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Brain Tumors with Review of Literature: Immunohistochemistry or Biomarkers Versus Histomorphology

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Abstract

Brain tumors show genetic heterogeneity and various immunohistochemical / biomarkers are now available for brain tumor diagnosis in addition to the advanced molecular techniques. However the basic routine histopathology remains the gold standard for diagnosis corroborating with the characteristic radiology and immunohistochemistry to substantiate or confirm diagnosis and MIB1/Ki67 for grading of tumors. A total of 150 brain tumors were retrospectively analyzed in this study. The histopathology was correlated with immunohistochemical findings to note the difference in result and correlate the histology with immuno-histochemistry. Out of total 150 patients, 65 were males and 45 were females. Out of the 150 brain tumors, 37 were glial tumors in which there were 05 grade 1 astrocytoma out which one was protoplasmic astro-cytoma, 01 grade 2 astrocytoma 05 anaplastic astrocytoma. 02 oligodendroglioma, 30 glioblastoma multi-forme and one was gemistocytic glioblastoma, 02 mediastinal seminoma in young males of average age 25 years, 46 meningiomas of which 30 were transitional type and 20 fibroblastic, 19 pituitary adenomas, 01 mediastinal germ cell tumor, 10 ependymomas of which 01 was myxopapillary type and 01 anaplastic type, 06 hemangioblastomas, 03 medulloblastoma, 01 atypical teratoid rhabdoid Tumor, 10 raniopharyngiomas, 02 cavernous angiomas, 05 neurocytomas, 01 adenocarcinoma deposits, 01 case of Tuberculosis. Immunohistochemistry with relevant antibody markers were performed for confirmation of diagnosis, differentiation of the tumors and MIB1 for grading of tumors. In some CNS tumors immunohistochemistry is useful but IHC panel can substantiate histopathology to grade and prognosticate the brain tumors but histopathology remains gold standard.

Keywords: Glioblastoma multiforme; Ependymoma; Tumors; Immunohisto-chemistry; Tomography; Oxidation

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Introduction

Advances in molecular pathology, biomarkers and immunohistochemistry are nowadays emphasized upon in diagnosis of brain tumors. Common Brain tumors which are diagnosed by histomorphology are glioblastoma multiforme, astrocytoma, oligodendroglioma, ependymoma, embryonal tumors medulloblastoma, meningiomas, nerve sheath tumors, germ cell tumors, craniopharyngiomas and lymphomas. The glial tumors which are astrocytic are diffusely infiltrating astrocytomas were diffuse grade II astrocytoma and anaplastic and gliomatosis cerebri were grade III and glioblastoma was grade IV. The special categories of astrocytomas were Pilocytic, Subependymal giant cell astrocytoma which are grade 1 and Pilomyxoid grade I astrocytoma. Oligodendroglioma were classified upto anaplastic grade III. Oligoastrocytoma grade II, anaplastic oligoastrocytoma grade III, glioblastoma with oligodendroglioma component grade IV. Ependymal grade II, anaplastic ependymoma grade III, myxopapillary ependymoma and subependymoma grade I, choroid plexus papilloma grade I, atypical choroid plexus papilloma grade II, and grade III choroid plexus carcinoma.

There are neuronal tumors grade I gangliocytoma, dysplastic

gangliocytoma, grade II neurocytoma and cerebellar liponeurocytoma. The neuronal glial tumors are grade I ganglioglioma, dysembryoplastic neuroepithelial tumor, desmoplastic infantile astrocytoma and ganglioglioma, papillary glioneuronal tumor, rosette forming glioneuronal tumor of fourth ventricle and grade III anaplastic anglio-glioma. The embryonal tumors are by definition grade IV, medulloblastoma and supratentorial PNET like medulloepithelioma. The other embryonal tumors are atypical teratoid/rhabdoid tumor and retinoblastoma. The meningothelial tumors are varied meningiomas upto grade III and melanocytic tumors [1,2]. Frozen section and histopathological diagnosis is beneficial in almost most of the brain tumors, but sometimes immunohistochemistry has to be resorted in odd cases for grading and differentiating the tumor entities.

Materials and Methods

Type and grade were systematically recorded. The histopathology was correlated with immunohisto-chemical findings to note the difference in result. In glial tumors, glial fibrillary acidic protein(GFAP), epidermal growth factor receptor EGFR, IDH1 and PHH3 and MIB1 was done to assess the proliferating potential and mitotic index for grading of tumors into I-IV. In germ cell tumors the IHC done was with CD30, CD117, OCT3/4, in meningiomas EMA and Ki67, Ependymoma GFAP and EMA. In medulloblastomas IHC done was synaptophysin, and neurofilament protein and in atypical teratoid rhabdoid tumors(ATRT) INI1 was done.

