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Original Article

Histopathological study of round cell tumors of the head and neck region in a tertiary care hospital

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ABSTRACT

Background: Small round cell tumors are heterogeneous, highly aggressive malignant tumors occuring in unusual sites with overlapping clinical and radiographic features. Their diagnosis is challenging using conventional histopathologic approaches because of indistinct features in small biopsy samples and hence immunohistochemistry is a must. This study was undertaken to evaluate the pattern, common types, age, sex distribution of round cell tumors of the head and neck region and to obtain morphological immunohistochemistry correlation.

Materials and Methods: It is a retrospective study of 99 cases which fulfilled the inclusion criteria. Paraffin blocks were retrieved and were reviewed by two independent expert observers and immunohistochemistry was repeated whenever necessary.

Results: Final diagnosis was given based on the immunohistochemistry pattern and our study showed 8 spectrums of round cell tumours. Lymphoma was the most common followed by neuroendocrine carcinoma. Most B-cell Non Hodgkin Lymphoma, undifferentiated carcinomas and Neuroendocrine carcinomas were observed in older group whereas, Ewing sarcoma /Primitive Neuro Ectodermal Tumour and T cell NHL were seen more in younger group. According to sex wise distribution, 70 (70.7%) cases were male and 29 (29.3%) females with male to female ratio of 2.4:1.

Conclusion: Round cell tumors can occur at any sites of the head and neck region. There are certain morphologic features for each tumor which may help the surgical pathologist to come to a probable diagnosis in addition to careful search of the detailed history, location of tumor, presentation, radiological findings and ultimately correlating with immunohistochemistry.

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INTRODUCTION

Round cell tumors are a heterogeneous group of neoplasms characterized by sheets of poorly differentiated cells with small, blue, round nuclei and scant cytoplasm.[1] They are highly aggressive malignant tumors and are characterized by small, round, relatively undifferentiated cells with increased nuclear-cytoplasmic ratio. These tumors often occur in bones or soft tissues and can be classified on the basis of: A) Pattern of round cells (Diffuse, lobulated, Alveolar, Rosettes etc), B) Size of round cells (Small or Large) or C) on the basis of cell of origin (Neurogenic, Mesenchymal, hematolymphoid and Uncertain types). Small round cell

tumors that commonly arise in the head and neck region include: Ewing's Sarcoma, Primitive Neuro Ectodermal Tumors (PNET), Rhabdomyosarcoma, Lymphoma, Neuroendocrine Carcinoma, Neuroblastoma, Malignant Melanoma and Undifferentiated/ Poorly differentiated Carcinomas.[3] These tumors often show overlapping clinical, radiographic and histological features which often makes definitive diagnosis a daunting challenge, especially for the pathologist. Establishing the correct diagnosis upon the tissue sample is of paramount importance because of the variations in management strategies and prognosis of these different types of tumors. Therefore, their diagnosis should not only be based on careful clinical evaluation and histologic review, but also upon the strategic use of immunohistochemistry (IHC) stains and even molecular analysis, if need arises. For a pathologist working in a cancer centre, it is important to know which type of round cell tumors are common in the population of that region for , so that he/she can correctly diagnose and them for a proper treat those cases which are of therapeutic approach importance.

Considering this background, our study was undertaken with the following aims and objectives-

