Original Article

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Pathology Section

Decoding Blue Round Cell Tumours using Immunohistochemistry- A Prospective Cohort Study

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ABSTRACT

Introduction: Small blue round cell tumours are heterogeneous group of neoplasms characterised by small, round and relatively undifferentiated cells. These tumours pose a great challenge to the histopathologist for definite diagnosis and Immunohistochemistry (IHC) plays an important role in the further evaluation of these tumours.

Aim: To analyse the round cell tumours according to site, gender and age of the patient and ascertain the significance of IHC for its accurate morphological characterisation.

Materials and Methods: This prospective cohort study was conducted at Department of Pathology, Guntur Medical College, Andhra Pradesh, India, which included 53 patients from August 2013 to August 2015. Immunohistochemical studies were done to categorise the tumours using the relevant panel of immunohistochemical antibodies streptavidin biotin detection method. Frequency and percentage statistics was used to present the results.

Results: Out of 53 cases there were 29 cases of Non Hodgkin Lymphoma (NHL), eight cases of Ewing's Sarcoma/PNET, four cases of Esthesioneuroblastoma, three cases of small cell carcinoma, two cases of medulloblastoma, each one case of ependymoblastoma, alveolar rhabdomyosarcoma, sinonasal Undifferentiated Carcinoma (SNUC), mesenchymal chondrosarcoma, nephroblastoma, desmoplastic small round cell tumour and small cell carcinoma ovary.

Conclusion: Most common tumour was NHL with highest incidence in males and age group of more than 40 to 60 years years. Immunohistochemistry represents an adjunctive tool for accurate typing and classification of round cell tumours.

Keywords: Ependymoblastoma, Ewing's Sarcoma, Non hodgkin's lymphoma, Sinonasal tumours

INTRODUCTION

Small blue round cell tumours are heterogeneous group of neoplasms characterised by small, round and relatively undifferentiated cells [1] with darkly stained nuclei and scant cytoplasm and is seen as blue appearance in Hematoxylin and Eosin stain (H&E) stained sections. The category of small round cell tumours include Ewing's sarcoma, peripheral neuroectodermal tumour, alveolar rhabdomyosarcoma, poorly differentiated synovial sarcoma, medulloblastoma, Non Hodgkin Lymphoma (NHL), retinoblastoma, neuroblastoma, nephroblastoma, small cell osteogenic sarcoma, small cell variant of melanoma, undifferentiated hepatoblastoma and desmoplastic small round cell tumour [2].

These tumours pose a great challenge to the histopathologist for precise and definite diagnosis due to histological similarity and lack of differentiating features and require adjunctive techniques like Immunohistochemistry (IHC) and cytogenetic studies [3]. The histopathological assessment with the aid of clinical and radiological findings helps in providing a differential diagnosis. A broad categorisation of undifferentiated tumours along the major lineages (i.e., epithelial, mesenchymal, lymphoid, and melanocytic) is done by the application of screening IHC markers and this provides the first clue to the nature of these tumours. Based on the result of the screening panel, a more specific panel is employed to further sub-classify the tumour or confirm a particular diagnosis [4]. The objective of performing IHC is to recognise cell constituents (antigens) and, to identify and classify specific cells within a cell population whose morphology is heterogeneous or homogenous.

A panel approach is always suggested so that an antigenic profile of positive and negative markers will provide the most precise characterisation of tumour [3,5]. Histopathological examination forms the basis for the diagnosis of blue round cell tumours and IHC represents a primary tool for confirmatory diagnosis to ensure specific treatment. The aim of the present study was to categorise the occurrence of round cell tumours according to site, gender and age of the patient and ascertain the significance of IHC for its accurate characterisation. The present study included round cell tumours with varied presentation involving multiple organs.

MATERIALS AND METHODS

This study was a prospective cohort study conducted at Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh, India, from August 2013 to August 2015. The results were analysed in the month of September 2015. Total 53 cases were included in the study.

