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ROUND CELL MALIGNANCIES OF ORAL AND MAXILLOFACIAL REGION- AN OVERVIEW

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ABSTRACT
Round cell tumors comprises of a wide group of malignancies predominantly affecting the children and adolescents. They include various malignancies of epithelial, neuroectodermal, lymphoreticular and mesenchymal origin. They are referred to as round cell tumors because they present themselves as small, relatively undifferentiated proliferation of round cells with higher nuclear hyperchromatism and increased nuclear cytoplasmic ratio in light microscopy. The diversity of the lesion and their uniform morphological appearance poses a great diagnostic challenge for the pathologist. Recently, with addition of cytogenetic, the diagnosis has been made quite easy for the pathologist. Adjuvant diagnostic parameters include immunohistochemistry, comparative genomic hybridization, polymerase chain reaction and fluorescence in situ hybridization. This article briefly reviews the various aspects of round cell tumors occurring in the maxillofacial region.

Keywords– Round cell, Immunohistochemistry, Cytogenetic, Histopathology.

INTRODUCTION

Small round cell tumors are group of neoplasm consisting of a pool of round cells with higher nuclear - cytoplasmic ratio. Tumor architecture depicts small round uniform cells with nuclei, containing fine chromatin, scanty or clear eosinophilic cytoplasm. Some tumors show large, ovoid or spindle-shaped with prominent nucleoli and irregular borders[1]. These round cell tumors lack unique morphological features creating a diagnostic challenge for the pathologists when evaluated under light microscope. Hence to make a conclusive and definite diagnosis, additional techniques such as immunohistochemistry and molecular based analysis often become necessary. Chromosome rearrangements which are specific and associated with particular tumor types also serve as a hallmark of the underlying genetic changes. Early and prompt diagnosis is the key for the initiation of treatment and also influences the prognostic outcome for the patients affected by this group of tumors. The most commonly occurring round cell tumors in oral and maxillofacial region includes Rhabdomyosarcoma, Ewing's sarcoma, Lymphomas and Olfactory neuroblastomas.

Round cell tumors of head and neck region

1. Lymphomas
2. Rhabdomyosarcoma
3. Ewing's Sarcoma
4. Peripheral Neuro Ectodermal Tumor
5. Neuroblastoma
6. Merkel Cell Tumor
7. Squamous Cell Carcinoma (Poorly Differentiated)
8. Plasmacytoma
9. Multiple Myeloma
10. Langerhan's Cell Disease
11. Desmoplastic small round cell tumor

RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) are a morphologically and clinically heterogeneous family of malignant soft tissue tumors related to the skeletal muscle lineage. They are the most common soft tissue neoplasm of pediatric population comprising approximately 5% of all childhood tumors and nearly 50% of soft tissue sarcomas arising in 0 - 14 years old children [2]. ERMS accounts for 70-80% of all RMS, and usually occurs in young children (median age of 6.5 years). ARMS accounts for the remaining 20-30% of RMS, and often occurs in older children and young adults (median age of 12 years). The most commonly affected sites are head and neck regions, genitor-urinary tract and extremities [3].Alveolar RMS and Embryonal RMS represent the two main histological patterns that must be differentiated from other small round cell tumors.

EMBRYONALRHABDOMYOSARCOMA

According to WHO , Embryonal Rhabdomyosarcoma presents itself as sheets of tumor cells ranging from small round to large elongated cells exhibiting varying degrees of myogenic differentiation [4]. Cell density often varies with highly cellular areas alternating with low cellular areas in a loose myxoidstroma. The lesion has a unique similarity to a developing muscle in fetus and embryo.

ALVEOLAR RHABDOMYOSARCOMA

The classical form of Alveolar RMShistopathologicallyshows distinctive nests of primitive-appearing round cells in a discohesive fashion. They are surrounded by hyalinized and highly vascular fibrous septa producing a pattern reminiscent of the alveoli of the lung [5]. Mitotic activity is very high along with pyknosis and necrosis[6].The nested pattern and cellular discohesion seen in the classical form is not seen in the solid form of RMS .

