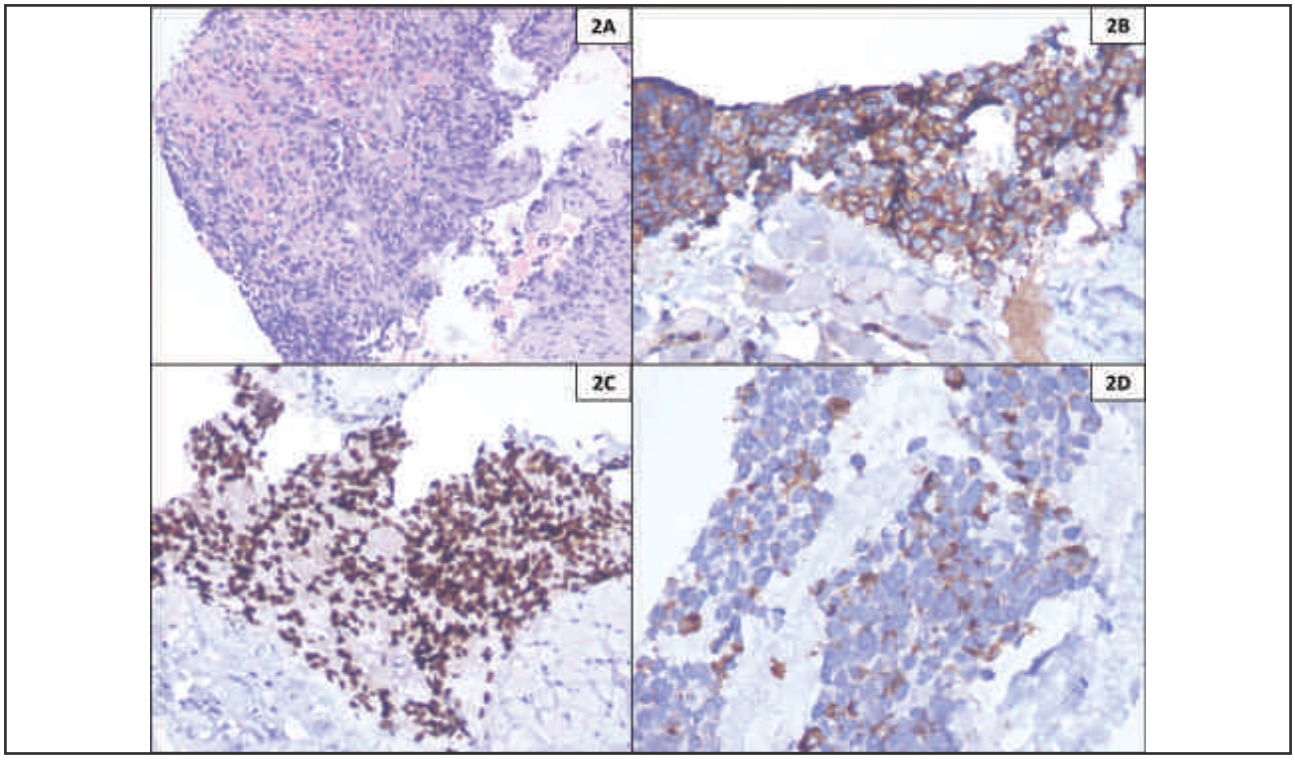
Table1: Clinico–pathological Characteristics, Treatment details of 3 patients

Pathological Images – Extraosseous Ewing Sarcoma Cases– Parotid, Nasal cavity/Nasopharynx, Oropharynx



