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To Evaluate the Utility of Immunohistochemistry in the Diagnosis of Different Types of Central Nervous System Tumours Using a Panel of Antibodies

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Abstract

Background: Central nervous system (CNS) tumors which constitute 1-2% of all tumors. They often present diagnostic dilemmas because tumors ofvarying histogenesis show considerable overlap in morphological features and divergent differentiation. Immunohistochemistry (IHC) has become an important tool in the diagnosisof brain tumors. The judicious use of a panel of selected immunostains is unquestionably helpful indiagnostically challenging cases as an accurate histologicdiagnosis helps in predicting the clinical outcome of various brain tumors. *Materials and Methods:* A total of 40 consecutive suspected CNS tumours wereevaluated using routine Hematoxylin and Eosin stain. In addition, an IHC panel comprising of glial fibrillary acidic protein (GFAP), S-100 protein (S-100), epithelial membrane antigen (EMA), vimentin (VIM), synaptophysin (Synapto), neurofilament (NFP), and cytokeratin(CK) were used for confirmation of diagnosis. Proliferation in all cases was assessed using MIB-1 labelling index. *Results:* Astrocytomas occurred most frequently in the study, followed by meningiomas. Other rare tumors included primary CNS lymphomasand mesenchymal tumors. Single case of rare primary CNS synovial sarcoma was also encountered. Grading of the tumors wasdone as per the revised World Health Organization criteria. *Conclusion:* This study highlights the utility of immunohistochemistry as an adjunct to routine histologic diagnosis for proper classification and grading of CNS neoplasms.

Keywords: Brain Tumors; Histopathology; Immunohistochemistry.

Introduction

The subject of central nervous system (CNS) tumours is looked upon with apprehension by practitioners with some justification as there is a plethora of terminologies and systems of classification and grading with bewildering names of lesions and their apparently endless histological variations.

Primary malignant brain tumours are rare. The annual global age-standardized incidence of primary malignant brain tumors is approximately 3.7 per 100,000 for males and 2.6 per 100,000 for females, while the age-standardized mortality for primary malignant brain tumors is approximately 2.8 for males and 2.0 for females per 100,000 [1].

They constitute 1-2% of all neoplasms**.**Astrocytomas are the most common primary tumors. Gliomas constitute 38.7% of CNS tumors of which high grade gliomas are 59.5% and low grade gliomas are 33.1% [2]. CNS is also the a common target of metastatsis. Approximately 10- 50% of patients with systemic malignancies, especially breast and lung carcinomas, develop brain metastasis during the course of their disease [3].

Although clinical inputs, modern imaging techniques, and peroperative findings offer some valuable clues to the diagnosis, histopathologic examination is the sine qua non of diagnosis of brain tumors. Nevertheless, histolopathological diagnosis of a brain tumor is not always straightforward and pathologists often face diagnostic dilemmas because of overlap in morphological features among different

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categories of tumors and also due to divergent differentiation within the same tumor [4]. Non-neoplastic lesions can also mimic tumors. Hence, application of immunohistochemistry (IHC) has become imperative for an exact diagnosis and subtyping. The judicious use of a panel of selected immunostains is unquestionably helpful in diagnostically challenging cases. In addition, IHC is also of great help in predicting the prognosis for certain brain tumors [3, 4].

Hence the study was designed to evaluate the immunoexpression pattern of different types of CNS tumours using a panel of antibody, in order to assess the immunoexpression pattern in various histological types andalso to correlate the utility of IHC in the accurate classification and grading of these neoplasms.

Material and Methods

In this prospective study, biopsies from 40 consecutive cases of suspected CNS tumours of varying grades and types were included in the study. Relevant clinical information was collected. The entire specimen received was processed to obviate any sampling errors.

Routine Histological Processing

Specimen was fixed in buffered formalin and paraffin-embedded. Four to six micrometer serial sections stained by routine hematoxylin-eosin (H&E) were studied under light microscope (LM). The type of tumour, nuclear pleomorphism, mitosis, vascular proliferation and necrosis was recorded in all cases.

Immunohistochemistry (IHC)

IHC was performed on 4micrometer formalin fixed tissue sections obtained on poly-L-lysine coated glass slides. Endogenous peroxidase blocking was performed, which was followed by incubation with primary monoclonal antibodies (prediluted: ready to use) at room temperature for 4 hours. This was followed by incubation with polymer-based detection system (M/S Dako) followed by chromogen solution (DAB). Sections were then counterstained with Meyer's haematoxylin and mounted using DPX. The panel of antibodies used were glial fibrillary acidic protein (GFAP), S-100 protein (S-100), epithelial membrane antigen (EMA), vimentin (VIM), synaptophysin (Synapto), neurofilament (NFP), cytokeratin(CK) and MIB 1.

