RESEARCH ARTICLE

IMMUNOHISTOCHEMISTRY: A DIAGNOSTIC TOOL FOR ACCURATE CHARACTERIZATION OF UNDIFFERENTIATED MALIGNANT TUMOURS

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ABSTRACT

Background: The impact of diagnostic immunohistochemistry for the surgical pathology is legendary especially when it provides true identity of undifferentiated tumours. This not only is important for prognostication & therapy but also provide further insights into the pathobiology of these tumours.

Aims & Objective: This study was undertaken to determine the role and significance of immunohistochemistry for accurate diagnosis and subtyping of undifferentiated malignant tumours as it is essential in guiding therapy and prognosis.

Material and Methods: Immunohistochemical staining (IHC) performed was based on Peroxidase Antiperoxidase (PAP) method on paraffin sections, using appropriate mono/polyclonal antibodies. Total 74 cases including six consultation cases were studied from August 2008 to November 2011, which were reported as undifferentiated or poorly differentiated malignant tumor using routine hematoxylin- eosin stains.

Results: The histopathology and IHC reports of 74 tumours were reviewed and assigned to appropriate categories. It was possible to arrive at a diagnosis in 73 cases (98.65%) with the help of IHC. Carcinoma was the commonest diagnosis (27 cases, 36.50%) followed by lymphoma (18 cases, 24.32%), sarcoma (14 cases, 18.92%), malignant melanoma (3 cases, 4.05%) and neuroblastoma (3 cases, 4.05%).

Conclusion: Immunohistochemistry is helpful in the majority of difficulties arising during histological diagnosis of undifferentiated malignant tumours and serves as a diagnostic, prognostic, and predictive tool.

Key-Words: Immunohistochemistry; Undifferentiated Malignant Tumour; Peroxidase Anti-Peroxidase Method; Differential Diagnosis

Introduction

Histopathology has been and always will be the cornerstone to tumour diagnosis. Tumours become more poorly differentiated as part of tumour progression; they are histologically described as undifferentiated, anaplastic, large cell, small round cell malignant tumours etc. It becomes very important to determine the histogenesis of undifferentiated tumours as to whether it is epithelial, lymphoid or mesenchymal in origin, because treatment protocols and thereby the prognosis are quite different.[1-5]

IHC has brought a 'Brown Revolution' to histopathology laboratories that point towards a specific histogenetic origin of histologically undifferentiated tumours and help in subtyping the tumour to provide targeted treatment.[4,6]

Materials and Methods

The present study was undertaken in the department of pathology in a tertiary care center. Total 74 cases were studied including six consultation cases from August 2008 to November 2011, which were reported as undifferentiated or poorly differentiated malignant tumor using routine hematoxylin-eosin stains. There were 43 males and 31 females, and their ages ranged from 2 year to 90 years. The histopathology and immunohistochemistry reports were reviewed and assigned to appropriate category.

The clinical history including age, gender and location of tumor were obtained from histopathology request forms. All surgical biopsies and representative part of resected specimen were fixed in 10% neutral buffered formalin & processed. After routine paraffin processing, sections were cut and stained by hematoxylin-

eosin method and relevant panel of immunohistochemical antibodies were applied. The technique used was based on PAP (peroxidase anti-peroxidase) method. 4 um sections were mounted on poly-l-lysine coated slides (pre-treatment with 1% acid alcohol), deparaffinized with xylene and blocked for peroxidase with 3% H2O2. Antigen retrieval was done by microwave (temperature according to target antigen) using citric buffer /Tris-EDTA buffer. Primary antibodies (DAKO and Bio genex) were applied and incubated followed by secondary antibody and peroxidase-antiperoxidase complex. 3-3' diaminobenzidine tetrahydrochloride (DAB) was used as a chromogen, and the counter stain with Harris' hematoxylin and mounted in distrene dibutylphthalate xylene (DPX).[6,7]

