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Histopathological study of Round Cell tumors- A retrospective study

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ABSTRACT
Background: Round Cell Tumors are heterogeneous malignancy featuring primitive undifferentiated small cell morphology. Small round cell tumors mostly occur in children, adolescents, and young adults. Because of their significant morphological overlap, have become a paradigm for an integrated approach to diagnosis. Immunohistochemistry (IHC) is the most common ancillary technique used for differential diagnosis of round cell tumors. Finding from all these studies are reviewed and interpreted in respect with clinical history, laboratory investigations, and diagnostic imaging finding.
Objectives: (i) To study the incidence, and age vs. sex wise distribution of round cell tumors. (ii) To study the Immunohistochemical (IHC) pattern of these different round cell tumors and correlate the morphological diagnosis with IHC to determine its role as a confirmatory or diagnostic marker of the round cell tumors.
Materials and Methods: As a part of study 75 (seventy-five) cases were selected during the year 2013-2015. Relevant findings were obtained. Biopsy tissues/ samples were fixed, paraffin embedded, sectioned and, stained with hematoxylin and eosin. IHC was performed on each case. Results were analyzed and compared.
Results: Out of 75 cases, there were 22 cases (29.33%) of Non-Hodgkin's lymphoma with the highest incidence. According to age wise distribution, the highest incidence was observed in 0-10 years of age group. According to sex wise distribution, a higher incidence was observed in males. There were 50 cases (66.66 %) of Males and 25 cases (33.33%) of Females. Overall M:F ratio was 2:1. Based on IHC, 22 cases of NHL were further classified into Burkitt's lymphoma, Lymphoblastic lymphoma, and Diffuse Large B-cell lymphoma. IHC study of PNET and Rhabdomyosarcoma showed CD 99(86.7%), NSE(73.3%) and Vimentin(100%) positivity and Desmin, Actin, CD 99 and Vimentin positivity respectively. IHC study of Neuroblastoma and medulloblastoma showed NSE, NF, Chromogranin, S 100 and Synaptophysin positivity and GFAP, Synaptophysin, Vimentin, and Ki67 positivity respectively.
Conclusion: Most frequent Round Cell Tumors are Non-Hodgkins Lymphoma, Neuroblastoma, Ewing/PNET and Rhabdomyosarcoma. Neuroblastoma, Retinoblastoma, Wilms Tumor, Hepatoblastoma show presentation in early childhood while Rhabdomyosarcoma is seen throughout childhood. The majority of round cells tumors have male predom- inance. This study emphasizes the role of immunohistochemistry (IHC) to arrive a definite diagnosis.
KEYWORDS: Small blue round cell tumors, Non-Hodgkin's lymphoma, Small cell undifferentiated tumors, Embryonal tumors, Primitive tumors, Childhood solid tumors

I. INTRODUCTION

Round Cell Tumors are heterogeneous malignancy featuring primitive undifferentiated small cell morphology.[1] Small round cell tumors mostly occur in children, adolescents, and young adults, and tend to involve the skeletal system or soft tissue. They constitute approximate 20% of solid tumor in children and because of their significant morphological overlap, have become a paradigm for an integrated approach to diagnosis

These tumors are often indistinguishable from each other microscopically. As a group, they have primitive or embry- onic appearance often present in misleading locations (Bone marrow metastasis from occult primary) and lack of specific morphological features that allowed for precise diagnosis without ancillary method.

The most common ancillary technique is IHC. Findings from all these studies are reviewed and interpreted in respect with clinical history, laboratory investigations, and diagnos- tic imaging finding. With the vast majority of small round cell tumors, this multimodal approach will yield a precise and differential diagnosis that direct further surgical intervention, oncologic management, follow-up, and prognosis.

So the aims & objectives of this study are:

1. To study the incidence and age & sex wise distribution of round cell tumors.
2. To study the Immunohistochemical (IHC) pattern of these different round cell tumors and

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correlate the morphological diagnosis with Immunohistochemistry (IHC) to determine the role of Immunohistochemistry (IHC) as a confirmatory or diagnostic marker of the round cell tumors.