Cytogenetics

Most cases of RMS occur sporadically without an apparent genetic predisposition. Most of the alveolar RMS cases are distinguished from Embryonal RMS and other solid tumours by the presence of one of two recurrent chromosomal translocations, which generate related fusion genes. t(2;13)(q35;q14) generates PAX3 - FOXO1 in 60% of alveolar RMS cases generates PAX7 - FOXO1 in20% of Alveolar RMS cases[7]. These translocations are said to result in altered expression, function, and sub cellular localization of the fusion products relative to the wild-type proteins contributing to the oncogenic behaviour by modifying growth, differentiation, and apoptosis pathways. Embryonal RMS is characterised by loss of heterozygosity on the short arm of chromosome 11 (11p15.5), suggesting inactivation of a tumour-suppressor gene[8]..In a study by Gordon T et al, thirty-six percent of the Embryonal RMS cases involved translocation breakpoints in the 1p11-q11 region. Alveolar RMS also demonstrated the presence of extra copies of chromosome 2,8,12 and 13[9].

Immunohistochemistry

Alveolar RMS typically expresses vimentin and muscle-specific antigens, such as desmin, muscle actins (including smooth muscle isoforms), myogenin and MyoD1.The most effective marker for this tumor is MAB 5.8A, which has the ability to locate and recognize MyoD1 gene. MyoDl is a specific and sensitive marker of RMS allowing its distinction from other small round cell tumours.R1.Myogenin can also be used for early detection of myogenic differentiation [10].

LYMPHOMAS

Malignant lymphomas represent approximately 5% of all malignant neoplasm of the head and neck and may involve nodal or extranodal sites. Malignant lymphomas are classically divided into two subgroups, Hodgkin's lymphomas (HLs) and non-Hodgkin's lymphomas (NHLs) depending on the presence or absence of Reed-Sternberg cells respectively. NHL has got a poorer prognosis as it presents itself in disseminated form at the time of diagnosis. Cervical lymphadenopathy is the most frequent head and neck presentation in both HL and NHL. The most common location of HL nodes is the lower cervical or supraclavicular region. HL usually arises in a single node or chain of nodes and spreads to a contiguous node or chain. NHL spreads more commonly to non-contiguous nodes. Abdominal involvement is more common in NHL. The head and neck region is the second most frequent anatomical site of extranodal lymphomas (after the gastrointestinal tract) [11]. About 50% of the of the extranodal lymphomas of the head and neck are located in Waldeyer's ring. Lymphomas arising within the oral cavity accounts for less than 5%. Lytic bone destruction can be caused by highly aggressive mature B-NHL

Cytogenetics:

Cytogenetic analysis has become a regular procedure for diagnosis for lymphoid malignancies. Cytogenetic abnormalities were first described in Burkitt's lymphoma. Translocation t (8;14)(q24;q32) in which the *MYC* gene and immunoglobulin heavy chain gene complex are involved. B-Cell lymphomas, which make up approximately 85-90% of lymphomas, are associated with cytogenetic changes of 12, 13q14, 14q32, 2p11, and 22q13. Recurrent translocations can be detected in > 90% of the cases of Burkitt's lymphoma, mantle cell lymphoma and follicular lymphoma. In diffuse large B cell lymphoma, multiple breakpoints and translocations are seen. B-Cell lymphomas,

which make up approximately 85-90% of lymphomas, are associated with cytogenetic changes of 12, 13q14, 14q32, 2p11, and 22q13. Translocations help to support the diagnosis of follicular cell lymphoma t(14;18),(q32;q21), mantle cell lymphoma t(11;14)(q13;q32), and Burkitt's lymphoma t(2;8),t(8;14) and t(8;22). T-Cell lymphomas may show changes in 14q11, 7 p or 7q (30). The features of Non-Hodgkins lymphomas are summarized in Table: 1.

Cytogenetics – Recently, study by Christian Steidet,al, more than 20% of cases showed number of alterations which included gains of 2p,9p,16p, 17q,19q and 20q and losses of 6q, 11q and 13q [12].