A primary panel of antibodies consisting of cytokeratin (CK), common leucocyte antigen (LCA), vimentin and S-100 was applied first. Additional antibodies were used for final diagnosis; in carcinoma the antibodies used were carcinoembryonic antigen (CEA), CK7, CK20, chromogranin (CGA), prostate specific antigen (PSA) and epithelial membrane antigen (EMA). In lymphoma CD20 and CD79a (pan B-cell markers), CD3 and CD5 (pan T-cell markers), CD15 and CD30 (Hodgkin lymphoma marker), CD10, CD23 and EMA were applied. EMA, desmin, smooth muscle actin (SMA), CD99, Bcl2, nonspecific enolase (NSE), CD68, myogenin, CGA, synaptophysin, neurofilament (NF), CD34, HMB45, glial fibrillary actin protein (GFAP) and other antibodies used to diagnose soft tissue sarcoma, malignant small round cell tumors, malignant melanoma and neural tumors.

In present study, weak/moderate/strong staining considered as positive staining and equivocal staining considered as negative staining according to the distribution patterns of immunostaining whether nuclear/cytoplasmic/membranous or any combination for final diagnosis.

Results

A primary panel of antibodies was applied first according to patient's age, tumor location and histological findings. Among 74 cases, bone/soft tissue was most common site followed by gastrointestinal tract (G.I.T), lymphoid tissue and respiratory tract (Table 1). It was possible to arrive at a diagnosis with the help of IHC in 98.65% of cases and in 1.35% (one case) IHC was not contributed as small biopsy was received and tissue block was exhausted so confirmatory diagnosis was not given. The most frequent diagnosis as shown in table II was carcinoma in 36.50% (27 cases) followed by lymphoma in 24.32% (18 cases). Other diagnosis was mentioned in table 2.

In present study out of 74 cases, 13 cases (17.60%) of poorly differentiated adenocarcinoma were diagnosed from which seven colon adenocarcinoma (CK+, CEA+, CK20+), three prostatic adenocarcinoma (CK+, vimentin+, PSA+), two gastric adenocarcinoma (CK+, CEA+, CK7-) and one metastasis in axillary lymph node (CK+, EMA+, Her2neu+). CEA was found reactive in all cases of poorly differentiated adenocarcinoma of colon and stomach.

Four cases (5.40%) of undifferentiated nasopharyngeal carcinoma were diagnosed. All were reactive for CK, one of four reactive for EMA, one of four reactive for NSE & vimentin. All four cases were non-reactive for LCA, S-100, synaptophysin and chromogranin. Three cases (4.05%) were diagnosed as poorly differentiated neuroendocrine carcinoma. Two of three cases were non-reactive for all four primary panel antibodies but reactive for chromogranin, synaptophysin, CD99 (focal positive) and EMA (focal positive). One of 3 was reactive for CD56, CK and vimentin. All three were reactive for NSE. There were four poorly differentiated squamous cell carcinoma (CK+, EMA+), one anaplastic carcinoma (CK+, vimentin+, S-100+,CK7-, CK20-, CD56-, CD117-, CEA-, HMB45-, CGA-, desmin-, SMA-) and one undifferentiated (sarcomatoid) carcinoma (CK+, vimentin+, AFP-, desmin-, HMB45-) diagnosed.

Lymphoma was accounted for 18 cases (24.23%, LCA+) out of 74 cases. All were diagnosed as non-Hodgkin's lymphoma (NHL) including nine cases of nodal and nine cases of extra nodal sites. Out of 18 cases, 14 were B-cell lymphomas (CD20+) including 12 cases of diffuse large B cell

lymphoma, one low grade lymphoma (CD5+, CD23+) and one Blastoid mantle cell lymphoma (CD5+, CD23-). Four cases were of T-cell type (CD3+) including one anaplastic large T cell lymphoma (CD30+, EMA-), one T- cell lymphoblastic lymphoma (CD99+, CD3+, CD5+, CD10+), one natural killer/T cell lymphoma nasal type (CD34+) and one peripheral T cell lymphoma.