1. To see the pattern of round cell tumors of the head and

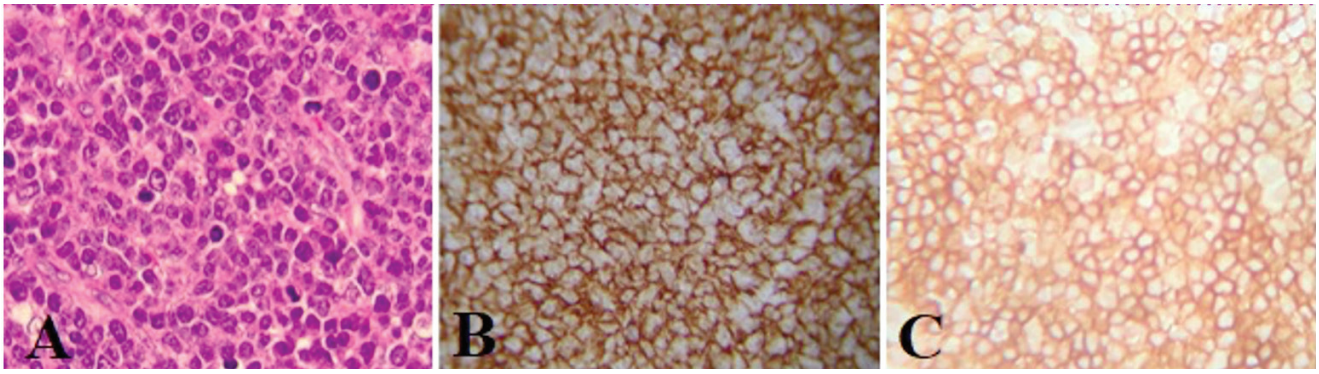

Figure 2: A: Non-Hodgkin Lymphoma (H&E, x400). B: Immunoshistochemical staining showing CD20 membranous positivity (x100). C: Immunohistochemical staining showing CD45 membranous positivity (x100)

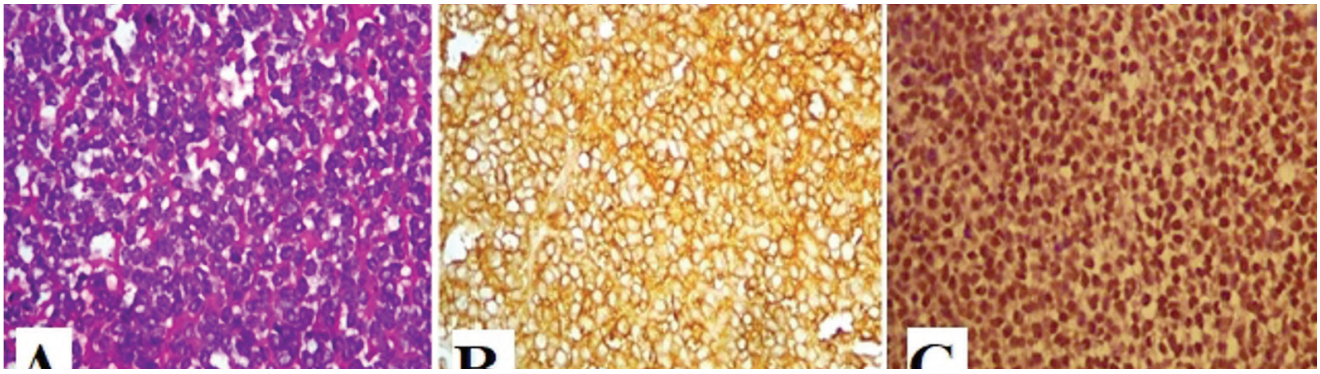

Figure 3: A: Ewing's sarcoma (H&E, x400). B: Immunohistochemical staining showing CD99 membranous positivity (x100). C: Immunohistochemical staining showing FLI-1 nuclear positivity (x100)

Table 1: IHC pattern of round cell tumors in the study

	CK+	EMA	CD45	CHR	SYN	MYO	DES	FLI-1	HMB 45	S100	VIM	CD 99
Lymphoma	-	-	++	-	-	-	-	-	-	-	-	-
ES/PNET	-	-	-	-	-	-	-	++	-	-	++	++
NEC	V	-	-	++	++	-	-	-	-	-	-	-
PDSCC	++	+	-	-	-	-	-	-	-	-	-	-
Neuroblastoma	-	-	-	+	+	-	-	-	-	-	-	-
Malignant melanoma	F+	F+	-	-	-	-	-	-	++	+	-	-
RMS	-	-	-	F+	-	++	++	-	-	-	-	-
Paraganglioma	-	-	-	++	++	-	-	-	-	+ *	-	-

CK: Cytokeratin, EMA: Epithelial Membrane Antigen, CD: Cluster Differentiation, CHR: Chromogranin, SYN: Synaptophysin, MYO: Myogenin, DES: Desmin, VIM: Vimentin, ES: Ewing's Sarcoma, PNET: Primitive Nueroectodermal Tumor, NEC: Neuro Endocrine Carcinoma, PDSCC: Poorly Differentiated Squamous Cell Carcinoma, RMS: Rhabdomyosarcoma

-: Negative, +: Positive, F+: Focally Positive, V: Variable, +: Positive in sustentacular cells*

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Table 2: Age distribution of round cell tumors in the study

