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CASE STUDY ON CIRCUMSCRIBED GLIOMAS, THEIR CLINICOPATHOLOGICAL CORRELATION IN A TERTIARY CARE CENTER

Pathology

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ABSTRACT

The histogenesis and biological behavior of primary tumors of the central nervous system(CNS) are very diverse. The majority of **gliomas** present as benign, slow growing lesions classified as **grade I or II (Low grade gliomas)** by the WHO classification of CNS tumors.
However, a significant fraction of gliomas develop over a short period of time and progress rapidly and are therefore classified as **WHO grade III or IV(High grade gliomas).**
Astrocytomas are primary central nervous system tumours that can develop in adults or in children. They arise from the Astrocytes. They can be divided into diffuse that generally have a higher grade and poorer prognosis and those that are localised that tend to be of a lower grade and have a better prognosis.
In this study, we outline the basic histological spectrum and features, epidemiological aspects and grade of circumscribed gliomas (localised) or other Astrocytic tumours according to WHO classification . These are the Pilocytic Astrocytoma, Pilomyxoid Astrocytoma, Subependymal giant cell Astrocytoma, Pleomorphic xanthoastrocytoma and Anaplastic astrocytoma . The knowledge of these tumours are important as they are one of the commonest cause of mortality and morbidity in both the young and old, accounting for about 60% of the glial tumours. Therefore neuropathological diagnosis and tumour characteristics will therefore profoundly influence the impact of treatment strategies.

KEYWORDS

Benign; Circumscribed; Glioma; Low grade; Astrocytoma

INTRODUCTION

Histological grading is a means of predicting the biological behavior of a neoplasm [2]. In the clinical setting, tumor grade is a key factor influencing the choice of therapies, particularly determining the use of adjuvant radiation and specific chemotherapy protocols [2].

Grading of **astrocytic tumours** has a three-tiered system[3].

Grade I was assigned to the circumscribed pilocytic astrocytoma, grade II to diffusely infiltrative astrocytictumors with cytological atypia alone, grade III to those showing anaplasia and mitotic activity and grade IV to those showing microvascular proliferation and/or necrosis[3].

AIM

To study the clinicopathological profile of patients with **circumscribed brain tumors(other astrocytic tumors)** attending Institute of Neurosurgery and department of Neurologyfor a period of 3 years in Madras Medical College, Rajiv Gandhi Government Hospital, Chennai.

OBJECTIVE

A retrospective analysis on patients with Circumscribed Gliomas, their clinicopathological correlation and their significance with grade in a tertiary care cente for a period of three years .

MATERIALS AND METHODS

Database search was performed for all circumscribed gliomas diagnosed and treated at Institute of Neurosurgery/ Neurology, Madras Medical College . Clinical information such as age, gender, anatomical site of tumour, clinical presentation, radiological and histopathology findings(according to WHO 2016) of patients with '**Other Astrocytictumors**' operated over 3 years (September 2016 to September 2019)and appropriate immunohistochemical study were done. Data's were collected retrospectively, and analyzed.

Exclusion Criteria:

Patients with diffuse astrocytoma and oligodendrocytic tumours , meningothelial, non meningothelial and embryonal tumours were excluded from the study.

RESULTS

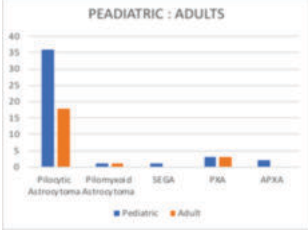
The Overall Statistics In The Year 2016 To 2019

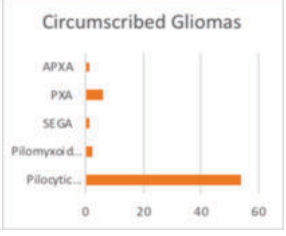
TOTAL CASES	2268
TOTAL NEOPLASTIC CASES	1235
TOTAL NON NEOPLASTIC CASES	1060
TOTAL GLIOMAS	1007

A total of **1007 Gliomas** was reported from the **year 2016-2019 in MMC**

Other Astrocytic Tumours(64 Cases)