Sarcoma 14 cases (18.92%, vimentin+) were diagnosed including three synovial sarcoma (CK+, EMA+, calretinin+, Bcl2+) followed by two Ewing's sarcoma (ES)/primitive neuroectodermal tumor (PNET) (CD99+) and two liposarcoma (S-100+, CD34+). Other diagnoses were one malignant peripheral nerve sheath tumor (S-100+, EMA+), one pleomorphic leiomyosarcoma (S-100+, desmin+, SMA+), one pleomorphic malignant fibrous histiocytoma (MFH) (CK+, EMA+, CD68+), one embryonal rhabdomyosarcoma (CK+, S-100+, desmin+, myogenin+), one osteogenic sarcoma (desmin+, CD99+) and one pleomorphic sarcoma (CK+, S-100-, desmin-, SMA-, HMB45-). IHC was noncontributory in one case due to block exhaustion.

Three cases (4.05%, vimentin+, S-100+, HMB45+) of malignant melanoma were diagnosed including one amelanotic melanoma (HMB45-), one malignant melanoma of soft part (clear cell sarcoma) and one small cell amelanotic melanoma.

Other cases diagnosed were three neuroblastoma (S-100+, NSE+, NF+), two desmoplastic small round cell tumor (desmin+, EMA+, NSE+), one germ cell tumor (anaplastic dysgerminoma; vimentin+, PLAP+, CD117+), one carcinosarcoma (CK+, vimentin+), one pleuropulmonary blastoma (vimentin+, S-100+, CD34-,CD99-, SMA-, desmin-), one Wilm's tumor (EMA+, NSE+, WT1-, desmin-), one pheochromocytoma (S-100+, CGA+, EMA-, calretinin-, CD56-, inhibin-, CK7-), one glioblastoma multiforme (GFAP+, EMA-) and one interdigitating dendritic cell tumor (CD3+, CD5+, CD23+, CD68+, Bcl2+, CD10-, CD79a-, CD20-, CD56-, CD21-, EMA-, HMB45- and CGA-).

In three cases entirely different diagnosis was made out after IHC study. First of three was interdigitating dendritic cell tumor which is a rare diagnosis. On morphology it was suspected as NHL and was picked after IHC study. Second case was Non-Hodgkin's lymphoma and suspected morphology was that of rhabdomyosarcoma. This case was sent for review from outside and showed positive markers for lymphoma. Third case was suspected as malignant small round cell tumor which showed non reactivity with all markers except vimentin and focally for CK. Later on case was referred to TMH, Mumbai and reported as poorly differentiated neuroendocrine carcinoma (focal CK+, NSE+, CD56+).

Table-1: Distribution of Study Cases on the Basis of Location of Tumor

Sites	N (%)
Bone / Soft tissue	18 (24.32)
Gastrointestinal tract	15 (20.27)
Lymphoid tissue	10 (13.51)
Respiratory tract	10 (13.51)
Male genital tract	7 (9.48)
Female genital tract	6 (8.11)
Skin	2 (2.70)
Central nervous system	1 (1.35)
Kidney	1 (1.35)
Adrenal	1 (1.35)
Lung	1 (1.35)
Others	2 (2.70)
Total	74

Table-2: Distribution of Cases on the Basis Of Morphological Diagnosis and Positivity of Primary Panel Antibodies