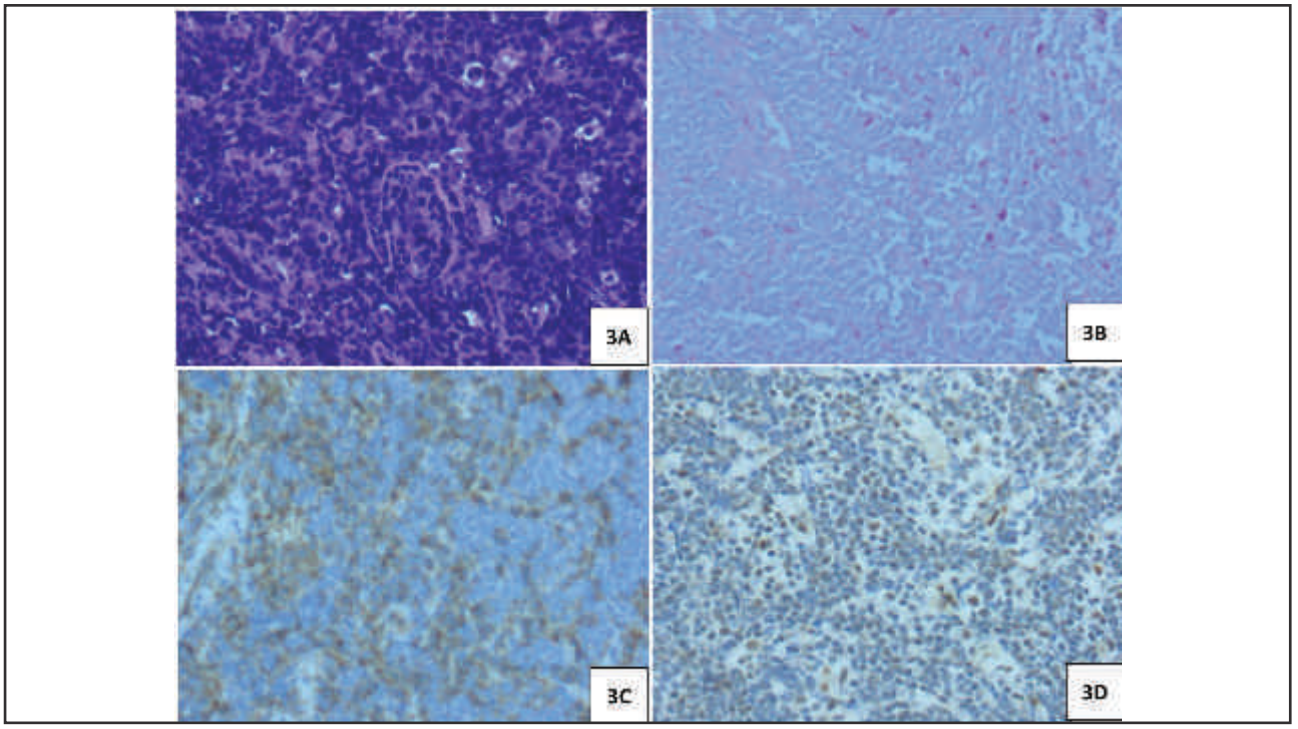
Case of Parotid Adamantinoma like Ewing Sarcoma

Photomicrographs show **1A)** an infiltrating tumour with peripheral rim of normal salivary gland tissue *(H&E, x40)* **1B)** tumor is composed of small round cells arranged as nests and lobules with a few entrapped normal salivary ducts (arrow head) *(H&E, x400)* **1C)** nests of small round cells with high grade nucleus surrounded by large, pale epithelial cells *(H&E, x400)*. On immunohistochemistry, tumor cells are **1D)** diffusely positive for pancytokeratin *(DAB, x200)* **1E)** CD99 *(DAB, x200)* **F)** the small round cells are positive for FLI–1 *(DAB, x200)*.



Case of Nasal Cavity/Nasopharynx PNET

Photomicrographs show **2A)** tumor composed of a relatively monomorphous population of small round cells arranged in sheets with fine chromatin, inconspicuous nucleolus and very scant cytoplasm *(H&E, x200)*. On immunohistochemistry, the tumor cells show **2B)** diffuse membranous positivity for CD99 (DAB, x400) **2C)** nuclear positivity for FLI–1 and NKX2.2 (DAB, x200) and **2D)** focal expression of NSE*(DAB, x400).*



Case of Oropharyngeal Ewing Sarcoma

Photomicrographs show **3A)** sheets of small round tumour cells with inconspicuous cytoplasm, exhibiting hyperchromasia and occasional mitoses. Well–formed rossettes are not seen. Haematoxylin and Eosin stain, x 400. **3B)** tumour cells which are sensitive to diastase treatment after Periodic acid Schiff stain, Periodic acid Schiff – Diastase stain, x 400. **3C)** tumour cells which show diffuse membranous expression for CD99. Immunohistochemistry with DAKO antibody, USA, Diaminobenzidine stain, x 400. **3D)** diffuse nuclear positivity for FLI1 in tumour cells, Immunohistochemistry with DAKO antibody, USA, Diaminobenzidine stain, x 400.

