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Small round cell Tumor of the head and neck Region: A review

Dr. Kanupriya Gupta

MDS, Oral and Maxillofacial Pathology, Senior Research Fellow, Faculty of Dental Sciences, IMS, BHU, Varanasi, Uttar Pradesh, India

Abstract
Small round cell tumors configure a heterogeneous group of malignant neoplasms that present clinical predominance in children and young adults. It encompasses a wide variety of undifferentiated primitive neoplasms which have in common the ability, with varying frequency, to present as a nondescript proliferation of round cells with high nuclear cytoplasmic ratio and hyperchromatic nuclei by light microscopy. Their differential diagnosis is influenced by the age of the patient, their site of occurrence, and slight degrees of differentiation exemplified by minor architectural and cytoplasmic features. All tumour types have special treatment modalities and the prognosis is dependent on the exact histological diagnosis confirmed by adjuvants like immunohistochemistry and Cytogenetics. This article reviews some of the most common small round cell tumors involving the head and neck region which includes Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and lymphomas.

Keywords: cytogenetics; head neck; Immunohistochemistry; small round cell; undifferentiated tumors

Introduction
Small-round-cell tumors (SRCTs) are a group of cytomorphologically similar neoplasms with varied origin. The neoplastic elements include undifferentiated, uniform, small round to oval closely packed cells with a solitary hyperchromatic nucleus and a high nuclear cytoplasmic ratio. The nucleoli may or may not be prominent [1, 2].

They lack any particular morphological features that would allow precise identification and represent a diagnostic challenge when examined by light microscopy alone. Thus their diagnosis requires an integrated approach which includes immunophenotypic and genetic analysis [3]. Immunohistochemistry is now successfully integrated into the diagnostic routine, as they give valuable complementary information.4 SRCTs occur mostly in children and young adults. They tend to involve the skeletal system or soft tissue [3].

The most common neoplasms capable of presenting as a SRCT are Ewing's family of tumors, rhabdomyosarcoma, neuroblastoma, lymphomas, and desmoplastic small round cell tumor (DSRCT) [2, 5, 6, 7]. DSRCT is predominantly an intra-abdominal tumor which sometimes includes pleura and tunica vaginalis [3]. The present article selectively reviews the salient histopathological, immunohistochemical and cytogenetic features of small round cell tumors in the head and neck region.

Ewing's sarcoma Family of Tumors (ESFTs)
ESFTs are those group of highly malignant SRCTs which are characterized by phenotyphic heterogeneity i.e. lack of overt differentiation along a single pathway, non-specific histotypic markers or complex patterns of multi-lineage differentiation with co-expression of neural, mesenchymal and epithelial traits.8 ESFTs comprise osseous and extra osseous Ewing's sarcoma (ES), peripheral primitive neuroectodermal tumor (pPNET), and Askin tumor of the thorax. Roessner *et al*. classified them into three subgroups, namely typical Ewing's sarcoma (TES), atypical Ewing's sarcoma and peripheral neuroectodermal tumor (PNET) [9]. ES and PNET are closely related tumors with the same t(11:22)(q24;q12) translocation. They represent opposite ends of ES family of tumors that ranges from undifferentiated neoplasms (ES) to morphological evidence of neural differentiation (PNET) [10]. In the Intergroup Ewing's Sarcoma Study (IESS) approximately 4% of the primary bone tumors arose in the bones of the head and neck [11]. Bone and soft tissue EFTs in the head and neck have been reported to represent anywhere from 1–7% of EFTs in some studies [13].

Histopathology: Conventional: The bone marrow is filled with monotonous population of round blue cells that acquire a nested, sheet-like or solid pattern without any intervening stroma. As the tumour invades soft tissues or periosteum, the stroma consists of reticular network and abundant vasculature and presents a filigree pattern (lace-like rest of tumoral cells enveloped in a dense fibrillar matrix). It shows three types of cells with transitional forms between them:

a. Principal / tumoral cells: small blue round cells, cell contours are less defined with scarce cytoplasm.
b. Dark cells: condensed chromatin and scarce cytoplasm conforming apoptotic figures.
c. Clear cells with poorly defined cytoplasmic borders filled with abundant amounts of glycogen which is considered a specific marker [14, 15].