Inclusion criteria: Cases diagnosed as small round cell tumours were included in the study.

Exclusion criteria: Biopsy specimens with inadequate samples and leukaemia cases were excluded from the study.

Study Procedure

In the present study, according to the patient's age, tumour location and histological finding, immunohistochemical studies were done to categorise the tumours. Relevant panel of IHC antibodies were applied using streptavidin biotin detection method, using the Dako kit. Formalin fixed paraffin embedded sections were used. Sections were deparaffinised, rehydrated and heat treated for antigen retrieval in a microwave in a citrate buffer. Sections were blocked in H_2O_2 blocking solution for 10 minutes and incubated with the primary antibody for one hour and then secondary antibody for 30 minutes at room temperature. After incubation with avid in biotin peroxidise complex for further 30 minutes, visualisation was performed with working Diaminobenzidine (DAB) solution. The slides were counterstained with Harris haematoxylin. Appropriate positive and negative controls were included to ensure quality and consistency of staining results. A primary panel of antibodies cytokeratin, (cluster of differentiation), vimentin and S100 were used for differentiation of tumour cells along epithelial, haematopoietic or mesenchymal origin respectively.

According to the results of primary markers, for further classification secondary markers were applied. The secondary markers used were CD3, CD20, CD99, desmin, Neuron Specific Enolase (NSE), synaptophysin, chromogranin, Human Melanoma Black (HMB45).

STATISTICAL ANALYSIS

Frequency and percentage statistics was used to calculate mean age, sex, site distribution and histopathological type of the tumour in study group.

RESULTS

A total of the 53 small round cell tumours were included in the present study. The distribution of round cell tumours with respect to type, site, age and gender were studied.

Out of 53 cases of malignant small round cell tumours, most common tumour was NHL (29 cases, 54.7%) followed by Ewing's Sarcoma/Primitive Neuroectodermal Tumour (PNET) (8 cases, 15.09%) [Table/Fig-1]. Most common site of involvement was lymph nodes (17 cases, 32%) followed by respiratory tract (11 cases, 20.7%) and central nervous system (9 cases, 16.9%) [Table/Fig-2]. Maximum number of cases were seen in the age group of >45-60 years (16 cases, 30.1%) followed by >60 years (15 cases, 28.3%) and 15-45 years (22.6%). This study shows male preponderance with male to female ratio of 1.65:1 [Table/Fig-3].

Round cell tumour	Number of cases	Percentage (%)
Non Hodgkin's lymphoma	29	54.7%
Primitive Neuroectodermal Tumour (PNET)/Ewings	8	15.1%
Esthesioneuroblastoma	4	7.5%
Small cell carcinoma	3	5.6%
Medulloblastoma	2	3.8%
Ependymoblastoma	1	1.9%
Alveolar rhabdomyosarcoma	1	1.9%
Sinonasal undifferentiated carcinoma	1	1.9%
Mesenchymal chondrosarcoma	1	1.9%
Nephroblastoma	1	1.9%
Desmoplastic small round cell tumour	1	1.9%
Small cell carcinoma ovary	1	1.9%

[Table/Fig-1]: Showing the distribution of round cell tumours based on H&E.

Site of round cell tumour	Number	Percentage (%)
Lymph nodes	17	32%
Respiratory tract	11	20.7%
Central nervous system	9	16.9%
Soft tissues and bone	9	16.9%
Gastrointestinal tract	2	3.8%
Orbit	1	1.9%
Mediastinum	1	1.9%
Peritoneum	1	1.9%
Kidney	1	1.9%
Ovary	1	1.9%

[Table/Fig-2]: Showing the distribution of round cell tumours according to location.