TYPE	TOTAL CASES	MALE: FEMALE	ADULT: PEADIATRIC
Pilocytic Astrocytoma	54	1 : 1	1 : 2
Pilomyxoid Astrocytoma	2	0 : 2	1 : 1
SEGA	1	0 : 1	0 : 1
PXA	6	1 : 1	1 : 1
APXA	1	0 : 1	0 : 1





* Other astrocytic tumors composed **6.4% of the Gliomas**.
* Majority of the cases seen were **Pilocytic Astrocytoma(84%).**
* Other few cases reported were **Pilomyxoid Astrocytoma(3%), SEGA(2%), PXA (9%)and APXA(2%)**
* These tumor showed a **Pediatric population** predominance with **65.6 %(Pediatric: Adult is 2.5:1)**
* With slight **Male** preponderance **(Male: Female is 1.3:1)**

TUMOR LOCATION

Circumscirbed Astrocytomas are well defined tumors, benign, very limited infiltration to surroundings and less often aggressive in nature.

SUPRATENTORIAL	15 cases
INFRATENTORIAL	49 cases

TUMOUR	LOCATION
Pilocytic Astrocytoma	Posterior Fossa-25 cases Cerebellum-12 cases Cerebral cortex- 10 cases Brain stem- 5 cases Ventricles- 2 cases
Pilomyxoid Astrocytoma	Intraventicular- 1 case Sellar- 1 case
SEGA	Third ventricle-1 case
PXA and APXA	Supratentorial

Literature Review:

In comparison to other studies, it was noted that one of most common primary brain tumour encountered is the **Astrocytomas**. Various National and international studies pointed out that China holds 29.9% of astrocytic tumors, Taipei accounts for around 39.9%, Japan around 38.6%, France around 32.9%, Brazil around 37.7%, United States around 33.1% and India around 49.7% among pediatric age group (figure:2)[27]. Among the Astrocytic tumours, **Pilocytic Astrocytoma** was seen to be the most common glioma which accounts for majority of 9.4% of cases according to the CBTRUS.In the present study it accounts for 2.38%(54 cases out of 64 cases)and Chen L et al [25] shows 496 cases out of 610 cases (1.69%) (Table:1).

Hospital based study in India was also taken up and compared[26]. This showed that majority of the astrocytic tumours fall under **WHO grade I**(Table:3, figure:4). In other words, **Low grade Gliomas**, tumours being less aggressiveand usually have a favourable outcome.

The present study was retrospectively analyzed from a pathological database from a single neurological center. Although it was not a large population study, and selection bias inevitably existed, the rapidity of the observed changes in the CNS tumor spectrum with respect to the affected population characteristics in China could model similar changes that will occur in other developing countries.

Table:1 Circumscribed Gliomas

HISTOLOGICAL TYPE	CBTRUS	Chen L et al.,	Present study
PILOCYTIC ASTROCYTOMA	9.4 (Other Astrocytoma-7.4)	1.69	2.38
PILOMYXOID ASTROCYTOMA	<1	0.07	0.08
SEGA	<1	0.10	0.04
PXA	<1	0.24	0.26
APXA	<1	<1	0.04

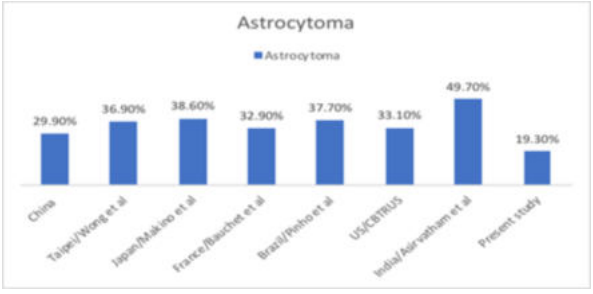


Figure:2 Percentage of Astrocytoma in different countries

Table:3 WHO Grade Of Astrocytoma In Hospital Based Studies In India

TUMOUR Grade (Astrocytoma)	AIIMS	NIMHANS	CMC	TMH	MMC (Present study)
I	23	29	34.9	17.4	20.9
II	2.7	1.1	5.3	1.1	5.08
III	2.4	4.8	2.9	1.4	1.69
IV	5.6	9.2	3.6	2.1	0
TOTAL	33.7	44.1	46.7	28.6	23.15
	819	648	1297	288	177