II. MATERIALS AND METHODS

As a part of a histopathological study of Round cell tumors 75 (seventy-five) cases were taken during the year 2012-2014. Those biopsy tissues showing poor or fragmented yield and extensive crushing artifact were excluded from the study. Patients without clinical details were not included. Relevant clinical history, laboratory investigations and radio- logical findings were obtained.

Biopsy tissues/samples were fixed in 10% neutral buffer formalin, paraffin embedded were sectioned and stained with hematoxylin and eosin. Besides Hematoxylin and Eosin, special histochemical stains were used whenever they were required. IHC was performed on tissue blocks from each case using ABC technique with antigen epitope enhancement by heat. After this, results were analyzed and compared with other studies.

III. RESULTS

Out of 75 cases selected in the present study, there were 22 cases (29.33%) of Non-Hodgkin's lymphoma with the high- est incidence followed by 14 cases (18.66%) of Ewing's sar-coma, 7 cases (9.33%) of Rhabdomyosarcoma and 7 cases (9.33%) of Neuroblastoma. According to age wise distribu- tion of cases in the present study, the highest incidence was observed in 0-10 years of age group having 31 cases followed by 11-20 years of age group having 22 cases. Lowest inci- dence was observed in cases having age more than 60 years. According to sex wise distribution of cases in the present study, a higher incidence was observed in males; 50 cases (66.66 %) were of Male sex and 25 cases (33.33%) were of Female sex. Overall Male to Female ratio was 2:1. Highest Male to Female ratio of 3.4:1 was observed in Non-Hodgkin's lymphoma.

Immunohistochemistry was performed in each case, results were obtained and analyzed (Table 4). Based on IHC, 22 cases of NHL were classified further into Burkitt's lymphoma (8 out of 22 cases) (Figure 2), Lymphoblastic lym- phoma (7 out of 22 cases) and Diffuse large B-cell lymphoma (7 out of 22 cases). All 22 cases showed variable LCA pos- itivity (43% to 75%), Burkitt's lymphoma and DLBCL cases showed CD 20 positivity (100%) (Figure 3) and Lymphoblastic

lymphoma showed CD 3 positivity (100%) (Figure 1) which conclude that all lymphoblastic lymphoma cases were of T-cell type. IHC panel of Ewings sarcoma/PNET showed CD 99(86.7%) (Figure 4), NSE (73.3%) and Vimentin (100%) positivity. IHC study of Rhabdomyosarcoma showed Desmin (Figure 5), Actin, CD 99 and Vimentin positivity. IHC study of Neuroblastoma (Figure 6) showed NSE, NF, Chromogranin, S 100 and Synaptophysin (Figure 7) positivity. IHC study of retinoblastoma showed NSE, S 100 and Synaptophysin pos- itivity. IHC study of Wilms tumors (Figure 8) cases showed EMA, Vimentin (Figure 9), NSE and NF positivity. IHC study of medulloblastoma showed GFAP, Synaptophysin, Vimentin and Ki67 positivity

Table 1: Incidence of Round cell tumors in present study

Final diagnosis	Number of cases (%)
Non-Hodgkin's lymphoma	22 (29.33%)
Ewing's sarcoma	14 (18.66%)
Rhabdomyosarcoma	07 (9.33%)
Neuroblastoma	07 (9.33%)
Wilms tumor	04 (5.33%)
Retinoblastoma	06 (8.00%)
Medulloblastoma	10 (13.33%)
Hepatoblastoma	01 (1.33%)
Small cell osteosarcoma	01 (1.33%)
Mesenchymal chondrosarcoma	03 (4.00%)
Total	**75 (100.00%)**

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Table 2: Age wise distribution of Round cell tumors in present study

Final diagnosis	Age in years					
	0-10	11-20	20-40	40-60	60>>60	Total
Non-Hodgkin's lymphoma	-	03	07	10	02	22
Ewing's sarcoma	04	08	02	-	-	14
Rhabdomyosarcoma	02	04	01	-	-	07
Neuroblastoma	05	02	-	-	-	07
Wilms tumor	04	-	-	-	-	04
Retinoblastoma	06	-	-	-	-	06
Medulloblastoma	08	02	-	-	-	10
Hepatoblastoma	01	-	-	-	-	01
Small cell osteosarcoma	-	01	-	-	-	01
Mesenchymal chondrosarcoma	-	02	-	-	-	03
Total	**31**	**22**	**10**	**10**	**02**	**75**