Vessels with hyalinised walls, surrounded by a rim of neoplastic cells are associated with necrosis which may be focal or extensive. Inflammatory cells are usually absent. Parallel rims of reactive bone consisting of osteoblasts, chondroblasts and giant osteoclasts are seen deposited in onion skin lamellar pattern.

Atypical: As compared to conventional ES, the cells are larger in size (20-24µm) and heterogeneous in morphology with better delimited cell contours. The cells consist of eosinophilic cytoplasm with irregular, grooved nuclei [14, 15].

PNET or ES with neuroectodermal differentiation:14 Morphological features are similar to conventional ES with at least one third of the tumor showing Homer-Wright rosettes

or pseudorosettes (includes a group of six to ten cells oriented towards a central core filled with fibrillar material). The nuclei of cells is round or elongated with condensed chromatin. In another pattern, a fibrillary background which may adopt a lobulated configuration intermingled with less densely packed cell population may be seen. Nests of tumoral cells remain within the collagen bundles.

Immunohistochemistry: Both ES and PNET express the membrane antigen p30/32MIC2/HBA71/CD99 or 12E7/O13; a MIC2 gene product. P30/32 and 12E7 are different epitopes on MIC2 gene product. Although, CD99 is not specific for ES/PNET (expressed even by lymphoblastic leukemias, weakly by alveolar rhabdomyosarcoma etc), combination with other markers like Friend Leukemia Integration 1 Transcription Factor (FLI1) - a gene product belonging to E-twenty six (ETS) transcription factor, Human Natural Killer 1 (HNK1)- a neuronally expressed adhesion molecule and caveolin-1 a product of a gene CAV 1 that encodes slowly inactivating L-type voltage-dependent calcium channel in skeletal muscle cells, gives more accurate diagnosis and helps to avoid erroneous diagnosis. Neuronal markers like neuron-specific-enolase, S-100, etc are positive in PNET but the cells are negative for chromogranin and synaptophysin [14, 16, 17].

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is composed of neoplastic mesenchymal cells showing varying degrees of striated muscle cell differentiation. It accounts for about 5% to 10% of all childhood malignancies [18]. Head and neck RMS when compared to other parts of the body have a distinct prognostic and biologic behaviour. They are anatomically divided into two categories: Parameningeal -- consisting of RMS of nose, nasopharynx, paranasal sinuses, middle ear, mastoid, infratemporal fossa and pterygopalatine fossa. Non-parameningeal -- consisting of RMS of the scalp, orbit, parotid gland, oral cavity, oropharynx and larynx [18] Horn and Enterline (1958) described four histologic subtypes of RMS: Pleomorphic, Embryonal, Alveolar and Botryoid types. Only embryonal RMS (generally seen in children) and alveolar RMS (common in adults) belong to the family of small round cell tumors [10].

The intergroup rhabdomyosarcoma studies have shown that in head and neck region 71% of tumors were of embryonal type and 13% of alveolar type.19 According to a study by J. Hicksa and C. Flaitz, primary head and neck rhabdomyosarcomas occur in 35% of children.20

Embryonal Rhabdomyosarcoma: (E-RMS)

According to the World Health Organization, E-RMS is "a variant of rhabdomyosarcoma featuring sheets of primitive round and differentiating rhabdomyoblasts admixed in various proportions" [10]. This lesion is named for its remarkable resemblance to developing muscle in embryos and foetus. Just as embryonal skeletal musculature appears to condense out of a primordial soup of gelatinous matrix and primitive mesenchyme, so is embryonal rhabdomyosarcoma and is typified by alternating areas of cellular condensation and laxity [21]. The tumor cells vary from being small undifferentiated round or spindle shaped cells to number of differentiated cells with eosinophilic cytoplasm characteristic of rhabomyoblasts floating in a sea of primitive mucous ground substance. Cross-striations are discernible in 50–60% of cases [1, 21].