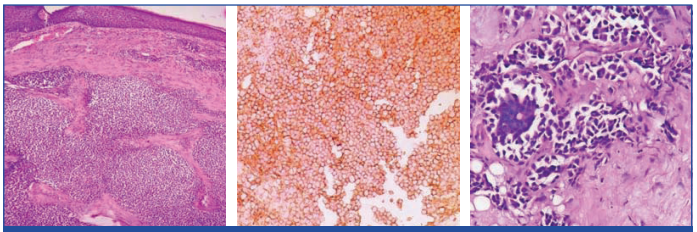
Variables	Males	Females
<5 years	2 (3.8%)	0
5-15 years	3 (5.7%)	5 (9.4%)
>15-45 years	10 (18.9%)	2 (3.8%)
>45-60 years	7 (13.2%)	9 (16.9%)
>60 years	11 (20.7%)	4 (7.5%)
Total	33 (62.3%)	20 (37.6%)

[Table/Fig-3]: Age and gender wise distribution of cases.

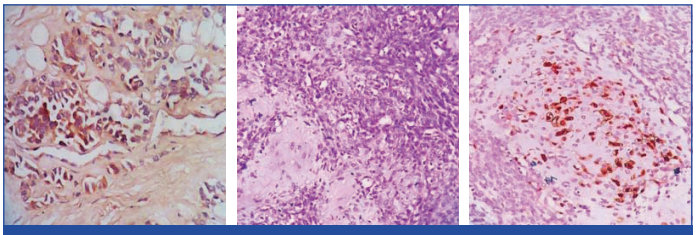
Out of the 53 cases of small round cell tumours, for 30 cases [Table/Fig-4] screening was done by panel of primary IHC markers to differentiate along the major lineages. Based on the result of the screening panel, a more specific secondary marker panel is employed for confirmatory diagnosis. In the remaining 23 cases, 17 cases were lymphnodal NHL which were provisionally diagnosed on H&E and basic lymphoma panel of IHC markers were done for further typing. The other six cases, two cases of small cell carcinoma lung, two cases of medulloblastoma, each one case of Nephroblastoma and mesenchymal chondrosarcoma provisional diagnosis was given on H&E and IHC markers were applied to confirm the diagnosis. [Table/Fig-5] shows two population of cells with some cells with hyperchromatic nucleus and scant cytoplasm and some with clear cytoplasm, showed membrane positivity for CD99 [Table/Fig-6] confirming the diagnosis of Ewings sarcoma. [Table/Fig-7] shows small round cells with hyperchromatic nuclei, scant cytoplasm arranged in alveolar pattern. Tumour cells showed cytoplasmic positivity for IHC marker Desmin [Table/Fig-8] confirming the diagnosis of alveolar rhabdomyosarcoma. [Table/Fig-9] showing biphasic pattern of tumour composed of undifferentiated small round cells interrupted by islands of cartilage, S100 positive in cartilage areas [Table/Fig-10] confirming the diagnosis of mesenchymal chondrosarcoma.

	Primary IHC markers panel				
	No. of cases positive/ total	No. of cases positive/ total	No. of cases positive/ total	No. of cases positive/ total	Secondary markers positive
Diagnosis	CK	LCA	Vimentin	S100	
NHL	0/12	12/12	1/12	0/12	CD20
PNET/Ewings	0/8	0/8	8/8	0/8	CD3
Esthesione-uroblastoma	0/4	0/4	0/4	4/4	CD99
Sinonasal undifferentiated carcinoma	1/1	0/1	0/1	0/1	NSE, Chromogranin
Small cell neuroendocrine carcinoma sinonasal	1/1	0/1	0/1	0/1	NSE
Alveolar rhabdomy-osarcoma	0/1	0/1	1/1	0/1	Chromogranin
Small cell carcinoma ovary	1/1	0/1	0/1	0/1	Desmin
DSRCT	1/1	0/1	1/1	0/1	NSE, Desmin
Ependym-oblastoma	0/1	0/1	1/1	0/1	NSE

