Review Article

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ROUND CELL TUMORS OF THE ORAL CAVITY: AN INSIGHT ON SALIENT FEATURES FOR ORAL AND MAXILLOFACIAL PATHOLOGISTS

Ramakant Gupta[1], Swati Gupta[2], Manju Gupta[3]

1.PG Student, Department of Oral Pathology,Sudha Rustagi College of Dental Sciences and Research,Faridabad, Haryana
2.Consultant, Department of Dental Services, Asian Institute of Medical Sciences, Haryana
3.Counsellor, Gupta Clinic, Indra Complex, Faridabad

ABSTRACT:

Introduction: Round cell tumors, although rare in oral cavity; but imposes a diagnostic challenge for pathologists due to their undifferentiated or primitive character. Differentiating these from others still remains in enigma. An accurate tumor diagnosis is of paramount importance for disease-specific therapeutic strategies, and the concomitant improvement in prognosis

Objectives: To categorize round cell tumors based on the predominance of round cells in the histopathology of the lesions of the oral cavity and to summarize the salient histopathological, immunohistochemical and cytogenetic features of the same.

Materials and methods: Scientific databases i.e. PubMed and Google scholar were searched for the literature using key words – round cells, oral lesions, round cell tumors, histopathology and immunohistochemistry of round cell tumors. Relevant articles were selected for review. A brief review was done.

Results: The round cell tumors of oral cavity include epithelial, neural, muscle, mesenchymal, reticulo- endothelial and miscellaneous tumors occuring in soft tissuse/ bone.

Conclusion: To render disease-specific therapeutic strategies, precise histological diagnosis of round Cell Tumours is important. Since these tumors are morphologically similar, a combination of histopathology, immunohistochemistry and cytogenetics helps in accurate distinction.

Keywords: Cytologically, Diagnosis, malignant neoplasms, Round cell tumors, undifferentiated.

INTRODUCTION

Round cell tumors are heterogenous group of malignant neoplasms, characterised by round and relatively undifferentiated cells.[1] Diagnosis of these tumors is difficult and imposes a challenge for pathologists due to their undifferentiated or primitive character.[1] Thus, differentiating these tumors with others still remains enigmatic. Cytologically, these tumors are composed of a nearly uniform population of round to oval cells with scanty, basophilic cytoplasm.[2] These are also called round blue cell tumors as the cells appear blue due to presence of large hyperchromatic nuclei and a thin rim of cytoplasm.[2] Malignant round cells in these tumors may be small or large in size. Small round cells have diameters up to approximately three times that of a small mature lymphocyte whereas large round cell have diameter approximately 4-5 times that of mature lymphocytes.[2]

*Corresponding Author Address: Dr. Ramakant Gupta E-mail: dr.ramakantgupta@yahoo.com

Classification

Although, various authors have elaborated their discussion on round cell tumours; however, there is no accepted working classification for round cell tumors of the oral cavity in the literature. Hence, we made an attempt to categorize round cell tumors of the oral cavity in Table 1 based on the predominance of round cells in the histopathology of the lesions of the oral cavity. This includes epithelial, neural, muscle, mesenchymal, reticulo-endothelial and miscellaneous tumors occuring in soft tissuse/ bone. This will be of use for the oral cytopathologists/oral pathologists who are dealing with oral neoplasms.

Salient Features and Diagnostic Approach

Round cell tumors, due to their primitive nature cannot be diagnosed accurately by conventional histopathological techniques. Therefore, a multimodal approach is employed to diagnose them. Principal ancillary techniques found to be useful are Immunohistochemistry and immunophenotyping by flow cytometry, Reverse transcriptase polymerase chain reaction (RT-PCR), Fluorescence in situ hybridization (FISH) and Electron microscopy[3-9]. The important histopathological features, immunohistochemistry and cytogenetics of the round cell tumors occurring in oral cavity have been summarized[3-9] in Table 2.

The precise histopathologic diagnosis of round cell tumors may appear to be less relevant since treatment of choice usually involves resection and radiotherapy. However, recent advances in disease-specific therapeutic strategies and the concomitant improvement in prognosis, has rendered accurate tumour diagnosis and their classification to be of paramount importance. Since these tumors are morphologically similar, a combination of histopathology, immunohistochemistry and cytogenetics helps in their accurate distinction.