Diagnosis		N (%)	Positive Cases/ Total Cases			
			CK	LCA	Vimentin	S-100
Carcinoma	Poorly Differe-ntiated Adeno	13(17.60)	11/13	0	3/13	2/13
	Poorly Differentiated	4(5.40)	4/4	0	1/4	0
	Undifferentiated	1(1.35)	1/1	0	1/1	0
	Anaplastic	1(1.35)	1/1	0	1/1	1/1
	Sarcomatoid	1(1.35)	1/1	0	1/1	0
	Nasopharyngeal	4(5.40)	4/4	0	1/4	0
	Neuroendocrine	3(4.05)	1/3	0	1/3	0
	Total	27 (36.5)				
Lymphoma		18(24.32)	0	18/18	6/18	0
Sarcoma		14(18.92)	6/14	0	14/14	6/14
Malignant Melanoma		3(4.05)	0	0	3/3	3/3
Neuroblastoma		3(4.05)	1/3	0	0	3/3
Desmoplastic Small Round Cell Tumour		2(2.71)	1/2	0	2/2	0
Glioblastoma Multiforme		1(1.35)	0	0	1/1	0
Pleuropulmonary Blastoma		1(1.35)	0	0	1/1	1/1
Carcinosarcoma		1(1.35)	1/1	0	1/1	0
Pheochromocytoma		1(1.35)	0	0	0	1/1
Wilm's Tumour		1(1.35)	1/1	0	1/1	0
Dendritic Cell Tumour		1(1.35)	0	1/1	1/1	1/1
Germ Cell Tumour		1(1.35)	0	0	1/1	0
Total		74				

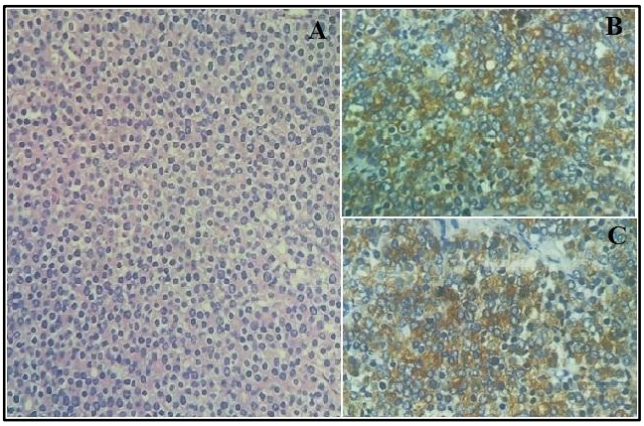

Figure-1: Rectal Mass: Poorly differentiated Adenocarcinoma. (A) Diffuse round cell infiltration (H&E, X20). (B) Tumor cells showing cytoplasmic carcinoembryonic antigen positivity and (C) cytoplasmic CK20 immunoreactivity (IHC-DAB, X20).

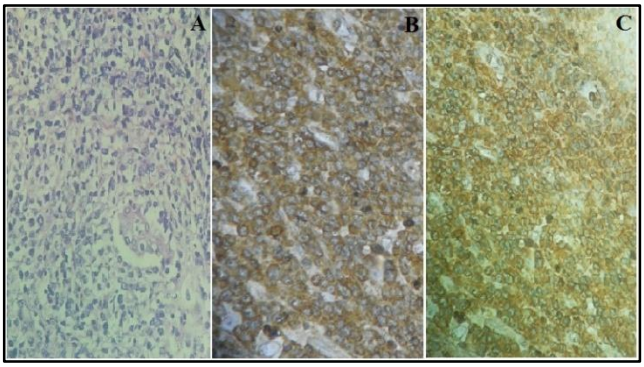

Figure-2: Left Testicular Mass: Diffuse Large B Cell Lymphoma. (A) Interstitial proliferation of tumor cells which surrounded and infiltrate the seminiferous tubule (H&E, X20). Tumor cells showing membranous immunoreactivity to leucocyte common antigen (B) and CD 20 (C) (IHC-DAB, X20).