		0-10 years	11-20 years	21-30 years	31-40 years	41-50 years	51-60 years	>60 years	TOTAL
Lymphoma	B-cell NHL	0	4	5	11	18	14	2	54
	T-cell NHL	3	1	1	3	2	2	1	13
ES/PNET		2	2	2	1	0	0	0	7
NEC		0	0	0	1	1	7	2	11
PDSCC		0	1	1	1	4	2	0	9
Neuroblastoma		0	1	0	1	0	0	0	2
Melanoma		0	0	1	0	0	0	0	1
RMS		0	1	0	0	0	0	0	1
Paraganglioma		0	1	0	0	0	0	0	1
TOTAL		5	11	10	18	25	25	5	99

NHL: Non-Hodgkin Lymphoma, ES: Ewing's Sarcoma, PNET: Primitive Neuro Ectodermal Tumor, NEC: Neuro Endocrine Carcinoma, PDSCC: Poorly Differentiated Squamous Cell Carcinoma, RMS: Rhabdomyosarcoma

Table 3: Sites of round cell tumors in the study

Site	Lymphoma	ES/PNET	NEC	PDSCC	NB	Melanoma	RMS	PGL	Total
Neck	45	2	4	1	0	0	0	1	53
Pyriform fossa	0	0	1	2	0	0	0	0	3
Base of tongue	4	0	3	1	0	0	0	0	8
Sino nasal tract	0	1	2	0	1	0	1	0	5
Tonsil	7	0	1	0	0	0	0	0	8
Eye	1	2	0	0	0	0	0	0	3
Maxilla	0	1	0	0	1	0	0	0	2
Buccal mucosa	0	0	0	0	0	1	0	0	1
Palate	2	0	0	0	0	0	0	0	2
Ary-Epiglottic Fold	1	0	0	1	0	0	0	0	2
Cheek	1	0	0	1	0	0	0	0	2
Naso-pharynx	6	1	0	3	0	0	0	0	10
TOTAL	67	7	11	9	2	1	1	1	99

ES: Ewing's Sarcoma, PNET: Primitive Neuro Ectodermal Tumor, NEC: Neuro Endocrine Carcinoma, PDSCC: Poorly Differentiated Squamous Cell Carcinoma, NB: Neuroblastoma, RMS: Rhabdomyosarcoma, PG: Paraganglioma

neck region coming to our hospital

2. To know the most common type, age and sex wise distribution of Round cell tumors of the head and neck region

3. To list out the possible differential diagnosis based on histopathology and correlate the morphology with immunohistochemistry (IHC) pattern for proper classification.

MATERIALS AND METHODS

A retrospective study of 3 years from July 2016 to June 2019 was carried out at Dr. B. Borooah Cancer Institute, Assam, India. All cases reported as round cell tumors from head and neck region were collected from the records of Oncopathology department of the institute. Cases with incomplete clinical details, without IHC correlation and scant material on paraffin blocks were not considered in our study. Ninety-nine cases were finally selected. Clinicopathologic history was obtained from the files and records of the patients. Paraffin blocks were retrieved and reviewed by two independent expert observers. Due to initial absence of all IHC markers in house, few cases that were reported as round cell tumors on histomorphology initially, underwent repeat IHC for confirmation of the diagnosis. As per the department protocol we performed the initial IHCs on the blocks reported as small round cell tumors with the following antibodies: CK, EMA, CD45, CD99, FLI-1, Synaptophysin, Chromogranin, S-100, HMB45, Myogenin, Desmin and Vimentin. Further IHC evaluation was done on those diagnosed as lymphoid neoplasm using following antibodies; CD3, CD20, CD15, CD30, CD10, CD23, CD5, CyclinD1, BCL2, BCL6, MUM1, Kappa, Lambda. All procedures performed in the current study were approved by Institutional Ethics Committee (IEC) [Reference number: BBCI-TMC/Misc-01/MEC/143/2020 date:28/05/2020] in accordance with the 1964 Helsinki declaration and its later amendments. As it was a retrospective study, formal written

informed consent was not required with a waiver granted by the IEC.

RESULTS

Final diagnosis was given based on immunohistochemistry findings as shown in Table 1. Out of the 99 selected cases, Lymphoma was the most common tumor comprising 67.7 % followed by Neuroendocrine carcinomas (NEC) with 11.1% (Fig. 1). Figure 2 and Figure 3 shows microscopy images of Non Hodgkin lymphoma (NHL) and Ewing sarcoma (ES) respectively that were diagnosed and included in our study.

According to age distribution as depicted in Table 2, most B cell NHL, Poorly differentiated squamous cell carcinomas (PDSCC) and NECs were observed in older group. In the pediatric and adolescent age group (0-20 years) the most common round cell tumors were NHL (both B and T cell) and ES/PNET.