CONCLUSIONS:

Accurate diagnosis of round cell tumours and typifying the same may have prognostic implications. Hence, better knowledge and understanding about these amongst oral pathologists will provide a better insight for adequate diagnosis

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TABLES:

Table 1. Round cell tumors of the oral cavity

Origin	Soft tissue tumors		Bony tumors	
	Small round cell tumors	Large round cell tumors	Small round cell tumors	Large round cell tumors
Epithelial	Poorly differentiated SCC, Melanoma Adenocarcinoma	SCC Melanoma	Poorly differentiated SCC (rare) Melanoma (rare)	
Neural origin	Olfactory neuroblastoma	Paraganglioma		
Muscle origin	Rhabdomyosarcoma	Rhabdomyosarcoma		
Mesenchymal origin	Extraskeletal osteosarcoma (small cell variant) Poorly differentiated		Small cell osteosarcoma Mesenchymal chondrosarcoma	

	synovial sarcoma			
Reticulo-endothelial	Lymphomas Plasmacytoma	Lymphomas	Lymphoma Myeloma plasmacytoma	Lymphoma
Miscellaneous	Ewing sarcoma PNET Merkel cell carcinoma Langerhans disease Granulocytic sarcoma Neuroectodermal tumor of infancy		Ewing sarcoma PNET Langerhans cell disease	

Tumor	Age	Histopathologic features	Immunohistochemistry	Cytogenetics
Ewing sarcoma	<30yrs Usually intraosseous	Uniform round cells Individual cells have round to ovoid nucleus approx 10-15 µm dia., Distinct nuclear membrane, fine powdery chromatin, 1-2 small nucleoli Cytoplasm ill defined, scanty, pale staining No rosettes Abundant to moderate glycogen	CD99 +ve FLI-1 +ve Less expression of neural markers	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
Primitive Neuroectodermal Tumor	>40yrs Usually peripheral	Irregular cells Small round cell containing darkly staining round to oval nucleus Coarse chromatin granules Prominent nucleoli Cytoplasm is indistinct except in areas where cells are more mature and elongated hair like extensions coalesce to form rossettes Rosettes are similar to	CD 99 +ve FLI-1 +ve Increased expression of neural markers	Same as ewing sarcoma

		neuroblastoma and contain solid core of neurofibrillary material (Homer wright rosette) Rarely resemble retinoblastoma containing central lumen or vesicle (flexener- winterstien rosette) Scant glycogen		
Hodgkin's Lymphoma	15-34 years and older >55years	Reed-Sternberg cells	CD30	HLA-DP alleles
Diffuse large B cell lymphoma	>50years	Large irregular or lobated nuclei, size 4-5 times that of small lymphocytes.	Positive for CD20, CD45 and monotypic Ig. Positive for CD20, CD 10, BCL 6	t(14;18)(q32;2) Trisomy gains of 3q, 18q21-q22 and loss of 6q21-22.
Small lymphocytic lymphoma (SLL)	Older individuals	Proliferation of non-activated, mature looking small lymphocytes selectively involving the interfollicular regions or B-zones of the node. The para-immunoblasts and pro-lymphocytes are hallmark of SLL.	CD 20 +ve, weak monotypic surface Ig. Ki 67 index is low	Deletions of 13q14.
Follicular lymphoma	>50 years	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).	CD19, CD20, CD10, BCL-2 positive.	t(14;18)(q32;q2)

Mantle cell lymphoma	Older individuals	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). Increased cyclin D1 expression.
Burkitt's lymphoma	Occur in children	Three variants: 1. Endemic: refers to Burkitt's occurring in African children. Epsten Barr Virus (EBV) + in all most all cases. 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, starry sky pattern due to admixed tingible body macrophages, high mitotic rate and necrosis.	Positive for CD 20, CD10, Monotypic Ig	80% with t(8;14) translocation, 20% t(2;8) or t(8;22)
MALT lymphoma	Any age group	Observed in salivary glands, thyroid, stomach etc, originate from marginal zone B cells, shows cellular heterogeneity with monocytoid B cells, small lymphocytes, plasma cells, and occasionally large lymphocytes. Two variants: 1. Few cases show prominent follicular growth pattern resulting from follicular colonization, centrocyte-like	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