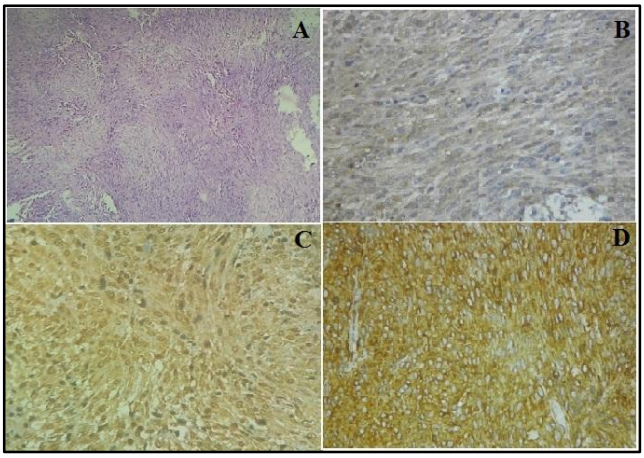

Figure-3: Retroperitoneal Mass: Synovial Sarcoma (Monomorphic Variant). (A) Monotonous population of spindle cells arranged in fascicles (H&E, X10). Immunoreactivity includes Cytokeratin (B) faint cytoplasmic, Calretinin (C) diffuse nuclear & membranous, Bcl-2 (D) intense cytoplasmic & nuclear noted (IHC-DAB, X20).

Discussion

The histologic diagnosis of cancer and the categorization of the proper tumour type are

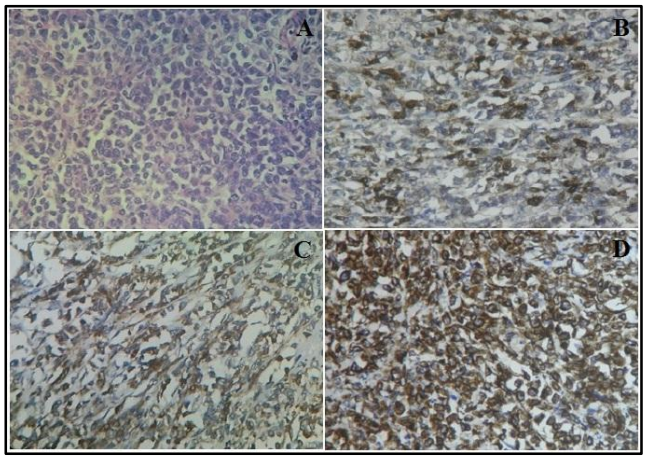

Figure 4: Left Testicular Mass: Interdigitating Dendritic Cell Tumor. (A) Diffusely arranged round to spindle cells with brisk mitotic activity (H&E, X20). Strong cytoplasmic and nuclear S-100 (B), diffuse cytoplasmic CD68 (C) and intense cytoplasmic Vimentin (D) immunoreactivity noted (IHC-DAB, X20).

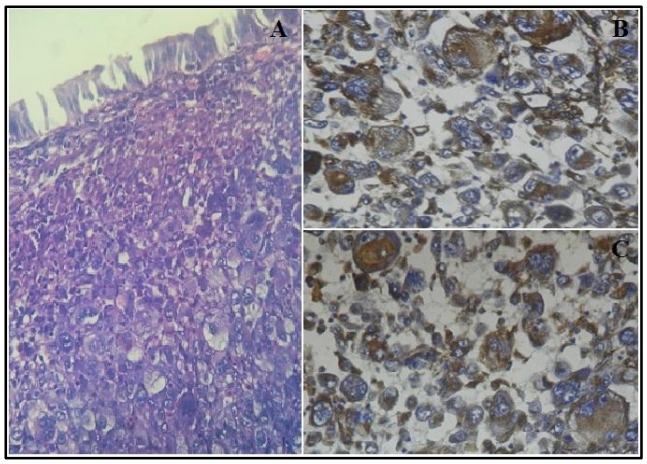

Figure-5: Gall Bladder Neck Mass: Sarcomatoid Carcinoma. (A) Pleomorphic diffusely arranged neoplastic cells extending up to submucosa (H&E, X40). Strong cytoplasmic immunoreactivity with Cytokeratin (B) & Vimentin (C) noted in tumor cells (IHC-DAB, X20).