Table 3: Sex-wise distribution of round cell tumors in present study

Final diagnosis	Sex distribution		M:F	Total
	Male	Female		
Non-Hodgkin's lymphoma	17	05	3.4:1	22
Ewing's sarcoma	09	05	1.8:1	14
Rhabdomyosarcoma	03	04	1:1.3	07
Neuroblastoma	04	03	1.3:1	07
Wilms tumor	03	01	3:1	04
Retinoblastoma	04	02	2:1	06
Medulloblastoma	06	04	1.5:1	10
Hepatoblastoma	01	00	1:1	01
Small cell osteosarcoma	01	00	1:1	01
Mesenchymal chondrosarcoma	02	01	2:1	03
Total	**50**	**25**	**2:1**	**75**

Table 4: Comparison of incidence of Round cell tumors in present study with another study

Diagnosis	Present study	Sajidhussain shah et al[2]
Non-Hodgkins lymphoma	29.3%	26.1%
Neuroblastoma	9.33%	5.1%
EWS/PNET	18.66%	8.7%
RMS	9.33%	7.7%
Wilms tumour	5.33%	5.1%
Retinoblastoma	8.00%	5.7%
Medulloblastoma	13.33%	10.81%

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Table 5: Comparison of age distribution of Round cell tumors in present study with another study

Diagnosis	Present study (Median age)	Sajidhussain shah et al[2] (Median age)
Non-Hodgkin's lymphoma	9	10-14
Neuroblastoma	3.5	0-4
Retinoblastoma	1.5	0-4
CNS tumor	12.4	10-14

