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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/17867
DOI URL: http://dx.doi.org/10.21474/IJAR01/17867

RESEARCH ARTICLE

CLEAR CELL TUMORS OF CNS: HISTOMORPHOLOGIC APPROACH TO DIAGNOSIS

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Manuscript Info

Manuscript History
Received: 15 September 2023
Final Accepted: 17 October 2023
Published: November 2023

Key words:-
Clear Cell Lesions, Histomorphological Features, Central Nervous System

Abstract

Introduction: Tumors of the central nervous system (CNS) that may assume a clear cell appearance are diverse in nature. Primary conditions in this category include oligodendroglioma, hemangioblastoma, clear cell meningioma, pleomorphic xanthoastrocytoma, and lipid-rich glioblastoma, chordoma, central neurocytoma.They can be correctly identified by giving attention to clinical presentation, location, radiographic findings, and histomorphological features, immunohistochemistry analysis wherever necessary.The literature was reviewed with emphasis on incidence, morphology and precise histopathological assessment of clear cells tumors of CNS.

Method: This study was prospective observational study of 33 Cases received from August 2020 to December 2022 for clear cell tumors of CNS. This prospective study was carried out in Department of Pathology of a tertiary care teaching hospital. The ethical permission has been obtained from Institutional Ethics Committee for conducting the study.

Result:Total 33 Central nervous system clear cell tumors were observed out of which 6 were benign and 27 were malignant cases. They can be correctly identified by giving attention to clinical presentation, location, radiographic findings, and histomorphological features in most of the instances. Two cases of metastasis identified in which immunohistochemistry in addition to morphological examination was performed to arrive at final diagnosis.

Conclusion:Clearing of cytoplasm or clear cell changes are seen in various entities of different locations due to diverse reasons. So whenever clear cell is encountered, algorithmic approach is required to further proceed. In most of the instances morphologic features directs us to reach at diagnosis along with clinical and radiological findings.

Introduction:-

Remarkable progress has been made in molecular medicine providing necessary information on tumors, clonality, gene expression profile, genetic alterations, prognosis, and predictive markers for response to target therapy.. But till now, the microscope has remained the most important and essential tool of the surgical pathologist in everyday

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practice. For the selection of the relevant molecular/immunohistochemical investigations always, a precise or a presumptive histological diagnosis is the starting point. It is surprising that the hematoxylin–eosin (H and E) stain, introduced more than a century ago, has stood the test of time as the gold standard stain for histological examination and diagnosis of human diseases.[1]

Mass lesions of CNS, which may assume a clear cell appearance, are diverse in nature and challenging to diagnose. .Primary clear cell tumors of CNS include oligodendroglioma (OG), neurocytoma, clear cell and chordoid meningioma, hemangioblastoma, clear cell ependymoma (CCE), pleomorphic xanthoastrocytoma (PXA)[2].

Oligodendroglioma:
They are commonly located at cerebral hemispheres with an often-protracted preoperative history of intermittent seizures or headache, and partial calcification on neuroradiological study. In the 2016 WHO scheme, both IDH mutations and chromosome 1p/19q codeletions are required for the diagnosis of the more common adult form of oligodendroglioma. Microscopically it shows sheet-like proliferations of uniform rounded nuclei surrounded by optically clear halos which is due to formalin fixation artefact and not seen in frozen sections and smear preparations. Also, it shows network of thin-walled branching blood vessels (chicken wire vasculature), microcalcifications and secondary structure of scherer. Necrosis and often accompanied by dense cellularity, enlarged epithelioid cells and obvious nuclear atypiaare features of the "anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade III.[3]