essential for the adequate treatment. Sometimes it is difficult or impossible to make correct diagnosis because of atypical clinical presentation or undifferentiated histopathology features and labeled as undifferentiated malignant tumor which comprises 5-10% of all diagnosed tumors.[5] It is possible to subtype malignant tumors accurately with the help of recent advances in technology.[8,9]

In present study, it was possible to arrive at a diagnosis in 73 (98.65%) out of 74 cases studied. The results were correlated with some authors.[1,4,9-13] Carcinoma was the most frequent diagnosis, as some of the poorly differentiated carcinomas were also included in this study for confirmation. The findings were similar to other studies.[1,9-12]

CEA was found reactive in all nine cases of poorly differentiated adenocarcinoma of colon and stomach. CEA positivity has no prognostic significance for either response or survival.[14] In present study two cases out of nine cases poorly differentiated adenocarcinoma were reactive for CK20 and all cases were non-reactive for CK7. Dabbs studied that colorectal carcinoma show CK7 non reactivity in 50% cases and CK20 non reactivity in 5% of cases, while gastric adenocarcinoma show CK7 non reactivity in 20% cases and CK20 non reactivity in 40% cases.[6] As current study included only poorly differentiated adenocarcinoma, increased percentage of non-reactivity for CK7 and CK20 were found.

The diagnosis of lymphoma was compared with others.[1,9-12] Not only lymphoma was the second common diagnosis but also accounted for such cases where the diagnosis was not suspected on H&E examination. This is because of the wide variety of morphological features seen in lymphoid tumors.[1] Positive reaction against only one antibody (LCA) in the panel excludes other possibilities except for few ALCL and lymphoblastic lymphoma. Immunohistochemical studies should be performed with a panel of antibodies to minimize errors in interpretation because of complex and overlapping antigenic expression by tumor cells.[1] Characterization of all Non-Hodgkin's lymphomas is done into B or T cell types according to the WHO classification of lymphoid neoplasms. In all suspected cases of lymphomas, a panel of antibodies including LCA, CD20 (Pan B-cell markers), CD3 (Pan T-cell markers), CD5, CD10, CD23, Bcl2, CD15 and CD30 were used. EMA and CD30 are also used in suspected cases of ALCL. Now a day's large number of cases of ALCL are diagnosed which in the past may have been misdiagnosed as Hodgkin's lymphoma or diffuse large B-cell lymphoma.[4] In present study one case of ALCL was diagnosed.

In this study one case was diagnosed as blastoid mantle cell lymphoma as it was reactive for CD20, CD5 and negative for CD23. However we advised cyclin D1 and further cytogenetic study for confirmation. In one case of T-ALL, focal CD10 positivity noted which is justified as few T-ALL can also express focal CD10.[6] One case of NK/T-cell lymphoma nasal type was diagnosed which showed reactivity for LCA, CD3, vimentin and non-reactive for CD5, EMA, NSE and chromogranin. However further IHC study for CD56 and granzyme B was advised for confirmation. There are prognostic and therapeutic differences between B and T Non-Hodgkin's Lymphomas which make immunohistological characterization very important and can used for targeted therapy.[4,15,16]

The diagnosis of sarcoma was compared with various studies.[1,9,12] This was a major area where morphology was invariably supplemented by IHC for establishing the histogenetic origin/ expression, since a variety of soft tissue sarcomas share common microscopic patterns. Diagnosis of sarcoma is not based on the expression of vimentin alone. In addition to mesenchymal cells, vimentin is also expressed in epithelial cells.[2] In carcinomas with spindle cell morphology, keratin expression may be lost and only vimentin may be expressed. Vimentin expression also serves as an internal control to assess antigenic preservation as its antigenicity is best preserved in frozen and formalin-fixed tissues and to select fields optimal for the expression of other markers so it is used as positive internal control in all cases.[1,2,17] In undifferentiated carcinomas vimentin is still reactive because, as the cells become dedifferentiated, they lose the characteristics of the origin tissue.[18] CK reactivity is seen in 76% of pleomorphic MFH and less than 10% in embryonal rhabdomyosarcoma.[6] Three cases of synovial sarcoma were diagnosed on the basis of its positivity for vimentin in the spindle cell portion and cytokeratin and EMA Positivity in the epithelial like are of the tumor. In one case out of four were CD99 and S-100 positive. Poorly differentiated synovial sarcoma shows CK7 positivity, which distinguish it from ES/PNET which is negative.[19]