of head and neck showed heterogeneously enhancing soft tissue malignant lesion in the oropharyngeal region involving mainly the epiglottis, bilateral vallecula and abutting the base of tongue with few subcentimetric isodense nodes. Biopsy revealed a malignant tumor with round cell morphology with scant cytoplasm and granular chromatin. On IHC with CD99 and FLI–1 positivity she was diagnosed as Oropharyngeal Ewing's Sarcoma as shown in figure 3A–3D. IHC and adjuvant treatment details are mentioned in Table 1. Post radiotherapy however, due to Covid–19, she defaulted further adjuvant chemotherapy treatment. On telephonic communication (6 months post RT), she was asymptomatic but not willing for further follow–up and treatment.

Radiological Images of all the three Extraosseous Ewing Sarcoma Cases i.e. Parotid, Nasal cavity/Nasopharynx, Oropharynx are shown in figure 4A–B, 5A–B, 6A–B respectively.

Discussion

The Ewing family of tumors (EFTs) of the head and neck are rare group of high grade sarcomatous malignancies which commonly affect bone and soft tissue. EES of head and neck sites which are reported as case series or case reports include– maxillary sinus[4], larynx[5], floor of mouth (sublingual gland)[6], parapharyngeal space[7], ethmoid sinus[8], retrotracheal[9], eyelid[10], parotid gland[11], submandibular gland[12], orbit, thyroid gland[13] and sinonasal tract[14].

Approximately 75% of the patients with EES usually present as painless rapidly enlarging mass in soft tissues with high propensity to spread locally, infiltrating fascial planes, and invading adjacent muscles and bone.[6] EES especially in indiscernible locations tend to present in advanced stages at diagnosis. One patient in our study presented with progressively increasing dysphagia of 1 month duration caused by local oropharygeal growth however patient with superficial visible and palpable painless swelling in parotid area presented after 6 months and patient with nasal cavity/nasopharyngeal growth presented in advanced stage with huge growth causing mass effect in form of nasal obstruction and stuffiness, epistaxis and eye swelling symptoms of 3 weeks duration.

Comparison of patient characteristics and outcomes among patients with EES and SES by Applebaum et al revealed that the mean age of onset is older in EES, with a bimodal distribution to its peak age of onset: >35 and < 5 years.[3] All of our three patients were females, two

Radiological Images – Extraosseous Ewing Sarcoma Cases– Parotid, Nasal cavity/Nasopharynx, Oropharynx

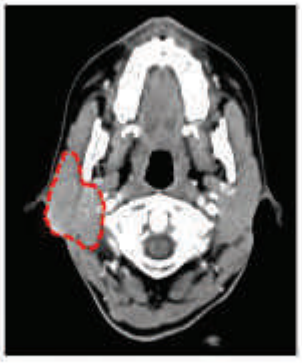


FIGURE 4A (Parotid case) Preop
well-defined heterogeneously enhancing soft tissue density lesion in the superficial lobe of the right parotid gland.

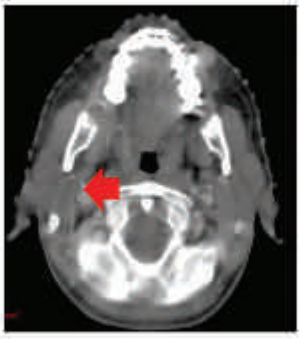


FIGURE 4B (Parotid case) Postop (Wide local excision), R1 Resection (Microscopic margin-Positive)

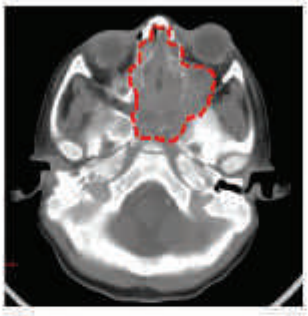


FIGURE 5A (Nasal cavity/Nasopharynx case) Preop
Heterogeneously enhancing mass in the nasal cavity extending to the nasopharynx, orbital apex, left parasellar and left medial temporal fossa region