[Table/Fig-4]: Expression of IHC markers based on primary panel of antibodies. CK: Cytokeratin; LCA: Leucocyte common antigen; NSE: Neuron specific enolase; NHL: Non hodgkin lymphoma; PNET: Primitive neuroectodermal tumour; DSRCT: Desmoplastic small round cell tumour



[Table/Fig-5]: PNET/Ewings (H&E,10X). **[Table/Fig-6]:** PNET/Ewings showing CD 99 membrane positivity (IHC,40X). **[Table/Fig-7]:** Alveolar rhabdomyosarcoma (H&E, 40X). (Images from left to right)



[Table/Fig-8]: Alveolar rhabdomyosarcoma showing Desmin positivity (IHC,40X).
[Table/Fig-9]: Mesenchymal Chondrosarcoma (H&E,40X).
[Table/Fig-10]: Mesenchymal Chondrosarcoma showing S100 cytoplasmic positivity (IHC,40X). (Images from left to right)

DISCUSSION

The family of neoplasms known as small round cell tumours are characterised by high cellularity, small cell size, diffuse pattern of growth and is seen in all age groups. This study analysed the round cell tumours and ascertains the significance of IHC for its accurate characterisation. Immunohistochemistry should always be used as an adjunct to the morphology and it is important to employ a correct panel of antibodies rather than a single marker for a conclusive diagnosis [6].

The most common round cell tumour in the present study was NHL (29 cases, 54.7%) followed by PNET/Ewing's sarcoma (8 cases, 15.1%) which correlated with the studies of Bashyal R et al., (21 cases, of NHL 52.5%,11 cases of PNET 27.5%) Patel MM et al., (26 cases of NHL 35%, 3 cases of PNET 3.75%) and D'Cruze L et al., (19 cases NHL 44%, 6 cases PNET 14%) [3,5,6]. Esthesioneuroblastoma was the third most common tumour in the present study constituting (4 cases) 7.5% of all tumours, whereas the distribution of other round cell tumours varied above mentioned studies [3,5,6]. Among the specific organs involved in the present study lymph nodes (17 cases, 32%) followed by respiratory tract (11 cases, 20.7%), central nervous system and bone/soft tissue (9 cases each, 16.9%). In the present study, the age of the patients ranged from 8 months to 77 years with predominant age group of 45-60 years (16 cases, 30.1%). In the study of D'Cruze L et al., majority of cases were in the age group of 15-45 years (19 cases, 44%) followed by above 60 years (9 cases, 20.9%) [6]. Male predominance was noted in our studies which were similar to other studies [6,7].

A total of 29 cases (54.7%) of NHL were included, out of which 17 cases were nodal (58.62%) and 12 cases were extra nodal (41.38%). Cervical lymph nodes (9 cases, 53.1%) were the major sites of involvement followed by axillary (4 cases, 23.5%). The extra nodal sites of involvement in the present study were central nervous system (3 cases, 25%), nasopharynx (3 cases, 25%), intestine (2 cases, 16.6%), mediastinum (1 cases, 8.3%), scalp (1 cases, 8.3%), cheek (1 cases, 8.3%) and jaw (1 cases, 8.3%). In the present study there was predominant nodal involvement of NHL which was similar to other studies extra nodal involvement [8-10].

In the present study, the nodal sites of NHLs were diagnosed provisionally as NHL on Fine Needle Aspiration Cytology (FNAC) and H&E and these cases were taken up for IHC studies. All the cases showed positivity for CD45 and 100% concordance noted between light microscopy and IHC studies. For the other 12 extra nodal NHL cases primary IHC markers were applied, showed positive results for CD45 suggesting lymphoma [Table/Fig-4]. Negative cytokeratin excluded poorly differentiated and undifferentiated carcinomas. Out of the 12 cases one case showed positivity for both Vimentin and LCA, similar results of Vimentin expression in NHL were seen in the study by Bhagat V et al., and Tamaru J et al., [11,12]. For all the cases which were positive for CD45, CD20 and CD3 were used and accordingly typed as B cell or T cell lymphoma. Out of 29 NHL cases, 23 showed positivity for CD 20, five cases were positive for CD 3 and the remaining one case (3.5%) showed positivity for both the markers hence remained uncategorised. In the present study, B-cell lymphoma cases outnumbered T-cell lymphoma cases and these results correlated with other studies [9,13].