Results

Total of 40 cases were studied with mean age of 41.02 years (range : 4 - 78 years) and male to female ratio of 1.2:1. The distribution of cases as per histological type is enumerated in Table 1.

Immunoreactivity of various CNS tumours is summarized in table 2 while immunoexpression pattern with tumour histology in terms of type, grade, mitosis, microvascular proliferation (MVP) and necrosis is summarized in Table 3.

Table 1: Frequency of brain tumours (N=40)

Brain tumours	No of cases	Frequency (%)
Pilocytic astrocytoma	1	2.5
Diffuse astrocytoma	6	15
Anaplastic Astrocytoma	2	5
Glioblastoma	5	12.5
Oligoastrocytoma	1	2.5
Oligodendroglioma	1	2.5
Ganglioglioma	1	2.5
Ependymoma	1	2.5
Meningioma	8	20
Medulloblastoma	1	2.5
Primary CNS Lymphoma	2	5
Pineal tumours	2	5
Mature Intracranial teratoma	2	5
Choroid plexus papilloma	1	2.5
Craniopharyngioma	1	2.5
Synovial sarcoma	1	2.5
Metastatic tumour	2	5
CNS primitive neuroectodermal tumour	1	2.5
Negative for malignancy	1	2.5

Table 2: Immunoreactivity patterns of CNS tumours (N=40)

S. No	TUMOUR (No of cases)	N	GFAP	S-100	SYN	NFP	EMA	CK	VIM
1.	Pilocytic Astrocytoma	1	+	+	-	-	-	-	+/-
2.	Astrocytomas (Grades II-IV)	13	+	+	-	-	-	-	+/-
3.	Oligoastrocytoma	1	+	+	-	-	-	-	+/-
4.	Oligodendroglioma	1	+	+	-	-	-	-	+/-
5.	Ganglioglioma	1	+	+	+	-	-	-	+/-
6.	Anaplastic Ependymoma	1	+	+	-	-	-	-	+/-
7.	Meningothelial	8	-	+	-	-	+	-	+
8.	Classical medulloblastoma	1	+/-	+/-	+	+/-	-	-	-
9.	Primary CNS Lymphoma*	2	-	-	-	-	-	-	-
10.	Pineocytoma	1	-	-	+	+	-	-	-
11.	Pineal parenchymal tumour of intermediate differentiation (WHO Gr III)	1	-	-	+	+	-	-	-
12.	Mature Intracranial Teratoma	2	+	+/-	+/-	+/-	+	+	+
13.	Choroid plexus papilloma	1	+/-	+	-	-	+/-	+/-	-
14.	Craniopharyngioma	1	-	-	-	-	-	-	-
15.	Synovial sarcoma	1	-	-	-	-	+	+	+
16.	Metastasis	2	-	-	-	-	+	+	-
17.	CNSPrimitive Neuroectodermal tumour	1	-	-	+	-	-	-	-
18.	Negative for Malignancy	1	+	-	-	-	-	-	-

(*DLBCLs were immunopositive for LCA and CD20)

Table 3: Immunoexpression Pattern With Tumour Histology In Terms of Type, Grade, Mitosis, Microvascular Proliferation & Necrosis

S. N.	Case	TYPE	MIB-1	Grade	Mitosis	MVP	Necrosis
1	Pilocytic astrocytoma	Glioma	<1	I	0	0	0
2	Diffuse astrocytoma	Glioma	1-2	II	1	1	1
3	Anaplastic astrocytoma	Glioma	3-7	III	0	0	0
4	Glioblastoma multiforme	Glioma	8-26	IV	0	0	0
5	Oligoastrocytoma	Glioma	<1	II	0	0	0
6	Oligodendroglioma	Glioma	<1	II	0	0	0
7	Anaplastic Ependymoma	Glioma	3-6	III	0	0	0
8	Meningioma	Meningioma	<1	I	0	0	0
9	Ganglioglioma	Other	1	I	0	0	0
10	Medulloblastoma	Other	60	IV	1	1	1
11	Diffuse Large B Cell Lymphoma	Other	34-40	NA	1	1	1
12	Pineocytoma	Other	1	I	0	0	0
13	Pineal parenchymal tumour of intermediate differentiation	Other	3.5	III	1	0	0
14	Mature Intracranial Teratoma	Other	<1	NA	0	0	0
15	Choroid plexus papilloma	Other	<1	I	0	0	0
16	Craniopharyngioma	Other	1.5	NA	0	0	0
17	Synovial sarcoma.	Other	12	NA	1	1	1
18	Metastasis	Other	20 - 36	NA	1	1	1
19	CNSPrimitive Neuroectodermal tumour	Other	18	IV	1	1	1
20	Negative for Malignancy	Other	0	NA	0	0	0