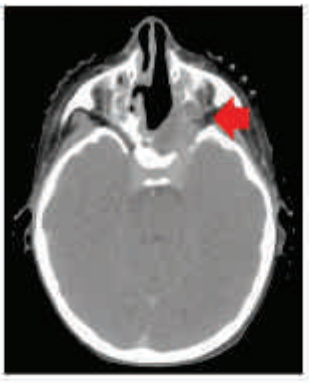


FIGURE 5B (Nasal cavity/Nasopharynx case) Postop Residual Disease , R2 Resection

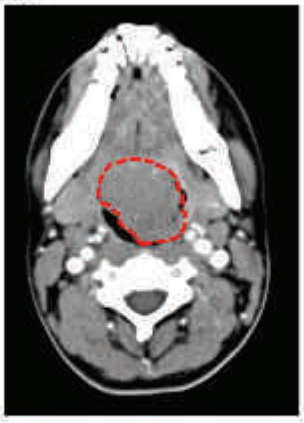


FIGURE 6A (Oropharynx case) Pre induction chemo
Partly defined heterogeneously enhancing soft tissue lesion oropharyngeal region involving the epiglottis, bilateral vallecula and abutting the base of tongue

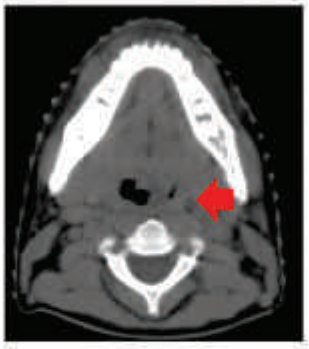


FIGURE 6B (Oropharynx case) Post induction chemo-Residual Disease

children (5 years and 12 years) and 1 adult (28 years). On literature review of EES of head and neck cases – youngest child had congenital eyelid swelling proven out as EES[10] and oldest case found to be 74 year old with laryngeal primary.[5]

Differential Diagnosis based on Morphology, Immunohistochemistry (IHC) and Molecular testing.

Differential diagnosis for small round cell tumors (SRCT) in head and neck region includes EFTs,

rhabdomyosarcoma, NUT midline carcinoma, olfactory neuroblastoma, lymphoma, melanoma, small cell carcinoma as well as AELS variant (Adamantinoma–like Ewing Sarcoma).[15]

Adamantinoma–like Ewing sarcoma (ALES) is a rare variant of EFTs having close resemblance to classic adamantinoma of bone. ALES is classified as a variant of Ewing sarcoma (ES) with complex cytogenetic profile demonstrating the pathognomic EWSR1–FLI1 translocation and corresponding immunohistochemical positivity for CD99 and NKX2.2, as well as harboring squamous epithelial differentiation including diffuse expression of cytokeratin and p40.[12]

ALES has been reported in soft tissues of head and neck in various anatomic subsites such as orbit, parotid, submandibular salivary gland, thyroid gland, and sinonasal tract.[12,13,16] First case of parotid ALES was reported by Cecilia Lezcano et al. highlighting the potential to be mistaken for primary salivary gland carcinomas, which in addition to basal cell adenocarcinoma include other basaloid tumors such as adenoid cystic carcinoma.[16] It was recently noted that ALES of soft tissues shows inclination towards salivary glands as 10/19 cases of ALES were reported in salivary glands (8 parotid and 2 submandibular glands) in a dedicated case series by Lisa et al. In this series all patients were adults, age ranging from 32 to 77 years with a mean age of 52 years.[12]

Molecular testing– Approximately 85% of ES/PNET are characterized by prototypical molecular abnormality i.e. translocation t(11;22)(q24;q12) that results in the fusion of the EWS gene on chromosome 22 to the FLI–1 gene on chromosome 11 and overexpression of FLI–1 protein.[17] RT–PCR (Reverse Transcriptase–Polymerase chain reaction) and FISH (fluorescence in situ hybridization) are valuable adjuncts for detection of these pathognomic translocations.[18]