Alveolar rhabdomyosarcoma: (A-RMS)

Most of these tumors are composed of round cells with scanty cytoplasm and nuclei that is uniform in size and shape with coarse chromatin. Sometimes it consists of one or two prominent nuclear folds. Nuclear necrosis and pyknosis with high mitotic activity is usually observed [10]. A-RMS usually consists of two patterns:

1. Classic: Are highly cellular, poorly differentiated, and aggressive-appearing lesions that typically form nests separated by a prominent framework of fibrovascular septa. From this fibrous buttress hang rows of tumor cells, with loss of tumor cell cohesion in the periphery of the alveolar nests and increased cohesion in their central portions [10, 21].
2. Solid: These variants show crowded, highly cellular, undifferentiated round cell without fibrovascular septa. Solid alveolar rhabdomyosarcomas have biological features and clinical behaviour identical to those of typical alveolar rhabdomyosarcomas [21].

Immunohistochemistry: Cells are positive for desmin and muscle-specific actin. A more sensitive maker for this tumor is MAB 5.8A, which recognizes the MyoD1 gene product. MYoD1 is a DNA-binding phosphoprotein that binds to the enhancer sequence of muscle-specific genes, regulating their transcription. Another specific marker is myogenin which is detected at the early stage of myogenic differentiation [22].

Cytogenetics: Alveolar RMS shows t(2;13)(q35;q14) translocation. The genes involved are PAX3 (paired box gene) on chromosome 2 and FKHR (Forkhead domain) on chromosome [13]. Embryonal RMS are usually hyper-diploid and do not show t(2;13). There is loss of heterozygosity for 11p15 region. The neoplasms have extra copies of chromosome [2, 8, 9, 11, 12] and [13, 8].

Olfactory Neuroblastoma

Primary pediatric head and neck Neuroblastoma is rare, with metastatic disease being the more common mode of involvement in this anatomic region [25]. Esthesino neuroblastoma (ENB) or Olfactory neuroblastoma is an uncommon malignant neoplasm of the nasal vault which was first described in 1924, in French literature. ENB represents about 5% of all nasal malignant tumors [24].

Skolnik *et al*. were able to find only about 100 reported cases in the world literature up to the year 1966. More recently, Broich and colleagues have found about 1000 new cases of ENB being reported [25]. According to a study, the mean age at presentation was 53 years, (range: 40-70years) with a moderate male predominance (male:female ratio being 55:45) [47].

Histopathology: ENB is thought to originate from basal cells of olfactory epithelium which express neural cell adhesion molecule and the mammalian homologue of Drosophila-achaete-scute (MASH) gene [25]. Cantrell *et al*. described characteristics of ENB as a lesion which is compartmentalized into lobules by slender vascular fibrous septa. The lobules contain cells with almost nonexistent cytoplasm, round nuclei with sharply defined chromatin and plexiform intercellular fibrils. True rosettes/ Flexner-Wintersteiner rosettes (consists of spaces lined by columnar

cells with nuclei oriented radially around the space) and pseudorosettes / Homer Wright rosettes are seen. Cytoplasm shows secretory granules similar to catecholamine granules [24, 25]. Robert *et al*. classified this tumor into three different types considering its clinical and histopathological appearance:

1. **Pattern I:** A tumor with sheets of small, round cell separated by connective tissues septa; pseudorosettes or Homer Wright rosettes are seen.
2. **Pattern II:** Consists of cells with round to oval nuclei with clear nuclear membranes, scanty cytoplasm and indistinct cell borders. True rosettes or Flexner-Wintersteiner are seen.
3. **Pattern III:** Pattern similar to neuroblastoma with production of neuropil, a wispy, light pink, fibrillar material produced by undifferentiated neuroblasts. Rosettes are seen with abundant haemorrhage, fibrosis and hemosiderin deposition. Clusters of lymphocytes and islands of dystrophic calcification are seen [24].