		(CCL) cells representing minimal Positive for CD20, and surface Ig D. Negative for CD10, CD5 2. plasma cell differentiation (follicular growth type). 2. Few cases show marginal zone distribution pattern of CCL cells, presence of plasma cells.		
NK/T cell lymphoma	>50 years	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.
Plasmablastic lymphoma		Found in HIV infected patients, diffuse infiltration of large neoplastic cells in the oral submucosa with eccentrically placed nuclei and paranuclear halo	CD 4-ve, and CD2-ve. VS38c + ve and CD79a	
Plasma cell neoplasias	60-65years	Three types: Multiple myeloma (multiple bones involved), solitary bone plasmacytoma, and 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.	Monoclonal immune-globulins i.e., Ig G, lambda, Ig kappa.	t(8;14), t(11;14) or t(14;18)

Olfactory Neuroblastoma	adults and occur over wide age range (mean: 53 years)	originate from basal cells of olfactory epithelium which express neural cell adhesion molecule and the mammalian homologue of Drosophila-achaete-scute (MASH) gene. Lesion 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. Pattern I: A tumor with sheets of small, round cell separated by connective tissues septa; pseudorosettes or Homer Wright rosettes are seen. 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. Pattern III: Pattern similar to neuroblastoma with production of neuropil, a wispy, light pink, fibrillar material produced by undifferentiated neuroblasts.	positive for neuron specific enolase and neural filament protein. S-100 and vimentin are positive in sustentacular cells.	express HASH, the human homologue of the MASH gene.

		Rosettes are seen with abundant haemorrhage, fibrosis and hemosiderin deposition. Clusters of lymphocytes and islands of dystrophic calcification are seen.		
Rhabdomyosarcoma	children Thought to arise from skeletal muscle progenitors	embryonal rhabdomyosarcoma (ERMS): 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 alveolar rhabdomyosarcoma (ARMS): 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.	Myogenin, Myo D	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 chromosome13. 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
Small cell ostosarcoma	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.

Mesenchymal chondrosarcoma	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.
Poorly differentiated synovial sarcoma	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).
SCC	Middle age	Rapidly growing, increased mitotic figures, highly pleomorphic cells	Cytokeratins	LOH of chr. 3, 17 Damage to H-ras on chr.17, PRAD-1 on chr. 11
Merkel cell carcinoma	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.	-
Small cell melanoma	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.
Adenocarcinoma	40 years	Solid tumor without cystic spaces	Cytokeratins	-

Paraganglioma	Middle age	Round or polygonal epitheloid cells organized into nests or ZELLBLLEN Zellbllen are larger and irregular in shape Nests consists of CHIEF cells which demonstrate centrally located, vesicular nuclei and somewhat granular eosinophilic cytoplasm Tumor is vascular Surrounded by thin fibrous capsule	Synaptophysin, Chromagranin	-
Langerhans cell histiocytosis/ histiocytosis X	10- 20 years	Diffuse infiltration of large mononuclear cells that resemble histiocytes Cells have cytoplasmic borders and rounded/ indented vesicular nuclei Varying number of eosinophils are interspersed among histiocyte like cells Plasma cells, lymphocytes and multinucleate giant cells are often seen Ultrastructuraly, langerhans cells contain rod shaped cytoplasmic structures known as Birbeck granules	S100, CD1a	HLA-DR allele
Granulocytic Sarcoma/ Myeloid Sarcoma (Chloroma)	1 −81 years	characteristic microscopic growth pattern of myeloid cells is either a diffuse or an Indian file pattern it is subclassified according to the most abundant cell type into granulocytic, monoblastic or	CD68/KP1, MPO, CD 117, CD 99, CD 68/PG-M1, lysozyme, CD34, TdT, CD56, CD61, CD30, glycophorin and	Nucleophosmin (NPM) 1 mutations with the consequent aberrant cytoplasmic expression of

		myelomonocytic and according to cell maturation into immature, mature and blastic types. blastic type is composed primarily of myeloblasts with little evidence of maturation. The immature type is an intermediate grade and consists of myeloblasts, promyelocytes and eosinophilic myelocytes. The differentiated or mature type is composed of promyelocytes and more mature cells with abundance of eosinophils	CD4. CD13, CD33, CD117 and MPO KI-67/MIBI is usually high, ranging from 50% to 95%	NPM

Table 2. Summary of salient histopathologic, immunochistochemical features and cytogenetics of round cell tumors of the oral cavity