Immunohistochemistry (IHC)– To differentiate EFTs from other small round blue cell tumors immunostaining with CD99 & FLI–1 can help in majority of the cases in absence of "gold standard" cytogenetic and molecular genetic identification of the ES/PNET–associated translocations. ES and PNET highly express MIC2 gene product, a 30/32 kD surface antigen.[19] The detection of this surface protein by CD99, though not specific, is very characteristic for EFTs when there is strong diffuse membranous immunoreactivity in the majority of cells. Similarly FLI–1 protein expression is seen in > 70% of ES/PNET with specificity of >90%.[18] Positivity in IHC with NKX2.2 is strongly correlated with t(11;22)(q24;q12) translocation which has been proven recently and can be used in a resource limited centres.[20]

Two of our cases were classified based on morphology and CD99 plus FLI–1 positivity as Extraosseous Ewing Sarcoma but case with parotid swelling showed positivity for cytokeratin along with CD99 positivity. Other histochemistry markers that also strongly favored Ewing's family tumors such as synaptophysin and FLI–1 positivity; leading to diagnosis of Adamantinoma like Ewing Sarcoma. Further confirmation in parotid case was done by FISH revealing EWSR1 rearrangement.

Table 2 shows the IHC Panel to differentiate EFTs from various small round cell tumors in head and neck region

Small round cell tumors	Immunohistochemistry Markers
Lymphoma	CD45 (LCA)+ve
Lymphoblastic Lymphoma	CD45–Frequently negative, CD99– Frequently positive
Rhabdomyosarcoma	Desmin +ve, MyoG+ve, CD99+ve
NUT Midline Carcinoma	+ve for NUT protein in>50% of cells, usually positive for pankeratin, p63, p40, and CD34, and occasionally, positive for synaptophysin, p16, TTF1, and CD99.
EES/PNET (Extraosseous Ewings' Sarcoma, Primitive Neuroectodermal tumor)	CD99+ve, FLI–1+ve
ALES (Adamantinoma like Ewing Sarcoma)	CD99+ve, FLI–1+ve, CK+ve, Synaptophysin+ve, p40+ve, Cytokeratin AE1/AE3
Olfactory Neuroblastoma	NEmk+ve (NSE+ve, Chromogranin A+ve, S–100+ve, CD56+ve)
Melanoma	S100 +ve, HMB45+ve
Neuroblastoma	NEmk+ve (CD56, Synaptophysin, Chromogranin A, NSE)
Small cell carcinoma	CK+ve, NEmk+ve (CD56, Synaptophysin, Chromogranin A)

Table 2: IHC Differential for Small round cell tumors in head and neck area
LCA– Leukocyte common antigen, CK–Cytokeratin, NEmk–Neuroendocrine marker, NUT–Nuclear protein in Testis

Investigations and workup– Diagnostic staging work up for EFTs is based on thorough exploration for local tumor extent as well as distant metastases. Apart from tissue diagnosis established by Primary site biopsy & IHC/Molecular testing,– staging workup includes, CT Scan and/or Magnetic resonance imaging (MRI) of primary region, bone marrow aspiration and biopsy, 99m–technetium whole–body radionuclide bone scan and Chest CT Scan or Whole body FDG–PET if available as single imaging modality to rule out distant metastasis.[21] Most common sites of distant metastases are lungs, pleural space, bones, and bone marrow or combination thereof. Metastatic disease at diagnosis is found in around 12.5% for ES of the head and neck, and 20% to 30% for ES of all sites in previous studies.[22]

Radiological features as described by Javery O et al. for Ewing's family of tumors are– isointense to hyperintense appearance on T1–weighted MR images and hyperintense on T2–weighted MR images, Smaller tumors appear homogeneous whereas large tumors tend to be heterogenenous due to hemorrhage and internal necrosis on unenhanced and contrast–enhanced images. On CT scan, tumors similarly show heterogeneous enhancement with hypoattenuating areas corresponding to necrosis and high density foci in cases of hemorrhage. Lymph nodal metastasis is reported rarely in 0–12% of cases.[23]

Multimodality Treatment – Prior to the era of chemotherapy treatment outcome was dismal in Ewing sarcoma. The introduction of systemic chemotherapy into the treatment regimen dramatically improved the response rates in EFTs and thus the cure rates. Although historically, patients with EES were treated with a rhabdomyosarcoma protocol but current evidence recommends that these patients benefit from skeletal Ewing sarcoma protocols instead.[24,25]