Discussion

CNS tumors, which constitutes 1- 2% of all malignancies, are associated with guarded prognosis because of their location [2]. In the present study, 40 cases of biopsies of suspected brain tumors were studied. Although, microscopic examination of H & E-stained sections and special stains will provide diagnosis in majority of cases but in cases with morphological variations and diagnostic dilemmas, IHC is invaluable to distinguish between different categories of lesions [6].

Gliomas are the most common primary brain tumors in adults, are heterogeneous. Grading of gliomas was done as per the revised WHO criteria [5]. In contrast to well circumscribed neoplasms of low proliferative potential i.e. pilocytic astrocytoma (WHO Grade I), diffusely infiltrating gliomas were encountered more frequently. These included diffuse astrocytomas (WHO Grade II) with increased cellularity; anaplastic astrocytomas (WHO Grade III) with raised mitotic activity in addition to increased cellularity; and glioblastoma multiforme (WHO Grade IV) having vascular proliferation and/or necrosis [7]. Diffuse fibrillary astrocytomas were the most frequent in the

study with 6 cases, while 2 cases were diagnosed as anaplastic astrocytoma.

Glioblastoma was diagnosed in 5 cases in the study accounting for 12.5% of all brain tumors and 29.41% of astrocytic tumors [Table 1]. Other workers reported higher frequency for glioblastoma in their series [8]. Primary variant of glioblastoma occursde novo, while the secondary variant arises within preexistent, differentiated astrocytic neoplasms [7,9]. Cellular heterogenicity and polymorphism in a glioblastoma can mimic metastasis or melanoma and IHC is necessary for confirmation in such cases [9,10]. Other features which can pose diagnostic dilemmas are lipid rich epithelioid cells, epithelial elements in the form of adenoid structures and mucinous background [9-11]. In such cases positive expression of GFAP by epithelial structures confirms unequivocally the diagnosis ofglioblastoma [3].

One case of oligodendroglial tumor was reported in the study (2.5%). Histologically it was a diffusely infiltrating cellular tumor composed of monomorphic cells with round uniform nuclei and perinuclear halos ('honeycomb' appearance). Mitotic activity, microvascular proliferation, and necrosis were not present clinching the diagnosis of oligodendroglioma of WHO Grade II [12].

One of the cases showed features of low grade glioma with areas resembling diffuse astrocytoma interspersed with oligodendroglial foci. It was labeled as oligoastrocytoma. Immunohistochemistry was unable to resolve this dilemma. In the lines of current recommendations, [13] this was finally confirmed by performing loss of heterozygosity for chromosomes 1p and 19q (LOH 1p/19q)[14].

One case of ganglioglioma (WHO Grade I) was described. Histologically it was characterized by the presence of glioma admixed with neuronal component. Spindle cell component along with multinucleated neurons andperivascular small lymphocytes were also seen [15]. The spindle shaped cells were positive for vimentin and GFAP, neuroepithelial component was GFAP positive and neuronal component was SYN positive [16].

A total of 8 cases of meningiomas were reported (20%). These findings are in accordance with other studies [17]. Meningiomas usually present within the cranial cavity and are dura-based. Uncommon sites include cerebellopontine angle, sphenoid ridge and extracranial locations. Characteristic arrangement of tumor cells in concentric whorls and presence of clear nuclei with pseudoinclusions and psammoma bodies are the striking histological features. Numerous variants are described of which chordoid, clear cell and atypical meningiomas fall in grade II and papillary, rhabdoid and anaplastic variants constitute grade III; while the remaining are grade I tumours. In this study, meningothelial (4 cases), fibroblastic (2 cases), angiomatous and transitional (1 each) variants were identified, all of which are of the grade I category [18]. IHC showed positive expression for EMA and vimentin (Table 2), whereas GFAP was negative [17,18]. The meningiomas in our study were all grade I with low proliferative index and no mitosis, microvascular proliferation (MVP) or necrosis.

One case of medulloblastoma was reported. This was a high grade malignant small round cell tumour displaying presence of small undifferentiated monomorphic cells packed in sheets with hyperchromatic, round and moulded nuclei and scanty stroma [9]. SYN expression was characteristic of these neoplasms along with presence of high proliferation index, brisk mitosis, MVP and necrosis.