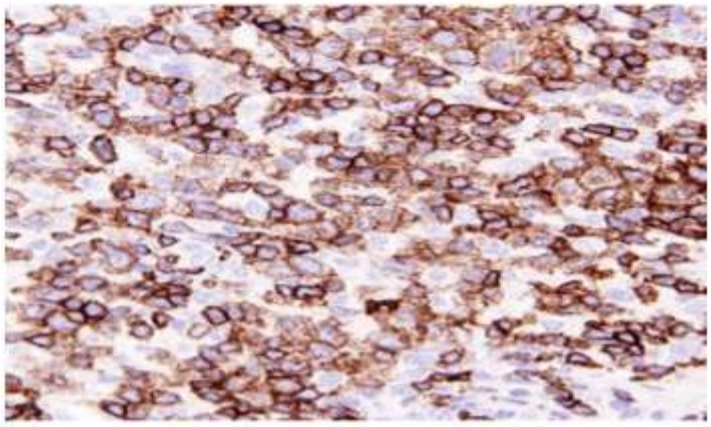

Figure1:CD3+ in Lymphoblastic Lymphoma 20x

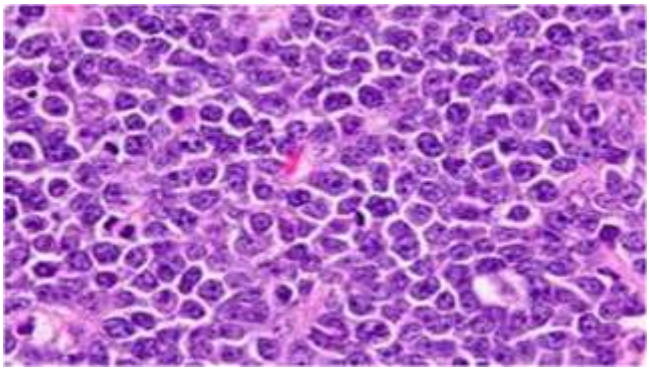

Figure2: Burkitt's Lymphoma40x

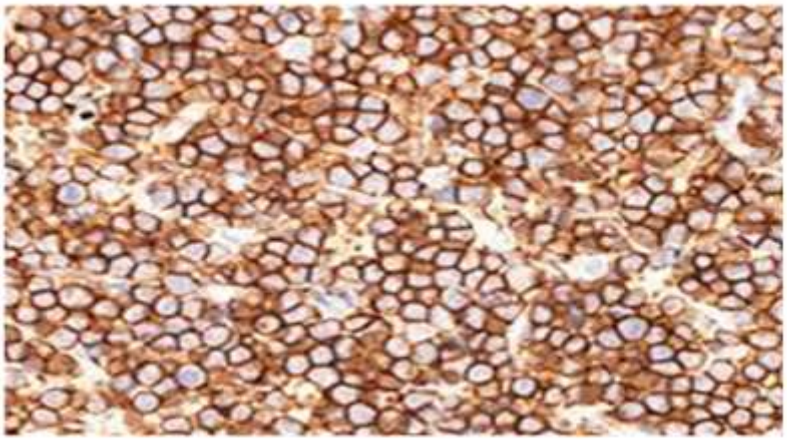

Figure3: CD 20+ in Burkitt's Lymphoma 40x

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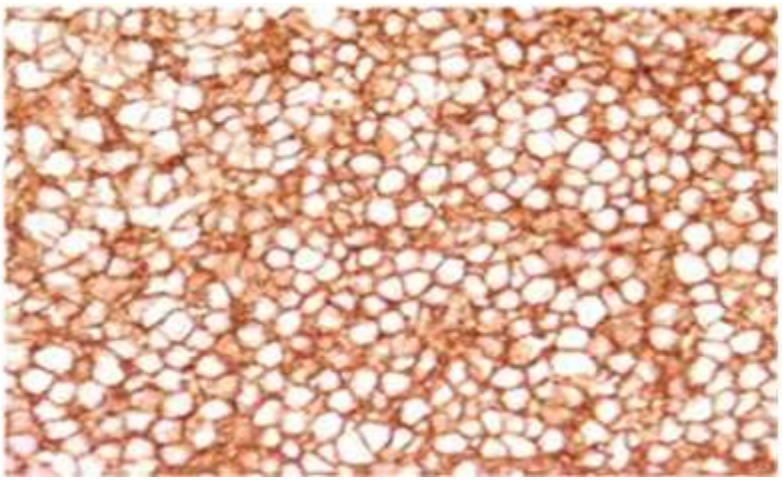