National Comprehensive Cancer Network (NCCN) recommends the treatment of EES on same guidelines as for skeletal Ewing sarcoma. Nonmetastatic tumors, should be preferably managed by a multi-disciplinary and highly specialized team, by either surgery, radiation or a combination for effective local control and multiagent chemotherapy for systemic control. Accepted local control treatment consists of R0 resection, (R1 resection + radiation therapy (RT), or RT and concurrent chemotherapy. Local therapy in the form of surgery or radiotherapy usually starts at 12 weeks of induction chemotherapy after restaging of primary site with Whole body FDG–PET–CT.[26] Local therapy decisions should be based on balancing the risks and morbidity of surgery and radiotherapy with potential benefits. Multiagent chemotherapy should continue for up to 10–14 cycles post local treatment. Recent literature demonstrates that about half of all patients with EES receive RT.[27]

Surgery and Margins– Wide local resection is recommended as best approach for SES and EES, where feasible with acceptable morbidity. However, surgical treatment of Ewing sarcoma of the head and neck region is challenging due to the rapid involvement of closely related tissue planes, anatomic complexity and its close proximity to vital structures, which makes it difficult to achieve negative surgical margins. As per Current Children's Oncology Group (COG) protocols for SES adequate margin status is defined as – $\geq$ 1 cm (ideally 2–5 cm) around the involved bone, soft tissue margin for fat or muscle planes is $\geq$ 5 mm and for fascial planes $\geq$ 2 mm.[28] On optimal surgical margin analysis in EES in children; Qureshi et al. concluded that three–dimensional tumor–free margin of resection correlated with local control irrespective of the quantitative extent of negative margins size.[29]

Radiotherapy and Radiation doses

In general local control is of utmost importance in the Ewing family of tumors (EFT). Owing to difficulty in achieving adequate margin in axial primaries or large residual tumors which respond poorly to induction chemotherapy; risk of local or combined failure is high if treated with surgery alone. The addition of post–operative radiotherapy (PORT) in these high risk patients has resulted in improved rates of local control and event–free survival in CESS and EICESS trials.[30]

Recommendation for post op Radiotherapy for EFTs can be extrapolated from review article by Laskar et al. wherein gross or microscopic positive margin, clear margin but poor histopathological response to chemotherapy (necrosis < 90% is the preferred minimum threshold, but <95–99% also has been used based on institutional practice), were the indications for addition of PORT. PORT is started within 6–8 weeks of surgery,– Initial phase (45 Gy/25#/5weeks): pre–chemotherapy tumor volume on CT/MRI with 1.5–2 cm margins with appropriate modifications, Boost phase (10.8 Gy/6#/1.1 weeks): post–operative gross residual disease with 1.5–2 cm margins. To reduce radiation induced long term normal tissue toxicities– use of conformal radiation techniques such as IMRT or VMAT with IGRT planning is recommended.[31]

In axial primaries such as head and neck where non–mutilating surgery with adequate margin is not feasible with a functional organ use of definitive radiotherapy as sole local treatment modality in dose range of 55–60 Gy with standard fractionation and 2 cm margin including original biopsy scar is recommended.[32]

Preop radiotherapy is also an option where radiological response to induction chemo is not adequate. Radiation Doses for pre op radiotherapy in range of 44Gy –54Gy are used in EICESS 92 trial depending upon expected close resection margin.[30]

Two out of 3 cases in our study nasal cavity/ nasopharynx and parotid underwent upfront surgery and received adjuvant radiotherapy in view of R2 and R1 resection respectively; sandwiched with systemic chemotherapy. Oropharyngeal case was deemed surgically morbid procedure and treated with radical radiotherapy sandwiched between systemic chemotherapy.