Anaplastic ependymoma (grade III) are malignant gliomas of ependymal differentiation with accelerated growth and unfavourable clinical outcome [19]. The incidence data varies considerably due to uncertainty regarding histological criteria for malignancy. One such case was seen characterized by increased cellularity with perivascular pseudorosettes, brisk mitosis, MVP and necrosis.

The incidence of primary CNS lymphomas has increased worldwide; from 0.8-1.5% to 6.6% of primary intracranial neoplasms [20]. Of these, diffuse large B cell lymphomas form more than 95% [21]. We encountered two cases of primary CNS lymphomas. They were characterized by typical angiocentric infiltration pattern with tumour cells forming collars in perivascular area with reticulin deposits and invading the adjacent brain parenchyma in diffusely infiltrating pattern. They had characteristic CD 20 and CD 45 positivity with high proliferative index, MVP and necrosis. Both were characterized as diffuse large B cell lymphomas.

Two cases of pineal tumors were encountered. One was a classical pineocytoma (WHO grade I) characterized by a moderately cellular neoplasm with small uniform mature cells in sheets and ill defined lobules. Positivity was observed with SYN and NFP. Other case had high cellularity with nuclear atypia, increased proliferative activity as seen in MIB 1 index and mitotic activity [22].

Two cases of mature teratoma were seen. CNS germ cell tumours comprise 2-3% of primary intracranial neoplasms, although incidence increases in pediatric age group [23]. They were composed exclusively of fully differentiated 'adult-type' tissue elements with

absent mitotic activity. Common ectodermal tissue encountered were skin, brain and choroid plexus Mesodermal components were bone, cartilage, muscle and fat. No undifferentiated area was seen because even if there is minor element with incompletely differentiated area resembling foetal tissue it mandates classification as immature teratoma [24]. Particularly common are hypercellular and mitotically active stroma in such lesions.

Choroid plexus tumours form 0.3-0.6 % of all CNS tumours [25]. In this study one case of choroid plexus papilloma was seen. Histopathology showed fronds of delicate fibrovascular tissue with lining of single layer of cuboidal epithelium having basally situated round to oval monomorphic nuclei. No mitosis or necrosis was seen. IHC revealed positivity for S-100, CK and EMA. Uncommon forms of choroid plexus tumours include atypical choroid plexus papilloma and choroid plexus carcinoma [25].

One case of admantinomatous craniopharyngioma was seen. These tumours form 1-5 % of all intracranial tumours [26]. It was characterized by squamous epithelium disposed in chords, trabeculae and lobules with palisading of columnar epithelium. Nodules of wet keratin and cystic cavities composed of squamous debris were seen. IHC did not show positivity in the panel used.

One case of synovial sarcoma was seen. Primary intracranial synovial sarcomas are extremely rare and most of the cases are in form of case reports. First such case was described by Scheithauer et al [27]. H&E-stained sections showed a characteristic biphasic pattern comprising spindle and epithelial-appearing tumor cells. The former consisted of cytologically uniform cells disposed in sheets and pseudopapillary arrangements in a fibrous, perivascular stoma. True glands were not seen. Mitosis and necrosis were seen. IHC showed positivity for CK, EMA and VIM.

Secondary involvement of the CNS by direct extension or hematogenous metastasis is a commoncomplication of systemic cancer. In the present study, 2 cases of metastatic tumors were reported Adenocarcinoma was the most common metastatic deposit. Commonest cause of brain metastases in adults are carcinomas of the lung and breast, followed by malignant melanomas, renal carcinomas, and colorectal adenocarcinomas [28]. Metastatic nodules are sharply circumscribed with pushing margins and usually reflect the histology of the primary site. In case of well-differentiated deposits, the histological diagnosis was straightforward. Poorly differentiated carcinomas can be distinguished from anaplastic gliomas by cohesive architecture, abrupt interface with adjacent neural tissue, and peritheliomatous pattern of tumor cell preservation about stromal blood vessels [9].

A solitary supratentorial tumour reported as small blue round cell tumour was redesignated as CNS primitive neuroectodermal tumour (CNS-PNET) on immunohistochemistry.

In another case, histology supported a low grade glioma, although it needed to be differentiated from reactive gliosis. Proliferation marker was detected to be very low (<1%) while GFAP highlighted the reactive astrocytes. It was thus labelled as negative for malignancy.

Conclusion

The present study shows that although histopathological examination is the mainstay in the diagnosis andgrading in majority of CNS tumors, IHC plays a crucial supplementary role in resolving diagnostic dilemmas in the routine practice of neurosurgical pathology.

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Nil

Conflict of Interests

All authors have none to declare

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