Immunohistochemistry: The cells are positive for neuron specific enolase and neural filament protein. S-100 and vimentin are positive in sustentacular cells [22].

Cytogenetics: In nineteenth century, ENB tumours were found to express HASH, the human homologue of the MASH gene. The demonstration by RT-PCR of HASH gene expression, although still investigational, could become the diagnostic procedure of choice to detect ENBs [25].

Malignant Lymphomas

Lymphomas are the heterogeneous group of clonal malignant disease that share the single characteristic of arising as the result of somatic mutation in a lymphocyte progenitor. A lymphoma may arise in lymph nodes or any organ, either by spread from lymphatic sites or as a manifestation of primary extranodal disease [26]. According to studies done by Pecorari *et al*. and Eisenbud *et al*., Lymphomas are the third most frequent malignant tumor of the maxillofacial region following squamous cell carcinoma and salivary gland neoplasms. According to Epstein *et al*. it is the second most common malignant disease in the oral region [27]. Most of the head and neck lymphomas are of B-cell origin [28]. Traditionally, the lymphomas are divided into Hodgkin's (HL) - shows presence of Reed-Sternberg cells and Non-Hodgkin's lymphomas (NHL) - no Reed Sternberg cells are seen because of their difference in histology and pattern of behaviour [27, 29].

Non-Hodgkin's lymphoma

NHLs are much less predictable than Hodgkin's disease and have a far greater predilection to disseminate to extra nodal tissues.27 Lymphomas account for 50% to 59% of the head and neck malignant neoplasms in children. A decided majority of non-Hodgkin's lymphomas arise in lymph nodes, 24% of these malignancies arise in extra nodal sites. Lymphomas arising within the oral cavity accounts for less than 5% of all oral malignancies and approximately 85% of the lesions involve the tonsils and palate [29]. To date, only 12 cases of the non-Hodgkin's lymphoma of the tongue has been mentioned in the literature [30]. Diffuse large lymphomas is most frequently encountered type27 and comprised of 50% of oral lymphomas in one series of study [26].

The frequent lymphomas occurring in nasopharynx and Waldeyer's ring are small B-cell lymphomas such as small lymphocytic lymphoma, mantle cell lymphoma, natural killer (NK)/T cell lymphomas and follicular lymphoma. In salivary glands, mucosa associated lymphoid tissue (MALT) lymphomas are common. The other types include plasmablastic lymphoma and Burkett's lymphoma [31]. In a study, diffuse large cell lymphoma (Fig 4) was diagnosed in 38% and small cell lymphoma in 27.4% of cases. The rest of the cases include plasmacytoma, Immunoblastic lymphomas and Burkett's lymphoma [29]. Increasing number of HIV cases present with oral lymphomas especially plasmablastic lymphomas [31, 32]. Some of the features of commonly found NHL in head and neck region along with IHC and cytogenetic features are elicited in Table 1.

Hodgkin's Lymphoma (HL)

Characterized histologically by infiltration of the involved organ with Reed-Sternberg or Hodgkin's cells in an appropriate cellular background [34].