Chemotherapy–drugs and regimens

The systemic treatment of EES has evolved from chemotherapy regimens similar to rhabdomyosarcomas to SES protocols. Systemic Chemotherapy with cyclic combinations, incorporating vincristine, doxorubicin, cyclophosphamide, etoposide, ifosfamide and occasionally actinomycin D given 2–3 weekly constitutes the usual approach for SES. Sequence of chemotherapy usually follows as 3–4 cycles of VAC/IE followed by local therapy followed by consolidative chemotherapy for total of 10–14 cycles. Maintaining adequate dose intensity of chemotherapy is of paramount importance. Interval compressed or dose dense chemotherapy with filgrastim support improves EFS and has the potential to improve overall survival with no increase in toxicity as reported in one of the Children Oncology Group (COG) study.[33] All three patients in our series underwent dose dense chemotherapy and well tolerated the regimen with filgrastim support. Following the potential benefit reported by two nonrandomized trials on results of high dose consolidative chemotherapy (BuMel) in high risk localized Ewing Sarcoma; improvement in event free survival and overall survival were also reported by latest randomized control Euro Ewing 99 (EE99) trial in patients with high risk localized disease by BuMel based HDC compared to conventional chemotherapy regimen. High risk factors were defined as tumor volume at diagnosis >200ml or patients showing poor histologic response to induction chemotherapy (residual viable cells >10%) or unresected tumors that show poor radiological response to induction chemotherapy (<50% reduction in soft tissue component on radiological imaging).[34] Whether same results can be extrapolated to EES with high risk features need to be investigated further.

Treatment outcome and Prognosis– In general for EFTs, – with the introduction of chemotherapy prognosis has been improved dramatically in localized disease from 10% with surgery and radiotherapy alone to 70% now. Poor prognostic factors include hypoalbunemia (<3.5g/dl), systemic symptoms (fever and weight loss), high LDH, tumor size >8cm, tumor Volume >200ml, axial primary, poor histologic response to chemotherapy (> 10% viable tumor cells as per Salzer–Kuntschik grading system).[32]

Allam et al. reported 5–year actuarial OS and DFS rates as 53% and 30%, respectively in retrospective analysis of 24 patients of Ewing sarcoma of head and neck with majority of patients treated with systemic chemotherapy and local irradiation. 87% had localized disease with most common sites being maxilla and mandible and majority (70%) had tumor size >10cm.[35]

As per Grevener et al. in data analyses of 51 ES Head and Neck patients from German Society for Pediatric Hematology and Oncology (GPOH) database who were treated according to EE99 trial and with over 10 year follow–up period– age, and stage were found to be important prognostic factors. The 3–year EFS was 81% for patients younger than 15 years compared to 40% for patients older than 15 years. Extraosseous/ exactly not known patients were only 13% in this case series where as other primary sites were arising from skeletal which included the skull (45%), maxilla (14%), mandible (12%), neck (10%), scalp (4%), and face (2%). The 3–year EFS and OS rates were 74% and 87%, respectively, for patients with localized disease.[36]

Muratori et al. reported surgery plus radiotherapy as better treatment compared to single modality alone EES case series (axial–17%) and found tumor volume >100 cm^3 (76.9% vs.28.6%) and inadequate margins as the strong prognostic factors for 5 year OS but not for EFS.[37]

Second Malignancies– Risk of Hematological malignancies (AML/MDS) was reported in the range of 2% and risk of solid tumors in range of 5% after 15 years in CESS Studies on risk of second malignancy in long term in Ewing Survivors. The cumulative risk of a second malignancy was 0.7% after 5 years, 2.9% after 10 years, and 4.7% after 15 years. Local therapy increased risk of secondary sarcoma but all were salvaged with subsequent treatment.[38] Kuttesch et al. analyzed radiation dose dependency of sarcomas in Ewing survivors and reported no secondary sarcomas development in patients who received less than 48 Gy dose after follow–up (Range– 4.7 to 17.9 years. Latency period for development of second malignancy was 7.6 years.[39]

Conclusion– Morphological identification along with correct use of molecular/cytogenetics or IHC markers represents the appropriate strategy in order to differentiate EES from small round cell tumors of head and neck and to minimize diagnostic inaccuracy. Extraskeletal Ewing's sarcoma is rare in head & neck region and sparse data are available addressing optimal oncologic treatment

modalities. EES of head and neck require multidisciplinary team to introduce multiagent induction chemotherapy in induction followed by incorporation of timely local treatment surgery or conformal radiotherapy (IMRT or VMAT with IGRT Planning) or both followed by consolidative chemotherapy in proper patient management. Stress of prolonged and intensive multidisciplinary treatment takes a toll on patient and caretakers. Noncompliance to the treatment is also an issue in such malignancies.

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Nil

Conflict of Interest

None

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