According to sex distribution, it was observed that round cell tumors were more common in males than females in our study sample (M:F ratio 2.4:1). Tumors like NEC (M:F ratio 2.6:1) and PDSCC (M:F ratio 3.5:1) had an even higher male preponderance. Lymphomas, the most frequently diagnosed round cell tumor in our study, also had a higher male predilection (M:F ratio 2.35:1). With regard to the location of round cell tumors in our study population, it was observed that they can occur at any subsite of the head and neck region (Table 3). However, they were most commonly found in the neck (53.5%) with Lymphoma in the cervical nodes being the most common diagnosis (45.5%). Nasopharynx (10.1%), tonsil (8.1%) and base of tongue (8.1%) were the other common subsites with again Lymphoma being the most commonly detected round cell tumors in these regions.

DISCUSSION

Small round cell tumors are a group of cytomorphologically similar neoplasms with varied origin and histologically are undifferentiated.[1] Round cell tumor may be classified on the basis of the pattern, size, shape and origin.[2] Separation and distinction between tumors are critical as they are managed differently. It is therefore, important to have a broad differential diagnosis for these tumors, where each of the diagnoses can be studied and evaluated further.[3] Lymphomas are the third most frequent malignancy and should thus always be taken into consideration in cases of undifferentiated carcinoma of head and neck area.[4] Large B cell lymphomas, representing approximately 30% of all lymphomas, are also the most common type of NHL in the head and neck.[5] Approximately 30% of NHLs show heterogeneous extranodal manifestations, such as in the major salivary glands, paranasal sinuses, mandible, maxilla and Waldeyer's ring.[4] Most of our case consisted of diffuse monomorphous to polymorphous, small to large cells, with

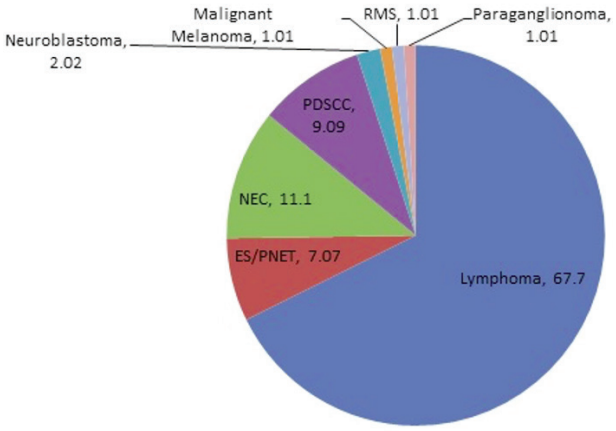

Figure 1: Different types of round cell tumors in our study

RMS: Rhabdomyosarcoma, NEC: Neuroendocrine carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma, ES/PNET: Ewing's sarcoma / Primitive neuroectodermal tumors

some cells having folded, cleaved and grooved nuclei. Moderate pleomorphism and high mitotic count was also noted in some cases. Necrosis and vascular proliferation were also noted in T cell NHL.

Neuroendocrine carcinomas of small cell type are included in the differentials. Generally, neuroendocrine tumors are rare in head and neck region and most common site of occurrence is larynx[1,6] which can be of epithelial or non-epithelial differentiation.[7] Whereas in our study, it was the second commonest tumor next to lymphoma and none of the cases presented in larynx. It is imperative to correctly differentiate it from the much more common squamous cell carcinoma (SCC) because their treatments differ.[6] Their histology consisted of tumor cells with small size and high nuclear to cytoplasmic ratio, crushing artifact, nuclear molding, moderate pleomorphism and inconspicuous nucleoli.

Rhabdomysarcoma (RMS) of embryonal and alveolar subtypes is included in the differentials of round cell tumor. They may arise from different anatomic sites with diverse clinical presentations and have widely variable prognosis. Besides histological classifications, the prognosis of RMS also depends on underlying genetic abnormalities like presence of PAX-FOXO1 fusion genes.[8] In the head and neck, RMS is primarily but not exclusively a disease of the pediatric population1 and in our study, the lone RMS case was a 20 years old patient who presented with nasal mass consisting of solid sheets of high grade round cells. Adult head and neck RMS, though aggressive with unfavorable prognosis, is curable and therefore, should be included in the differentials.[9]

Poorly differentiated, non-keratinizing variant of SCC may exhibit histopathologic features that overlap with

other RCTs. In our study we got 9 cases of poorly differentiated carcinoma which showed strong positivity for CK and EMA and negative for other markers. Franchi et al[10] reported different cytokeratin staining patterns in keratinizing SCC, non-keratinizing SCC, and sinonasal undifferentiated carcinoma (SNUC). SCC is almost always immunoreactive for EMA whereas less than 50% of SNUCs are EMA positive. Morphologically they consist of round to polymorphic undifferentiated cells with solid growth, inconspicuous nucleoli and high mitotic count with area of necrosis.