Histopathology: WHO classifies Hodgkin's lymphomas as:

- Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL): Multiple crowded or well-separated nodules consisting of bland-looking small lymphocytes interspersed with pink-staining histiocytes. L and H cells are found within or in between the nodules. IHC shows L and H cells to be positive for CD 20, BCL-6, J-chain, EMA and CD 40, polytypic B lymphocytes (Ig M and Ig D +) and CD 3+ T lymphocytes form rosettes around L and H cells.
- Classical Hodgkin lymphoma
- Nodular sclerosis: Lymph node capsule is thickened with multiple broad birefringent vascularised collagen bands extending into the parenchyma resulting in the formation of multiple nodules. The nodules shows presence of lacunar cells arranged singly, in aggregates or in sheets. The background shows small lymphocytes, plasma cells, eosinophils, neutrophils and histiocytes.
- Mixed cellularity: The lymphnode is partially or fully effaced and consists of RS cells in the background of eosinophils, neutrophils, lymphocytes, plasma cells and histiocytes.
- Lymphocyte rich classical HL: Characterized by diffuse or nodular growth consisting of mononuclear and rare diagnostic RS cells scattered in a background of small lymphocytes. Do not show presence of L& H cells.
- Lymphocyte depletion: Two types:
- Diffuse fibrosis type: Diagnostic RS cells are rare with background showing disorderly distributed reticular, fibrous and amorphous, proteinaceous material. There is depletion of all cellular elements.
- Reticular Type: Hypercellular with abundance of RS cells but other mature inflammatory cells are sparse. Disordered non-birefringent fibrosis and necrosis are present [34].

Immunohistochemistry: The Hodgkin's or RS cells (H-RS cells) are positive for CD30, CD15 (forms paranuclear globule with or without cell membrane staining), HLA-DR, CD25, CD40, CD138 and negative for BCL-6, J-chain and EMA. Background cells are usually CD4+ve. Latent membrane protein 1 is positive if the patient is EBV infected. IHC in NLPHL shows L and H cells to be positive for CD 20,

BCL-6, J-chain, EMA and CD 40, polytypic B lymphocytes (IgM and IgD+) and CD 3+ T lymphocytes form rosettes around L and H cells [35].

The Hodgkin's or RS cells (H-RS cells) are positive for CD30, CD15 (forms paranuclear globule with or without cell membrane staining), HLA-DR, CD25, CD40, CD138 and negative for BCL-6, J-chain and EMA (Epithelial Membrane Antigen). Background cells are usually CD4+ve. Latent membrane protein (LMP) 1 is positive if the patient is EBV infected.34 Variants of RS cells [37]

1. **RS cells of lymphocytic and histiocytic (L and H) type:** These RS cells with folded, overlapping nuclear lobes (popcorn) are commonly observed in the lymphocyte predominance type.
2. **RS cells of Lacunar type:** Characteristic for the nodular sclerosis type of Hodgkin's lymphoma, these cells have abundant, lightly acidophilic or water-clear cytoplasm, lobulated nuclei and small nucleoli.
3. **RS cells of anaplastic type:** Commonly seen in the lymphocyte depletion type, these cells are large and markedly pleomorphic, with hyperchromatic bizarre nuclei with prominent nucleoli.
4. **RS cells of mummified variant:** A degenerated or apoptotic cell that may be seen singly or in clusters. Cells have darkly staining eosinophilic cytoplasm and a dense pyknotic nucleus.

Hodgkin's cells: 37 Neoplastic large ovoid cells with indistinct cell borders, indented vesicular nucleus with thick nuclear membrane and huge hyperchromatic intensely acidophilic nucleolus.

Reed-Sternberg cell: (RS cells): Large cell with two or more often mirror-image nuclei, each containing a single prominent nucleolus. The nucleoli are typically large and round and often resemble inclusion bodies. Chromatin is usually condensed at the nuclear membrane, giving rise to a thickened nuclear border and a clear halo-like space around the nucleolus. The cytoplasm is abundant and slightly eosinophilic.42

Cytogenetics: Translocation, t(11;22) (q24;q12) i.e., fusion between the 5'end of the EWS gene from chromosome band 22q12 with the 3' portion of the 11q24 FLI1 gene is seen. This EWS/ETS fusion protein blocks the differentiation of pluripotent marrow stromal cells. Rest 10-15% of the cases have t(21;22) (q22;q12) fusing EWS to a closely related ETS gene.16