Immunohistochemistry- Immunohistochemistry (IHC) with various antibodies identifies the specific lineage and developmental stage of the lymphoma. A panel of markers is decided based on morphologic differential diagnosis (no single marker is specific) which includes leukocyte common antigen (LCA), B-cell markers (CD20 and CD79a), T-cell markers (CD3 and CD5) and other markers like CD23, bcl-2, CD10, cyclinD1, CD15, CD30, ALK-1, CD138 (based on cytoarchitectural pattern).The RS cells can express B- lineage antigens (CD20, CD79a). Lymphoma which exhibits B-cell differentiation expresses PAX5, CD20 and CD79a. Secondly the T-cell markers includes CD2, CD3, CD4, CD5, CD7 and CD8.

Histopathology - The diagnosis of Hodgkin's lymphoma is mainly based on histological finding of Reed-Sternberg cells. Reed-Sternberg cells are large, with two or more mirror-image nuclei, which contain a single prominent nucleolus. Condensation of chromatin is noticed at nuclear membrane. Cytoplasm with mild eosinophilic areas are appreciated [13].

WHO classification of Hodgkin's lymphoma

Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis (Majority)
Mixed cellularity
Lymphocyte-rich (5%)
Lymphocyte-depleted (1%)

EWING'S SARCOMA FAMILY OF TUMORS

Ewing's sarcoma family of tumors group of tumors are characterized by morphologically similar round-cell neoplasm .It includes osseous and extraosseous Ewing's sarcoma, peripheral neuroectodermal tumors (PNET), and Askin'stumor. ESFT have a wide spectrum of neural differentiation, have a uniform immunohistochemical, cytogenetic, and molecular uniformity and identical response to Ewing-based chemotherapy regimens. So it was determined that these sarcomas are related and that they originate from unique mesenchymal stem cells capable of multilineage.

Differentiation [14,15]..Ewing sarcoma (ES) and primitive neuroectodermal tumor (PNET) are closely related, high-grade, round-cell tumors with a neuroectodermal phenotype. ES usually develops in bone and is more undifferentiated, while PNET tends to involve soft tissue and demonstrates more pronounced neuroendocrine features.

Ewing's sarcoma is the third most primary sarcoma of bone after osteosarcoma and chondrosarcoma. It occurs most commonly in children and adolescents. It is an aggressive osteolytic tumor with propensity for dissemination. Local regional pain is the most common symptom. Pain can be intermittent in nature and does not completely disappear during night time[16].. Histologically, Classic Ewing's sarcoma, as first described by James Ewing in 1921, shows a monotonous population of small round cells with increased nuclear to cytoplasmic ratio[17]. Mitotic activity is generally less. These tumor cells contain glycogen which can be expressed in periodic acid Schiff stain.

Cytogenetics- There is a translocation of t (11;22) (q24;q12) which leads to the fusion of 5' end of EWS gene from chromosome band 22q12. Following this rest of the cases have t (21;22) (q22;q12) mixes EWS and is related to ETS gene [18].

Immunohistochemistry- Both Ewing sarcoma and PNET express the membrane antigen p30/32MIC2/HBA71/CD99 or 12E7/O13; a MIC2 gene product.

PERIPHERAL NEUROECTODERMAL TUMOR

PNET is defined as a unique group of neoplasm of neuroectodermal origin with lots of cell differentiation[19]. They mostly involve the soft tissues. Tumor presents itself as a very aggressive lesion with lots of local recurrence and metastasizing property to lungs, brain and lymph nodes, but till now only few cases have been noticed in head and neck region worldwide[20]. Coagulative necrosis is appreciated in most of the cases.

Immunohistochemistry- MIC-2 (CD99) positivity is noticed.

Histopathology- Histolgically, the presence of rosettes of Homer–Wright type, indicating neural differentiation holds the most important diagnostic criteria for PNET. ES/PNETs are made up of diffuse, densely cellular sheets of uniform, small tomedium-sized round cells with scant vacuolated cytoplasm . The nuclei are round witha fine, delicate to coarse chromatin distribution and small nucleoli (figure 2). Mitotic figures are common. Coagulative necrosis is frequently identified. Occasionally there is a greater degree ofnuclear pleomorphism with a rosette formation. Conceptually, the tumor is classified as a *small,round, blue-cell neoplasm*, which requires the application of special studies to confirm thediagnosis. The tumor cells contain glycogen, which is highlighted with a periodic acid-Schiff(PAS) stain (figure 2).