Figure4:CD 99+ in Ewing's Sarcoma 40x

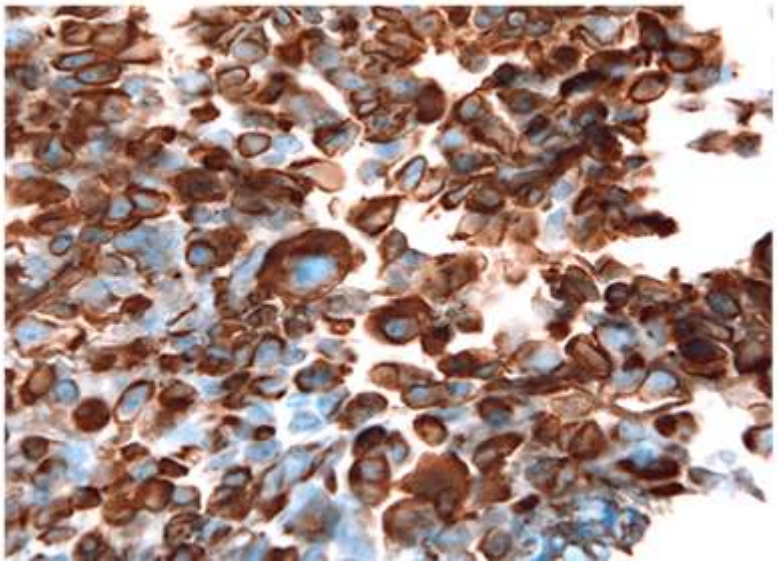

Figure5: Desmin Rhabdomyosarcoma.40x

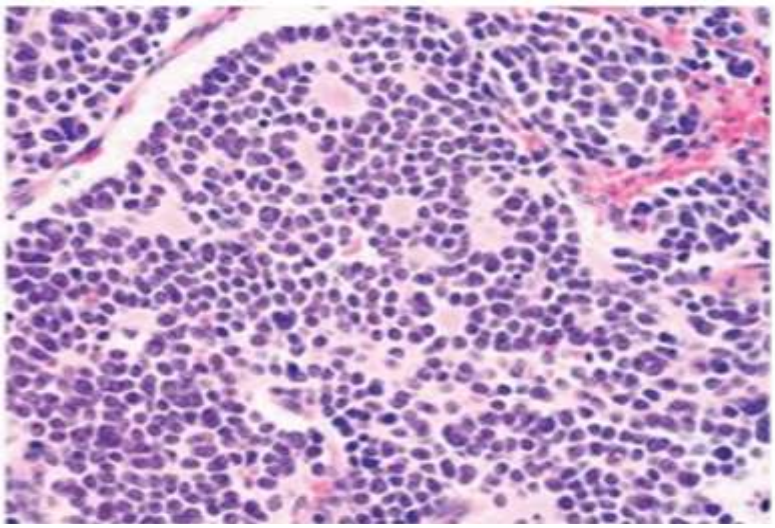

Figure6: Small round cells with rosettes in Neuroblastoma 40x

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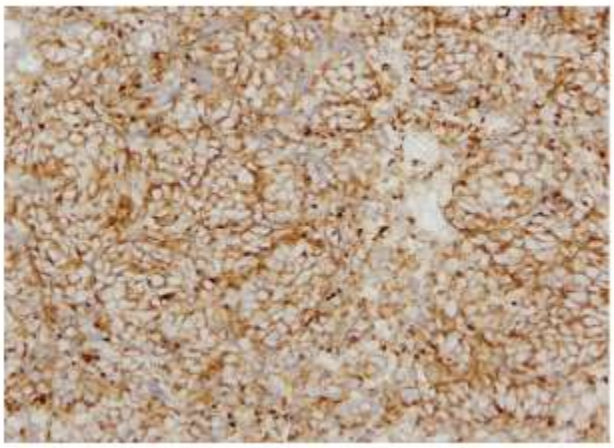

Figure7: Synaptophysin in Neuroblastoma 20x

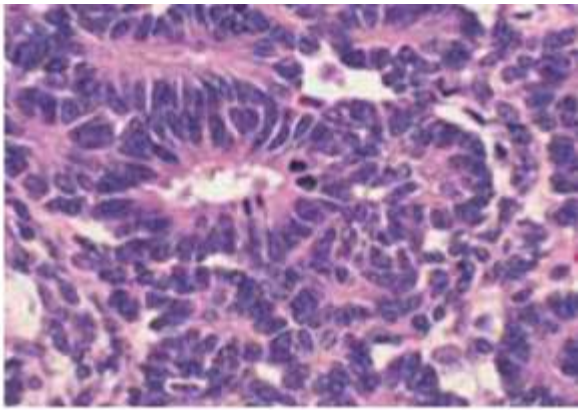

Figure8: Wilmstumor-Primitiveepithelial differentiation

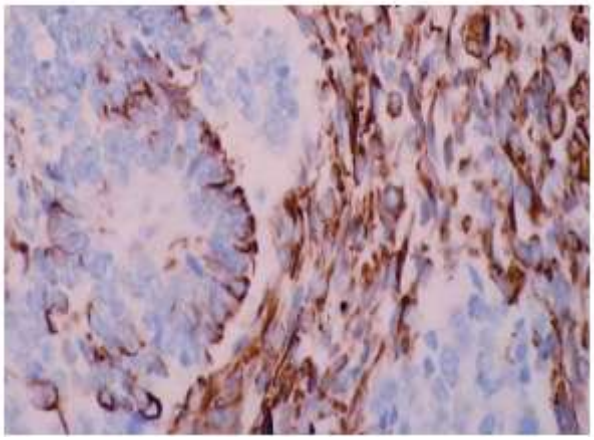

Figure9: VimentininWilmstumor40x

in cases of Non-Hodgkin's lymphoma of which results are comparable with the study of Sajidhussain shah et al2 hav- ing a median age of 10-14 years of age group. Same results were also obtained for neuroblastoma and retinoblastoma with median age of 3.5 years and 1.5 years in present study respectively and 0-4 years of age group in Sajidhussain shah et al.2 In comparison of sex ratio among round cell tumours, Non-Hodgkin's lymphoma, neuroblastoma, retinoblastoma and RMS cases showed male:female ratio of 3.4:1, 1.3:1, 2.5:1 and 1:1.3 respectively, and results of which are compa- rable with study of Sajidhussain shah et al.[2] having male:fe- male ratio of 5.6:1, 1.2:1, 2:1 and 1:1.4 respectively.