(AIIMS-All India institute of medical sciences; NIMHANS-National institute of Mental Health and Neuroscience; CMC- Christian Medical College, TMH- Tata memorial hospital)

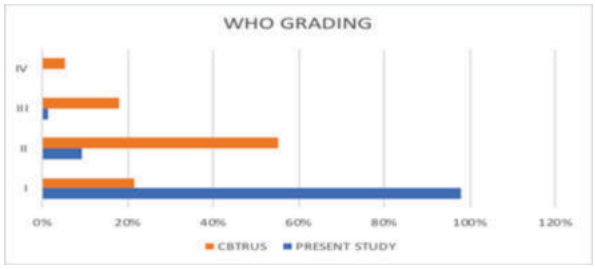


Figure:4 WHO Grade Of Astrocytoma In CBTRUS vs Present Study

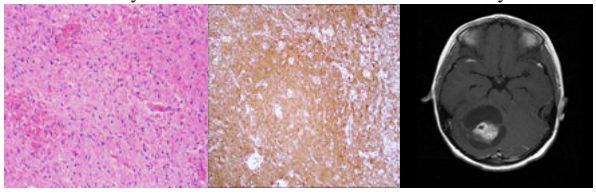
DISCUSSION

General Presentation Of Circumscribed Astrocytoma In Cases Studied

PILOCYTIC ASTROCYTOMA (n=54)

It is the most common pediatric glioma and the most common **pediatric** cerebellarneoplasm. The tumor is most often **WHO grade I** with a high 10 year survival rate of over 90%[4][5].

Cases reported as **Pilocytic astrocytoma** were 54 cases out of 64, of these, 51 cases shows classical picture of pilocytic astrocytoma, as shown in figure (a)showingcharacteristic **biphasic** architecture with *alternating compact areas* showing bland bipolar glial cells and variable **Rosenthal fibers** and more *loose areas* with multipolar cells, microcysts and occasional **eosinophilic granular bodies. [4]**Two caseswere **recurrent PA** where a patient presented again with the same features after 2 years and another showed recurrence after 4 years.



a)HPE picture of PA. b) GFAP positive. c) CT image

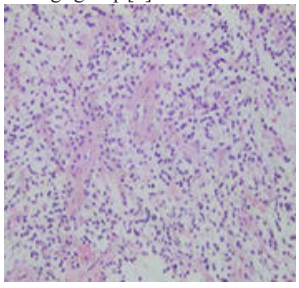
One case show features of focal anaplasia. ***PA with focal anaplasia*** *showed features of increased cellularity, nuclear atypia, diffuse brisk mitosis and areas of necrosis*and another case of **optic glioma** was seen which showed a unique presentation [4]. Grade Contrast enhanced, T1-weighted MRI demonstrating typical *superficial cystic mass with an enhancing mural nodule [4];*as seen in figure (c).

Most common location (46.2%) seen is in the *posterior fossa*. Supratentorial PA consists of 20% of brain tumours in children with only 5% arising from suprasellar region.

The KI67 proliferation rate is typically quite low and the vast majority are designated WHO grade I. **GFAP shows positivity [4].**

PILOMYXOID ASTROCYTOMA(n=2)

Pilomyxoid astrocytoma shares similar features with pilocytic astrocytoma with subtle histologic differences[6]. Two cases showing classical picture, one presented over the sellar region and another seen in the intraventricular region. These tumour showed *a prominent* ***myxoid*** *matrix and an* ***angiocentric arrangement*** *of monomorphous, bipolar tumor cells.* They lack Rosenthal fibers and eosinophilic granular bodies and their grading has not been assigned. This tumour was seen in the older age group [6].



The **clinical presentation of Pilocytic and Pilomyxoid Astrocytoma** depends on location. Both presented as posterior fossa tumors, hence presenting with a predominant mass effect with signs of raised intracranial pressure, especially when hydrocephalus is present.

PLEOMORPHIC XANTHOASTROCYTOMA(n=6)

PXA is an uncommon tumor that comprises of approximately 1% of all astrocyticcentral nervous system(CNS) tumors. PXAs have a favorable prognosis with a 10-year survival probability of>70% and are **WHO grade II** neoplasms[7].