Table 1: Features of NHL (DLBCL: Diffuse large B-Cell lymphoma, CD: Cluster of Differentiation, NF: Neurofilament, BCL: B-Cell lymphoma, EBV: Epstein - Barr virus, MALT: Mucosa associated lymphoid tissue, TCR: T-cell receptor, HIV: Human Immunodeficiency virus, LMP: Latent membrane protein, SLL: Small lymphocytic lymphoma, CCL: Centrocyte-like)

S. No	Small round cell tumor	Immunohistochemistry	Cytogenetics
1.	Ewing's sarcoma Family of Tumors	P30/32 and 12E7 along with FLI1, HNK, and CAV1	1. t(11;22)(q24;q12) 2. t(21;22) (q22;q12): 10-15% of cases
2.	Rhabdomyosarcoma	MAB 5.8, myogenin	1.t(2;13)(q35;q14)
			2.Loss of heterozygosity for 11p15 region
			3.extra copies of 2,8,9,11,12 and 13
3.	Olfactory Neuroblastoma	NSE, NF, S-100	Express HASH gene
4.	Non-Hodgkin's Lymphoma	Summarized in table 1	Summarized in table1
5.	Hodgkin's lymphoma	H-RS positive for CD30, CD15, CD40	Gains of 2p, 9p, 16p, 17q, 19q, 20q, and losses of 6q, 11q, and 13q.

Table 2: Summary of immunohistochemical and Cytogenetic feature of SRCTs

S. No	Name of the tumor	Age	Histopathological Feature	IHC	Cytogenetics
1.	Small cell ostosarcoma:2,43	Peak in 4th decade of life	The cells grow in solid nests or in lobules with densely cellular central areas and decreasing cellularity with deposition of more extracellular material (osteoid) at the periphery	Osteocalcin Osteonectin	CBFA 1 gene positive.
2.	Round cell liposarcoma: 2,43	adults, rarely children	Round to angulated small cells containing one or more lipid droplets, arborizing vasculature, scant myxoid matrix	Vimentin and S-100 positive.	t(12:16) (q13:p11)
3.	Poorly differentiated synovial sarcoma: 2,43	Adults	The tumor arises from pluripotential mesenchymal cells near joints surfaces, tendons - rarely involves head and neck region. Solid small cell areas with round to oval nuclei and scant cytoplasm.	Cytokeratin, EMA positive.	t(X:18) (p11:q11).
4.	Small cell melanoma: 2,43	Adults	Primitive small cells with scant cytoplasm. Ultrastructure shows melanosomes.	Positive for S-100, Human Melanoma Black -45 (HMB-45).	Chromosomes 1, 6, 7, 9, and 10 are preferentially affected.
5.	Mesenchymal chondrosarcoma: 43	peak in second decade	Primitive small oval and round cells, hemangiopericytoma vascular pattern, islands of cartilage or hyalinization.	CD 99, S-100 positive and collagen II positive.	Has unique del (13; 21) (q10; q10) translocation.

6.	Small cell carcinoma:44	Median age 60 years.	Oval to angulated cells with hyperchromatic nuclei and scant cytoplasm, destructive growth pattern, necrosis.	Positive for epithelial membrane antigen, cytokeratin, and chromogranin.44	
7.	Merkel cell carcinoma: 45	Adults	Tumor originates either from neural crest or stem cell and consists of small blue round cells.	Positive for CK 20 (paranuclear dot), NSE, NF, EMA, chromogranin, and synaptophysin.	

Conclusion

A precise histological diagnosis of SRCTs was of less relevance when treatment simply involved resection and radiotherapy, but the continued development of disease-specific therapeutic strategies, and the concomitant improvement in prognosis, has rendered accurate tumour diagnosis and classification of paramount importance. Thus, a correct diagnosis is essential for patients with a small round cell tumour. 49 Since these tumors are morphologically similar, a combination of histopathology, immunohistochemistry and cytogenetics helps in accurate distinction.

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