Immunohistochemistry was performed for each case in present study and results were

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obtained, analyzed and com- pared with other studies. The immunohistochemical pattern obtained in present study and comparison with other studies are given in Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12.

Our study revealed that most frequent Round Cell Tumors are Non-Hodgkins Lymphoma, Neuroblastoma, Ewing/PNET and Rhabdomyosarcoma. Neuroblastoma, Retinoblastoma, Wilms Tumor, Hepatoblastoma show pres- entation in early childhood while Rhabdomyosarcoma are seen throughout childhood and Ewing/PNET, Non-Hodgkin lymphoma, and central nervous system tumors are com- monly seen in adult and elderly. The majority of round cells tumors have male predominance. The age, site, light microscopy and other investigations do give some idea about the likely diagnosis, but this study emphasizes the role of immunohistochemistry (IHC), a panel of antibodies to arrive a definite diagnosis. The absence of antigen expres- sion does not rule out the diagnosis, especially incorrect clinicopathological settings. Thus the use of other ancillary technique like cytogenetics and ultrastructural studies are recommended.

Diagnosis	Present study (M:F)	Sajidhussain shah et al[3] (M:F)
Non-Hodkins lymphoma	3.4:1	5.6:1
Neuroblastoma	1.3:1	1.2:1
Retinoblastoma	2.5:1	2:1
Wilms tumour	3:1	2.2:1
RMS	1:1.3	1:1.4
EWS/PNET	1.8:1	5:1

Table 6: Comparison of sex ratio of Round cell tumors in present study with another study

Diagnosis	IHC Marker	Positive (%)
Burkitt's lymphoma	LCA	57%
(8 out of 22 cases of NHL)	Ki 67(>90%)	100.0%
	CD20	100%
	CD10	57%
Lymphoblastic lymphoma	LCA	43%
(7 out of 22 cases of NHL)	CD99	29%
	CD3	100%
Diffuse large B-cell lymphoma	LCA	75%
(7 out of 22 cases of NHL)	CD20	100%
	CD3	12.5%

Table 7: Immunohisto chemical pattern in Non-Hodgkins Lymphoma

Table8: Comparison of immunohistochemical pattern in Ewing's sarcoma/ PNET

IHCmarker	Presentstudy	Brahmi Vetal[3]	Chang TKetal[4]	Domogalaetal[5]
CD99	86.7%	60.0%	70.0%	94.0%
NSE	73.3%	75.0%	83.0%	-
Vimentin	100%	-	100.0%	84%

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Table9: Comparison of Immunohistochemical pattern in Rhabdomyosarcoma

IHCMarker	Presentstudy	Van Unniketal[6]	Rossia[7]	Afshin[8]
Desmin	85.7%	95.0%	>90%	97%
Actin	42.8%	95%	-	-
CD99	28.5%	-	5%	27.4%
Vimentin	85.7%	-	88%	-

Table10: Comparision of immunohistochemical pattern in Neuroblastoma

IHC Marker	Presentstudy	Brahmi Vetal[3]	Chang TKetal[4]	Domogalaetal[5]
NSE	85.71%	66.0%	-	70.0%
NF	71.42%	25.0%	30.0%	-
Chromogranin	71.42%	-	100%	100%
S100	14.28%	-	-	-
Synaptophysin	57.1%	-	-	-

Table11: Comparison of immunohistochemical

IHC Marker	Presentstudy
NSE	66.7%
S100	50.0%
Synaptophysin	83.3%

These are common IHC marker which were comparable to studydonebyDevoek etal[9]

Table12: Immunohistochemical pattern inWilm's tumor

IHC Marker	Positive (%)
EMA	25%
NF	25%
NSE	100%
Vimentin	100%

IV. CONCLUSION

Most frequent Round Cell Tumors are Non-Hodgkins Lymphoma, Neuroblastoma, Ewing/PNET and Rhabdomyo- sarcoma. Neuroblastoma, Retinoblastoma, Wilms Tumor, Hepatoblastoma have presentations in early childhood while Rhabdomyosarcoma are seen throughout childhood. The majority of round cells tumors have male predominance. This study emphasizes the role of immunohistochemistry (IHC) to arrive a definite diagnosis.

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