The most common presentation seenare seizures and headaches[7].

Most of the PXAs seen are located **supratentorially,** with a predilection for the temporal lobe followed by parietal, frontal and occipital lobes.

The cases studied showed histologic features of marked **cellular pleomorphism** and **lipidization**, Six cases of PXAshowed cells with **epithelioid appearance and scattered xanthic cells**. Cells are seen to be hyperchromatic, with pleomorphic nuclei, at times, multinucleated with only scant bright eosinophilic granular bodies [7][8].Despite the pleomorphic appearance and cellularity, *mitotic activity was very low with Ki-67 index from low to focally moderate (4-6%).*

The reticulin stain highlighted the presence of **pericellular reticulin network** which was helpful in differentiating PXA from higher grade gliomas. The tumor cells were diffusely immunoreactive for glial fibrillary acidic protein (GFAP), S100,focally immunoreactive for synaptophysin and negative for chromogranin.

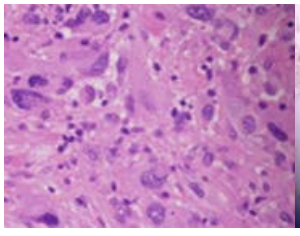


Figure (d)

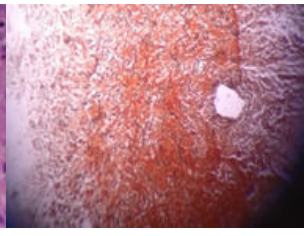


Figure (e)

d) High power magnification(100X) showing typical pleomorphic, multinucleated giant cells,Xanthomatouscells with foamy cytoplasm seen.

e)Reticulin stain around tumour cells.

RECURRENT PXA:

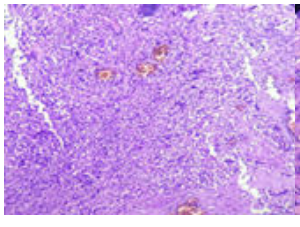
PXAsare known for their recurrence and aggressive nature. Certain clinical parameters have been reported to effect survival probability in PXAs[9]. For instances tumors in atypical or "difficult" locations, their size, extent of surgical resection and age of the patient has been reported to have a less favorable outcomes[9].

Similar situation was encountered in our study were we reported two cases belonging to pediatric age group, both having a **recurrent frontal space occupying lesion** even after treatment and were again diagnosed as recurrent PXA. The tumour cells were immunoreactive to GFAP, focally positive for synaptophysin and Ki67 proliferation index showed 5-6%.

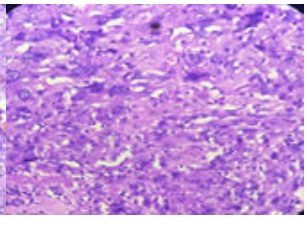
Another case of a 12 year old boy having a left eye retinoblastoma with a right parietal space occupying lesion. Squash picture showed a possibility of either a metastasis from The retinoblastoma or either a high grade tumour. After evaluation and histopathological examination it was concluded as PXA. PAS was positive for eosinophilic granular bodies and reticulin stain was highlighted by the tumour cells.

ANAPLASTIC PLEOMORPHIC XANTHOASTROCYTOMA

A case reported as recurrent PXA of a 15 year old female child having a recurrent right frontal space occupying lesion presenting with recurrent seizures in our setting with the following



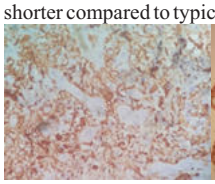
HPE: low power view



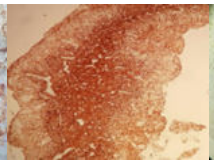
HPE:high power view

features. The tumour showed **increased mitotic activity(>5/10 high power field), necrosiswithout pseudopalisading** and **rhabdoidmorphology[10]**. These tumors are known to be aggressive in nature and are often classified as **APXA , WHO grade III** as per current WHO classification[10].