Results

Out of total 150 brain tumors, 65 were males and 45 were females. 37 were glial tumors in which there were 05 grade 1 astrocytoma, 01 grade 2 astrocytoma 05 anaplastic astrocytoma 02 oligodendroglioma, 24 glioblastoma multiforme and one was gemistocytic glioblastoma, 03 mediastinal seminoma in young males of average age 25 years, 46 meningiomas of which 30 were transitional type and 20 fibroblastic, 19 pituitary adenomas,10 ependymomas of which 01 was myxopapillary type and 01 anaplastic type,06 hemangioblastomas, 03 medulloblastoma, 01 atypical teratoid rhabdoid tumor,10 craniopharyngiomas, 02 cavernous angiomas, 05 neurocytomas, 01 adenocarcinoma deposits, 01 Tuberculosis. Astrocytic and ependymal tumors were common in male patients, with a ratio of 2:1 within the age range from 30 to 60 yrs, whereas meningiomas were common in female patients in ratio 3:1 with age group 20-40 yrs. The metastatic tumor adenocarcinoma was found in older age group of 62-64 yrs with total 05 cases of which 03 were in males and 02 in females. The primary site was delineated by immunohistochemistry and in male the tumor was positive for TTF1 in 02 cases proving primary to be lungs and in one case GI primary with CK20 and CEA positive. In 02 females WT1 was positive proving primary to be Ovarian. The commonest clinical presentation was headache and vomiting.

The radiology was suggestive of intracranial space occupying lesions in all the cases. In one case there was clinicoradiopathological discordance with the diagnosis of tuberculosis with presence of caseating necrosis and epithelioid cell granulomas however acid fast bacilli was not demonstrated.

GFAP was used for confirmation of diagnosis of glial tumors in all 37 cases. Epidermal growth factor receptor EGFR used to detect mutations which was confirmed by immunohistochemistry and IDH in all cases of glioblastoma multiforme. MIB1 and PHH3 for mitotic index is important in astrocytomas grading. Placental alkaline phosphatase (PLAP), c-Kit (CD117), CD30 and OCT3/4 in combination was used for germ cell tumor differentiation.

Immunohistochemistry positive in ependymomas with GFAP, EMA and in medulloblastoma synaptophysin and neurofilament proteins were positive. Hemangioblastoma was differentiated from metastatic tumors from other site with use of CD10, InhibinA and EMA. Claudin and EMA was used in meningiomas for confirmation. Atypical teratoid/rhabdoid tumors (ATRTs) were confirmed with INI1 **(Table 1).**

Discussion

Brain tumors morphology recognition and grading is important for example in astrocytomas, glioblastoma multiforme and others. Classic histomorphology with palisading necrosis is present in Glioblastoma multiforme and GFAP is used for confirmation of diagnosis. Epidermal growth factor receptor EGFR is used to detect mutations which can be confirmed by immunohistochemistry. MIB1 and PHH3 for mitotic index is important in astrocytomas grading. Colman et al. [3,4] studied PHH3 staining with MIB1 and found that the combination of both with regards to grade and prognosis was better which is concordant with our study in which 36 glial tumors were positive for GFAP with PHH3 and corresponding Ki67 staining however the gemistocytic glioblastoma was negative for GFAP.

In our study there was 01 case of germ cell tumor which was mediastinal germinoma. Germinomas are the most frequent germ cell tumor arising in the pineal and sellar regions. In germinoma the morphology was classic of uniform population of large polygonal cells with pale to clear cytoplasm and central vesicular nucleus. IHC was positive for OCT4 and cKit (CD117) which was used later to substantiate the diagnosis of a germinoma. Takeshima et al. [5] reported that IHC c-Kit, CD30, OCT4 were immunoreactive in germ cell tumors. Cheng et al. studied that OCT4 was positive in ovarian dysgerminomas(germ cell tumors) while negative in non-dysgerminomatous tumors.

In our series of CNS tumors, there were 06 cases of Hemangioblastomas which were diagnosed on the basis of histomorphology then substantiated with IHC CD10, EMA and inhibin to rule out a metastatic carcinoma. This is important for treatment purposes. We had three cases of embryonal tumor, medulloblastomas which on histopathology were classic, densely cellular with closely packed primitive cells with fibrillated intercellular matrix and which on IHC were found to be positive in synaptophysin and neurofilament. This finding is consistent with other studies [6,7].

In our series of 150 CNS tumors we had one case of Atypical teratoid/rhabdoid tumors (ATRTs) in young child in the posterior fossa. Microscopically the abundant eosinophilic cytoplasm of the tumor cells gives the rhabdoid appearance to this embryonal

Table 1 Summarizing the brain lesions (n=150).