Two cases of ES/PNET were diagnosed. CD99 positivity is seen in almost all cases of ES/PNET, although it is not very specific because it is shown in several other soft tissue sarcomas (i.e. synovial sarcoma, granulocytic sarcoma and mesenchymal chondrosarcoma) and lymphoblastic lymphomas.[6,20] In both cases diagnosis was given in context with tumor morphology, anatomical

site, clinical & radiological findings. One case diagnosed as T-cell lymphoblastic lymphoma which showed positivity for CD 99 but showed negative staining to vimentin hence the possibility of EWS/PNET was eliminated.

The term MFH is preferably replaced by pleomorphic high grade sarcoma, not further specified, or pleomorphic (myo) fibrosarcoma but it's a contextual issue. It is best defined immunophenotypically by the presence of vimentin in the absence of any lineage-specific markers.[6,17] In present study one case was identified as pleomorphic MFH.

Pleomorphic liposarcoma are commonly highly pleomorphic, resembles MFH except for the regular interspersion of pleomorphic lipoblasts or signet-ring cell type which shows focal positivity for S-100.[17,21] It should be expected that pleomorphic and dedifferentiated liposarcomas manifest immunoreactivity patterns like those of MFH. Such tumors are typically nonreactive for epithelial and myogenic markers.[6,17] As reported in present study, two cases were non-reactive to CK, EMA, desmin, SMA and positive for vimentin and S-100.

One case diagnosed as osteogenic sarcoma although focal positivity was present for desmin, however morphology was that of osteogenic sarcoma. It can also express desmin, CK, S-100, SMA, EMA, CD99 and that should not lead to diagnostic pitfall.[6] Three cases of malignant melanoma were diagnosed; HMB 45 was negative in one case. Melan A was not available. HMB45 is a highly specific marker and S-100 protein is a sensitive marker for melanomas, including amelanotic and spindle cell variants.[20,22] One study of Matthew et al (2002)[22] showed that the specificity of HMB45 for detecting melanoma was 96.9% and, thus, considerably higher than that of S-100 (88%). However, HMB45 is detectable in only 50% to 75% of all melanomas. Therefore, it is less sensitive as a marker for melanoma than S-100 protein. In addition, spindle cell and desmoplastic melanomas tend to be nonreactive with HMB45.

One case diagnosed as glioblastoma multiforme as it showed strong reactivity for GFAP, vimentin and negative for EMA, which ruled out possibility of anaplastic meningioma. Sarcoma is easily confused with glioblastoma on H&E staining, but GFAP reveals the glioblastoma.[6] One case of interdigitating dendritic cell tumor was diagnosed. It was previously diagnosed as NHL on the basis of morphology as it is rare tumor. Further IHC for CD1a and ultra-microscopy study was advised for further confirmation. One case of pleuropulmonary blastoma was confirmed. IHC is helpful to differentiate it from rare cases of cystic synovial sarcoma of the lung or chest wall, as pleuropulmonary blastoma is nonreactive for CK, EMA and CD99.[23]

Conclusion

A panel approach which is composed of carefully selected antibodies is always recommended so that an antigenic profile of positive as well as negative markers will provide the most accurate characterization of tumor. Though IHC is most rapid and cost effective method for melding morphological analysis of neoplasm, molecular technique and electron microscopy should be integrated selectively in future at the discretion of the pathologist to provide rapid and comprehensive solutions for problem cases because of the presence of overlapping morphologic and immunophenotyping features.

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