The next common tumour in the present study was PNET/Ewings sarcoma (eight cases) accounting for 15.09% of cases with the most common location in soft tissues (five cases 62.5%) followed by CNS (two cases 25%) and bone (one case 12.5%). Predominant extraskeletal distribution was noted in the present study similar to other studies [5,6]. FNAC was done in two cases and reported as small blue round cell tumour. Three cases out of eight were provisionally diagnosed as PNET/Ewings sarcoma. The other five cases, primary panel of IHC markers were applied showed cytoplasmic positivity for vimentin and negativity for cytokeratin, Leucocyte Common Antigen (LCA) and S 100. LCA and S100 being negative, the possibility of lymphoblastic lymphoma and neuroblastoma was ruled out, respectively. CD99 showed strong membrane positivity in all the cases (100%) [Table/Fig-6] and NSE was positive in three cases (37.5%) which points towards neuroectodermal differentiation, a conclusive diagnosis of PNET/Ewings was made.

In the present study, nine sinonasal round cell tumours were included. The differential diagnosis of round cell tumours from the sinonasal region is wide, includes Sinonasal Undifferentiated Carcinoma (SNUC), Neuroendocrine Carcinoma (SNEC), esthesioneuroblastoma, melanoma and lymphoma [14]. In our study, four cases of Esthesioneuroblastoma, three lymphomas, each one case of SNUC and SNEC were reported. The integration of histopathologic findings and IHC panel cytokeratin, CD45, S100, NSE and HMB45 in the present study led to the correct diagnosis of these tumours. SNUC in the present study showed small hyperchromatic cells arranged in sheets and nests with no evidence of squamous or glandular differentiation or rosettes or fibrillary matrix. Immunohistochemically showed strong positivity for cytokeratin and negative for CD45, S100, NSE which excluded lymphoma, SNEC and olfactory neuroblastoma respectively. One case of small cell neuroendocrine carcinoma was included showed positive staining for cytokeratin, NSE, S100, synaptophysin confirmed the diagnosis of SNEC. Four cases of olfactory neuroblastoma were included one case typically showed uniform small tumour cells with salt and pepper type of chromatin arranged in lobules with focal areas of neurofibrillary material, diagnosis of olfactory neuroblastoma was given on morphology. IHC showed positivity for S100, NSE, chromogranin in all four cases. Negative results for cytokeratin, CD45 and HMB45 ruled out other round cell tumours in that area. Three cases of NHL in the nasal area were diagnosed, morphologically showed monotonous proliferation of tumour cells with condensed chromatin. IHC showed positivity for CD45 and CD20, typed as NHL-B cell type. Among these one case showed widespread subcutaneous swellings and histopathological examination of these swellings showed the morphological picture of NHL.

In the present study, three CNS tumours other than lymphomas were included. Squash cytology for intraoperative diagnosis was done in two cases and diagnosed as small blue round cell tumour. Out of the three cases one was diagnosed as Medulloblastoma-Desmoplastic/Nodular variant. Other case presented with D12 spinal cord mass, had past history of cerebellar medulloblastoma, based on morphology and IHC positivity for NSE diagnosed as secondary deposit medulloblastoma in the spinal cord and this was explained by the inherent tendency of the tumour to metastasise via CSF pathways [15].