MULTIPLE MYELOMA

Multiple myeloma is defined as the cancer of plasma cells in bone marrow. Multiple myeloma accounts for almost 1% of all cancers and 10% of all hematological malignancy. Pathophysiology begins with the genetic alterations of B lymphocyte at the time of isotype switching which transforms the normal plasma cells into malignant myeloma cells. Clinical symptoms include bone pain, loss of weight, frequent urination, nausea and vomiting. Cytokine pathways which are held responsible for both osteoblast inhibition and osteoclast stimulation have been evaluated thereby increasing the better understanding of myeloma bone disease. Diagnostic criteria involve the tests for blood, urine, bone and bone marrow[21]. Initiation of pathogenesis begins with the emergence of limited number of plasma cells primarily called as monoclonal gammopathy of undifferentiated significance [22].

Cytogenetics-The pathogenecity of the disease can be taken into account due to genomic instability exhibiting translocations in heavy-chain immunoglobulins switches its regional position at 14q32 and over-expressed Cyclin D 9[22,23]. Recently many advances have been made in the field of molecular cytogenetic, gene and proteomic studies of tumor cells, which has enhanced the pathologists to come up with better understanding and frame the treatment protocols. Newer therapeutic drugs are used which directly inhibits osteoclast differentiation for treating these patients who have bone disease [24].

PLASMACYTOMA

Plasmacytoma are malignant tumors of plasma cells that can grow within soft tissue or within the axial skeleton. There are three distinct groups of plasmacytoma defined by the International Myeloma Working Group: Solitary Pasmacytoma of Bone (SPB), Extramedullary Plasmacytoma (EP) and Multiple Plasmacytomas that are either primary or recurrent. Solitary Plasmacytoma mostly occurs in the bones of the axial skeleton, such as vertebra and skull [1, 2].ExtraMedullary Plasmacytoma is generally observed in the head and neck and most frequently in the nasal cavity and nasopharynx. Extramedullary plasmacytoma (EMP) is a rare entity and accounts for around 3% of all plasma cell neoplasm. These malignant tumors have male predominance seen mostly in 6^{th} to 8^{th} decades of life[25]. The Extramedullary plasmacytoma is generally observed in the head and neck and most frequently in the nasal cavity and nasopharynx. Typical clinical feature shows pain, swelling and mostly nasal obstruction due to the tumor mass. Etiology is unknown but it involves around viruses, gene abnormalities, irradiation in reticuloendothelial system[26].The differentiation criteria for SBP and EMP from myeloma is lack of increased **c**alcium, **r**enal insufficiency, **a**nemia, or multiple **b**one lesions(CRAB Features).

Immunohistochemically – The neoplastic cells demonstrates monoclonality and stain with kappa and lambda light chain. These plasmacytoid cells are specific with CD138. The treatment option mainly comprises of chemotherapy, radiotherapy and bone-marrow transplant.

DESMOPLASTIC SMALL ROUND CELL TUMOUR (DSRCT)

This round cell tumor is a distinct entity which differs from the other childhood tumors because of its clinical features, morphology and immunohistochemical features. DSRCTs occur in the adolescent males and are located in the intra abdominal, pelvic, retroperitoneal and scrotal sites. These are aggressive tumors with 90% mortality within 6 months to 4 years of diagnosis. Histolgically, the DSRCTs show a nesting growth pattern of small round blue tumor cells separated by a desmoplastic stroma. reaction. The amount of tumor cells versus stroma varies from field to field. In the more desmoplastic areas, tumor cells may be arranged as thin trabeculae or in a single-file fashion. Peripheral palisading of the tumor cells can be observed in some nests. Rosette like structures may be observed. Tumor cells are small to medium-sized, with round to oval hyperchromatic nuclei and inconspicuous nucleoli. The cytoplasm of tumor cells is usually scanty, and cell borders are indistinct[27].

Immunohistochemistry- Reveals divergent differentiation with epithelial (Fig. 3B), myogenic (Fig. 3C) and neural markers

Cytogenetics- A t(ll;22)(pl3;ql2) has been described in certain tumors. This involves the fusion of the *EWS* gene with the Wilm's tumor 1 gene (*W11*).