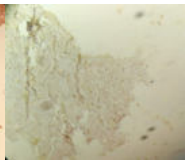
In addition **to increased mitotic rate**, *the well described* ***dense reticulin*** *network of typical PXA was* ***found to be lost*** *in APXA[10][24].* The tumour was diffusely positive to GFAP, s100 positive, synaptophysin showing focal positivity and Ki67 index was 7-8%. Once anaplastic, the survival yprobability was considered shorter compared to typical PXAs.



f) GFAP positive



g)s100 positive



h) Ki67-7 to 8%

It has been much easier to diagnose APXA if a malignant tumor arose in the same location as a classic PXA, and is histologically and genetically similar to the primary tumor.

SUBEPENDYMAL GIANT CELLASTROCYTOMA

SEGA has a major diagnostic criteria for **Tuberous sclerosis complex**, an autosomal dominant disorder characterized by hamartomas and benign neoplasms of multiple organ systems, including the CNS[13].This is a rare tumor that occurs usually in the **wall of the lateral ventricle and foramen of Monro and rarely in the third ventricle[13], fig (k).**

In our setting a case was reported of a well circumscribed mass seen in the third ventricle exhibiting partial calcification and cyst formation belonging to a paediatric patient. The patient presented with hypo pigmented patches on the face. The mother and her sibling also showed similar patches, hence giving a family history of **Tuberous Sclerosis; fig(I).**

Other presentation seen, like
A- Ashleaf spots
S- Shagreen patches
H- Heart rhabdomyosarcoma
L- Lung hamartomas
E- Epilepsy from cortical tubers
A- Angiomyolipoma in kidney
F- Facial angiofibroma

Its diagnosis is based on clinical, radiological, histological and immunohistochemical arguments.Histologically, **SEGA** showed a characteristic*triple cell components.* In a **fibrillary** background, large **astrocyte like cells** with **perivascularpseudopalisading** was seen with **calcification[24] fig (j)**. The tumor cells, showed wide rangingfrom gemistocytic astrocytes to long fibrillated and spindle cells, as well as large giant cells, some of them with a ganglionicappearance with large eosinophilic and finely granular cytoplasm, the nucleus seen were rounded to oval, large, and eccentric[24].

Fig. i).

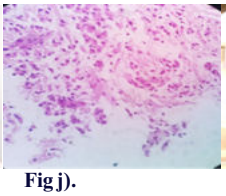


Fig j).

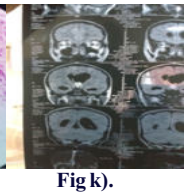
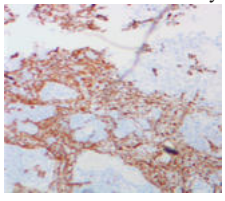
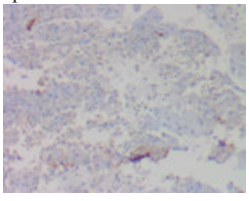


Fig k).

The **clinical features** presented by this childare raised intracranial pressure and seizures due to hydrocephalus .



a) GFAP positive.



b) synaptophysin focally positive

This tumor show patchy immunoreactive for GFAP and synaptophysin focally positive.

They belong to WHO grade I. Radical and early surgery is the treatment of choice, it is associated with a better prognosis.

CONCLUSION

WHO grading is one component of a combination of criteria used to predict a response to therapy and outcome[23][24]. Other criteria include clinical finding, such as age of the patient, neurologic performance status and tumor location, radiological features such as contrast enhancement, extent of surgical resection, proliferation indices and genetic alterations[14][24]. For each tumor entity, combinations of these parameters contribute to an overall estimate of prognosis.

In our study, out of 64 cases, majority of the cases fall upon WHO grade I around 89%, 9.3% belongs to grade II and as a small fraction of 1.5 % falls under grade III. Hence majority of the circumscribed Gliomas comes under **Low Grade Gliomas** and they usually have a favourable prognosis which is similar to other studies discussed below .**These tumour also showed pediatric predominance of 65.6% which is similar to other studies.**

Continued analysis of multicenter studies, will potentially lead to further understanding of the interactions of genes and environment in the development of gliomas.This study gives a glimpse of varied incidence of circumscribed gliomas which could be used to provide a baseline data for the better understanding of the epidemiological profile of gliomas.

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