Ependymoblastoma is a rare tumour included in the present study, microscopically tumour is highly cellular composed of small cells in diffuse sheets intervened by true rosettes and canals characterised by radial arrangement of cells with focal areas of hyalinisation. IHC markers Vimentin and NSE [16] showed strong positivity. Considering the morphological features and IHC markers other differentials anaplastic ependymoma, medulloepithelioma and medulloblastoma were excluded and a confirmatory diagnosis of Ependymoblastoma was made. Vimentin reactivity in ependymoblastoma was present in most cells throughout the tumour and its intensity was stronger indicating a later stage of maturation in the Ependymoblastoma [17].

Two cases of small cell carcinoma in lung, IHC showed positivity for cytokeratin, NSE and chromogranin, demonstrated the neuroendocrine differentiation. One case of small cell carcinoma ovary showed total replacement of ovarian architecture with montonus proliferation of round cells with few areas showing follicle formation. Immunohistochemistry showed diffuse and strong positivity for AE1-AE3 and negative for CD45, synaptophysin and chromogranin which ruled out malignant lymphoma and carcinoid respectively. A differential diagnosis of small cell carcinoma of ovary hypercalcaemic type and small cell carcinoma of ovary pulmonary type were given

as the preoperative calcium levels were not known. A single case of alveolar rhabdomyosarcoma in the retroorbital area included microscopic picture revealed clusters of small hyperchromatic tumour cells with scant cytoplasm and focal resemblance to alveolar patterns seen. Vimentin and desmin showed strong cytoplasmic positivity. CD45, CD99 and HMB45 were negative which ruled out lymphoma, Ewings sarcoma and small cell variant of melanoma respectively. Myogenin has been demonstrated to be extremely specific for rhabdomyoblastic differentiation.

A case of Nephroblastoma was included, the classical clinical presentation and microscopic characteristic triphasic appearance of epithelial component in the form of tubules, blastemal component against the myxoid stroma [18] made the diagnosis unmistakable, immunohistochemical markers were not done for the case. A single case of mesenchymal chondrosarcoma was included in the present study, morphologically tumour showed biphasic pattern, composed of undifferentiated mesenchymal small round cells interrupted by differentiated islands of hyaline cartilage. The IHC showed S100 protein positive in cartilaginous areas, negative in small cell component, hence confirming the diagnosis. CD99 was done which was negative in the undifferentiated component. According to Shakked RJ et al., vimentin positivity of the mesenchymal component was noted in 100% cases, S100 positivity in the cartilaginous component in 82% cases, and CD99 positivity in the non cartilaginous component in 67% cases [19]. A single case of Desmoplastic Round Cell Tumour (DSRTC) was included a trilinear co-expression of epithelial marker keratin, mesenchymal markers desmin and vimentin, and the neuronal marker NSE confirmed the diagnosis of desmoplastic small round cell tumour in the present case. CD99 can be positive in DSRCTs which is not seen in our case, but the staining pattern is usually cytoplasmic, as opposed to the membranous staining observed in Ewing sarcoma/PNET [20].

In the present study 96% cases of small round cell tumours were diagnosed based on morphology and IHC. IHC played an imperative role in diagnosing rare tumours like Ependymoblastoma, Small cell carcinoma ovary, DSRTC and other cases like Round cell tumours of nasal cavity, NHL extra nodal sites, PNET occurring in rare sites. In cases like medulloblastoma, small cell carcinoma lung, mesenchymal Chondrosarcoma a provisional diagnosis was offered based on morphology; however, IHC played a vital role for confirmation of the provisional diagnosis.

Limitation(s)

The limitation of this study was that the sample size was small and there was no follow-up of the cases.

CONCLUSION(S)

Small round cell tumours are a heterogeneous group of malignant neoplasms. Most common tumour was NHL with highest incidence in males and age group of >45-60 years. The present study highlighted the combined morphological and immunohistochemical approach for accurate typing and classification of round cell tumours. The IHC represents a rapid and cost- effective adjunctive tool to provide clear distinction among various tumour types as to categorise the patients in order to ensure an appropriate and specific treatment. The IHC combined with molecular studies provide a better diagnostic and prognostic workup.

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