MERKEL CELL CARCINOMA

Merkel cell carcinomas are defined as an aggressive rare malignant lesion which is more often fatal. The Merkel cells where first described by Friedrich Merkel in 1875 as clear cells related with nerve fibers[28]. Clinically, lesion presents itself as rapidly growing, asymptomatic, reddish-blue cutaneous papule or nodule that develops over the due course of time. The most common clinical features of Merkel cell carcinoma is by the acronym AEIOU: asymptomatic, expanding rapidly, immunosuppression, older than 50 and UV-exposed location[29].These carcinomas are dermally placed and their cells exhibit ill-defined, scanty cytoplasm, and round vesicular nuclei with "salt and pepper" chromatin and few mitotic figures.

Immunohistochemistry -CK20stains nearly 80-90% of all Merkel cell carcinomas in a unique paranuclear dot-like pattern [30]. These cells also stain positively with neuroendocrine markers such as chromogranin A, neuron-specific enolase and synaptophysin[31].

OLFACTORY NEUROBLASTOMA

Olfactory Neuroblastoma or Esthesioneuroblastomais a rare neoplasm of neuroectodermal origin mainly composed of neuroblasts which are derived from olfactory membrane of sinonasal tract [32, 33]. The first case was first described by Berger and Luc iin 1924..It is a very uncommon and comprises about 2% of all sinonasal tract tumors with an incidence of approximately 0.4 per million population[34,35]. Olfactory neuroblastomas can have varying growth potential from an indolent growth to a highly aggressive neoplasm capable of rapid widespread metastasis[36]. The tumour spreads submucosally in all directions to involve paranasal sinuses,nasal cavity and surrounding structures like oralcavity, orbit and brain[35].This neoplasm has also been identified as a direct cause of ectopic arginine vasopressin production leading to inappropriate antidiuretic hormone secretion[37].

Histopathology- It shows a *lobular* architecture comprised of "primitive" neuroblastoma cells. The tumor cells are small, round, blue cells slightly larger than mature lymphocytes. The cells are often in a syncytial arrangement with a tangle of neuronal processes forming the background. The matrix is finely Fibrillar .There are two types of rosettes which can be identified.Pseudorosettes (Homer Wright) seen in up to 30% of cases, and true rosettes (Flexner-Wintersteiner) seen in about 5% of cases. The delicate, neurofibrillary and edematous stroma forms in the center of a cuffing or palisaded arrangement of cells in Homer Wright pseudorosettes while a "gland-like" tight annular arrangement is seen in Flexner-Wintersteiner rosettes. The latter is comprised of gland-like spaces lined by non-ciliated columnar cells with basally placed nuclei [36].

Immunohistochemical studies - Olfactory Neuroblastomas shows positivity for synaptophysin, chromogranin, CD 56, neuron specific enolase, NFP and S-100 protein. The small round cells are usually positive for the first five markers whereas the S-100 protein-positive cells are found at the periphery of the tumor lobules and correspond to Schwann (sustentacular) cells. These same peripheral cells may be positive with glial filament acidic protein (GFAP)[36].

Cytogenetics–When ON where analyzed using array comparative genomic hybridization demonstrates chromosomal gains in 7q11 and 20q and deletions in 2q, 5q, 6p, 6q, and 18q have been confirmed. The *HASH1* gene is involved in olfactory neuronal differentiation and is expressed in immature olfactory cellsthus distinguishing Olfactory neuroblastomas from other poorly differentiated small blue cell tumors [38]. DNA over expression on the entire chromosome 19, few gains of the long arm of chromosomes 8, 15 and 22 and deletion of the entire long arm of chromosome 4.

CONCLUSION

Round cell tumors are a wide variety of malignant neoplasms. Hematoxylin and eosin section along with immunohistochemistry provides the diagnostic backbone for these types of tumors. Early detection also improves the prognosis. Antigenic markers, both positive and negative approaches will render an accurate characterization for such tumors. Recently, better molecular genetic studies and markers has enhanced the diagnosis and prognosis for these tumors.