Paragangliomas (PGL) of the head and neck region are rare tumors.[1] Head and neck PGLs are often non-secreting tumors and thus often discovered on imaging studies or revealed by the presence of cervical/skull base masses with or without compression or infiltration of adjacent structure.[11] In Vagal PGL, a predilection for women exists.[1] In our study, a single case of vagal paraganglioma was a 47-year-old female with a small biopsied material consisting of nest of monomorphic cells with round nuclei and dense chromatin. The correct diagnosis was possible only with clinical correlation and IHC.

Ewing sarcoma/primitive neuroectodermal tumor is a high-grade primitive small round cell sarcoma with neuroectodermal differentiation defined by the presence of a EWSR1 gene translocation.[1] Fonseca et al[12] states that Ewing sarcoma/ PNET of head and neck is unusual, and it is more common in males than females. Ewing sarcoma/ PNET in the head and neck region occur more commonly in the paranasal sinus, nasal cavity and neck with an aggressive behavior and high rates of distant metastasis at presentation.[13] In our study, 7 of the cases showed varied location and morphologically most of them showed round medium cells, vacuolated cytoplasm, fine chromatin, frequent mitoses, necrosis, rosettes seen in some case and showed no fibrillary matrix.

Olfactory neuroblastomas (ONB) is a malignant neuroectodermal neoplasm thought to arise from the olfactory membrane of the sinonasal tract.[1] ONB is an uncommon malignant neoplasm representing approximately 2% to 3% of sinonasal tract tumors. No sex predilection is seen. ONB occurs over a very wide age range from 3 years to the ninth decade, with a bimodal peak in the second and sixth decades of life.[1] Both cases of NB in our study showed small round cells with small to inconspicuous nucleoli. Neurofibrillary matrix was present forming pseudo rosettes in one case.

Approximately 15% to 25% of all malignant melanomas arise in head and neck areas.[1] Of the head and neck malignant melanomas, more than 80% are of cutaneous origin. Mucosal malignant melanomas of the upper aerodigestive tract represent from 0.5% to 3% of malignant melanomas of all sites.[1] Irrespective of the site of occurrence, mucosal malignant melanomas are more common in men than women. In our study we had a 29 years old male who presented with a growth on buccal mucosa. Morphology of the biopsied material show nest of relatively uniform cells, bland and oval nuclei with eosinophilic nucleoli. There was no pigment. Diagnosis was confirmed with clinical history and IHC correlation.

Our study found that the histopathology section of our department has reported 8 spectrums of round cell tumors with lymphoma being the commonest. Because of sampling difficulty in some part of head and neck region yielding tiny materials, it is important to think broadly of the probable diagnosis and put up the antibodies for IHC accordingly. We noticed considerable cross-reactivity among various tumors and antibodies in our studies. So, keeping in mind the limitations of IHC like aberrant expression of antigens and cross reactivity with other antigens, further history should be reviewed and further investigations should be carried out wherever applicable.[14] Cytogenetic and molecular studies like Flourescence in situ hybridization (FISH) and Reverse transcription polymerase chain reaction (RT-PCR) have now been able to detect specific chromosomal abnormalities pertaining to a small round cell tumor and should be used in conjunction with IHC whenever the diagnosis needs further corroboration.[15]

CONCLUSIONS

Round cell tumors in the head and neck region can occur at any subsite, with certain entities having a predilection towards specific age group and location, with an overall male preponderance. A careful evaluation of the detailed history, examination findings, location of tumor and imaging is essential to overcome the overlap of morphological patterns that these tumors may display. Incorporation of multiple IHC markers in an appropriate morphological context is imperative for diagnosis and availability of cytogenetic studies and molecular analysis provides further help. A surgical pathologist must be aware of the different phenotypic presentations and genetic abnormalities of commonly encountered round cell tumors to guide their accurate diagnosis and optimum management.

Conflict of interest: None

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