Broad headings of CNS lesions	Brain space occupying lesion SOL N=150 Subtyping	No of Cases (Total 150)	Males 65	Mean Age Yrs	Females 45	Mean Age yrs	Microscopy	Grade of tumor	IHC
1) Astrocytic tumors	Pilocytic astrocytoma	05	04	01	-		bipolar cells with long pilocytic (hair-like) processes	I	PHH3, MIB-1/KI-67, AND p53
	Diffuse fibrillary	01	01	60	-		Astrocytic cells	II	GFAP, MIB1
	Anaplastic astrocytoma	05	03	60	02	40	Astrocytic with cellular atypia	III	GFAP, MIB1
	Glioblastoma	26	20	65	06	45	Necrosis, mitosis increased and vascular proliferation.	IV	GFAP, MIB1
2) Oligodendroglial	Oligodendroglioma	02	02	60			round, central nuclei and oval, water-clear cytoplasm, which has been likened to the fried egg with its yolk.	I	KI67
3) Ependymal	Myxopapillary	01	01	10			Tumor cells around vessels with mucoid degeneration	I	S100, GFAP
	Anaplastic	01	-		01	05	Hypercellularity with nuclear hyperchromasia and/or nuclear pleomorphism Numerous mitoses seen throughout the lesion Microvascular proliferation Pseudopalisading necrosis	III	S100, GFAP
	Ependymoma	10	08	08	02	10	Perivascular pseudorosettes (anuclear zones formed by radially arranged tumor cell processes surrounding central blood vessels)	I	S100, GFAP
4) Neurocytoma	Central Neurocytoma	05	03	40	02	42	sheets of non-pleomorphic cells with modest cytoplasm and neurophil	I	Synaptophysin, chromogranin,MIB1
5) Embryonal	Medulloblastoma	03	02	10	01	08	poor cellular differentiation, nuclear molding, and minimal indistinct cytoplasm.	IV	(GFAP), S-100 neuron-specific enolase (NSE) neurofilament
	Atypical teratoid rhabdoid tumor ATRT	01			01	10	Large rhabdoid cells	IV	INI1
6) Meningeal tumors	Meningiomas	46	14	40	32	32	Syncytial or transitional or fibroblastic	Grade I, II	PHOSPHOHISTONE-H3, MIB-1/KI-67, AND CLAUDIN-1
7) Germ cell tumor	Seminoma	03	03	20			uniformcells, vesicular nuclei, prominent nucleoli,		CD30, CD117
8) Sellar	Craniopharyngioma	10	08	32	02	40	Papillae formed by nonkeratinizing squamous epithelium	Low grade	CK

9) Pituitary	Pituitary adenomas	19	10	40	09	35	One cell type with lack of reticulin network		TSH, ACTH, PRL
10) Angiomatous	Cavernous angioma	02	02	34	-	-	Vascular channels		CD34, CD31
	Hemangioblastoma	06	04	40	02	32	Foamy cells with vasculature Benign tumor		Inhibin, CD10
11) Inflammatory	CNS Tuberculous	01	01	32			Epithelioid cell granulomas		Zeihl neelson stain
12) Metastases	Papillary adenocarcinoma	05	03	64	02	62	Papillary tumor	Mets	CEA, CK20, WT1

tumor. Immunohistochemistry with vimentin highlights the inclusions and lack of immunostaining for BAF47(INI1) is present. INI1 immunostaining indicated in histologically dubious cases [8-10].

In our series we had 10 cases of Ependymomas which are ependymal tumors arises from neuroepithelium of ventricles [11] and mostly occur as Posterior fossa tumors. Microscopically, ependymomas have round blue cells with individual processes in the perivascular pseudorosettes, Immunohistochemistry was positive for EMA And GFAP. Wolfsberger et al. [12] studied 103 cases of ependymoma and studied the prognostic and survival patterns which was not analysed in our study.

Conclusion

Histomorphology is the gold standard for the CNS tumors. IHC becomes mandatory for distinction between hemangioblastoma and metastatic renal cell carcinoma as the treatment and prognosis is different. Distinction between But combined use of inhibin A (and D2-40) and epithelial markers (EMA, CAM 5.2, and CD10). INI1 is unique in its negative nuclear staining in ATRTs, and can be used in indeterminate histological features or in small biopsies. PHH3 and MIB1 which are mitosis-specific markers and can be used predicting prognosis in meningiomas, astrocytoma, and ependymoma. IHC panel can substantiate histopathology to grade and prognosticate the brain tumors but can't replace histopathology.

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