Table:1: The features of Non-Hodgkins lymphomas

TUMOR	HISTOPATHOLOGY	IMMUNOHISTO CHEMISTRY	CYTOGENETICS
Diffuse large B cell lymphoma	• Large irregular or lobated nuclei, • Size equal to or exceeding the nuclei of normal macrophage with scant cytoplasm.	Positive for CD20, CD45 and	t(14;18)(q32;2), gains of 3q, 18q21-q22 and loss of 6q21-22.

	• 2 types: -Germinal centre like DLBCL. -Activated peripheral blood B-cell type	monotypic Ig, CD 10, BCL 6	
Small lymphocytic lymphoma (SLL)	• Proliferation of non-activated, mature looking small lymphocytes selectively involving the interfollicular regions or B-zones of the node	CD 20 +ve, Ki 67 index is low	Deletions of 13q14.
Follicular lymphoma	• Nodular growth of monotonous cells. • Three types: 1. Contains small cells (size of normal lymphocyte) 2. Has large cells (2 to 3 times the size of normal lymphocyte, resembles mitotically active germinal centre cell) 3. Intermediate (contains both small and large lymphocytic cells). • Internodular and intercellular reticulin is more abundant.	CD19, CD20, CD10, BCL-2 positive.	t(14;18)(q32;q2)
Mantle cell lymphoma	• Medium to large sized monomorphic round neoplastic cells • Arranged in diffuse or nodular pattern, • Hyalinised small blood vessels, and scattered epithelioid cells..	Positive for CD5, CD20, CD43, BCL 1, negative for CD10, BCL 6	t(11;14)(q13;q32).
Plasma cell neoplasias	• Three types: 1)Multiple myeloma (multiple bones involved), 2)Solitary bone plasmacytoma, and 3)Extramedullary plasmacytoma. • Shows proliferation of mature and immature plasma cell (eccentrically placed nuclei with cartwheel appearance), • bone marrow plasmacytosis, osteolytic lesions, • M-protein in serum, and • Bence-Jones protein in urine.	To identify monoclonal immune-globulins i.e., Ig G, lambda, Ig kappa.	t(8;14), t(2;8) or t(8;22),.
Plasmablastic lymphoma	• Found in HIV infected patients, • Diffuse infiltration of large neoplastic cells in the oral submucosa with eccentrically placed nuclei.	CD 4-ve, and CD2-ve and CD79a + v	
Burkitt's lymphoma	Three variants: 1. Endemic: African children. Epsten Barr Virus (EBV) + in most . 2. Sporadic: Occurs in all geographic areas. EBV + in 15%-30% of cases. 3. Immunodifficiency associated: Common in HIV+ patients. May show plasmacytoid differentiation. Uniform or slightly pleomorphic medium sized cells, moderate amount of cytoplasm, squaring off edges between the neighbouring cells, starry sky pattern due to admixed tingible body macrophages, high mitotic rate and necrosis.	Positive for CD 20, CD10	80% with t(8;14) translocation, 20% t(2;8) or t(8;22)
MALT lymphoma	• Observed in salivary glands, thyroid, stomach etc, • originate from marginal zone B cells, shows cellular heterogeneity with monocytoid B cells,	Positive for CD20, and surface Ig D. Negative for CD10, CD5	Trisomy 3, t(11;18) (q21;q21),27-32 t(1;14) (p22;q32),33 and t(14;18) (q32;q21). 34.49

	small lymphocytes, plasma cells, and occasionally large lymphocytes. • Two variants: 1)Few cases show prominent follicular growth pattern resulting from follicular colonization, absence of lymphoepithelial lesions, centrocyte-like (CCL) cells representing minimal plasma cell differentiation (follicular growth type). 2. Few cases show marginal zone distribution pattern of CCL cells, presence of colonized follicles lymphoepithelial lesions and plasma cells.		
NK/T cell lymphoma	• Tissue densely populated by abnormal lymphocytes (small, intermediate and large), • areas of necrosis and angiocentric and angiodestructive growth pattern.	CD56 +ve and CD2 +ve. Absence of surface CD3 but presence of cytoplasmic CD3.	Lack of TCR genes rearrangements.

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