Clear cell ependymoma:
They are practically restricted to the supratentorial compartment and often construed as oligodendroglial, a mischance made all the more inviting by the frequent presence of intratumoral calcospherules and a plexiform vascular network. Tumors of this kind often exhibit high-grade histologic features (e.g., high mitotic activity and MVP) and are prone to recur, often after relatively brief postoperative intervals. Again, these retain identifying ependymal attributes at the electron microscopic and immunohistochemical level, typically manifesting at least focal immunoreactivity of truncated perivascular cell processes for GFAP. On careful search they may be found to display dot-type EMA, CD99 and D2-40 expression, combined with no more than sparse OLIG2 expression and a solid rather than infiltrative growth pattern, as evidenced by lack of entrapped neurofilament-positive axons. These attributes permit their segregation from oligodendrogliomas and other potentially clear cell neoplasms, including extra ventricular neurocytomas.[3]

Clear cell meningiomas:
These are characterized by a predilection for young subjects (including children) and are most often found in the spinal canal, cerebellopontine angle or foramen magnum region. They are usually extra-axial and dura based but may be associated with cranial nerves, spinal roots or the cauda equina. Microscopically, composed of glycogen-rich, water-clear cells that are often disposed in pattern less sheets traversed by bands of homogeneous to amianthoid-like interstitial and perivascular collagen, these unusual tumors typically manifest little or nothing in the way of classic meningothelial attributes (e.g. whorls or nuclear pseudoinclusions) and may be only focally and faintly immunoreactive for EMA, a marker of specialized arachnoidal cells expressed by most meningiomas in diffuse fashion. High recurrence rates, a potential for CSF-borne spread and increased mortality characterize this intrinsically aggressive meningioma variant.[3,4]

Hemangioblastoma:
They are known as the hallmark of VHL disease, an autosomal dominant disorder caused by germline mutations of a tumor suppressor gene localized to chromosome 3p25–26. Microscopically, neoplasm's defining "stromal" cells are most readily visualized when lipid accumulation imparts a foamy or vacuolated quality to their pale cytoplasm. A clear demarcation from adjacent native tissues is typical of the hemangioblastoma, its characteristic reddish-brown and yellow coloration reflecting, respectively, a rich vasculature and high lipid content.[3]

The pleomorphic xanthoastrocytoma (PXA):
PXA (WHO grade II) is a histologically alarming, yet biologically favorable neoplasm that typically presents in later childhood or early adult life and exhibits a predilection for the cerebral hemispheres, particularly the temporal lobes.[5.6]Neuroradiological demonstration of a well demarcated and partially cystic lesion containing superficially positioned, contrast-enhancing mural components of nodular or plaque-like contour is especially suggestive. The tumor is named for its potentially bizarre cytologic characteristics and the tendency of its constituent cells to

intracytoplasmic lipid accumulation, although the latter is not a uniformly conspicuous feature.[1]The abundant cytoplasm of these cells may appear foamy or coarsely vacuolated/clear attesting to advanced lipidization but more commonly assumes a ground-glass, finely granular or hyalin quality. Reactive lymphoid infiltrates (at times extensive) and aggregated eosinophilic granular bodies round out the histologic picture. The latter, an important clue to the diagnosis.[3]

Method:-

The present study will be a prospective observational study carried out in histopathology department, B.J. medical college, Civil Hospital Ahmedabad. The study will be carried out during the period between August 2020 to December 2022.

The clinical records of the cases will be recorded from electronic database of the department.

After the specimen is received, thorough gross examination will be done. Then specimen will be fixed in 10% neutral formalin. Next day after gross examination, sections will be taken and processed in automated tissue processor. Sections will be cut and stained using H & E stain following which microscopic examination will be done. Special stain and immunohistochemical examination were done whenever needed.

Results And Observations:-

During study period total 33 clear cell tumors of CNS are seen in present study out of which 6 lesion were benign and 27 malignant and two case of metastasis.

Table I:- Spectrum of lesions in CNS.

Sr. no.	**Clear cell lesion**	**Total:33**
Benign		
1.	Hemangioblastoma	6
Malignant		
2	Oligodendroglioma	7
	Pleomorphic xanthoastrocytoma	7
3	Central neurocytoma	5
4	Clear cell ependymoma	3
5	Chordoma	2
7	Anaplastic ependymoma	1
8	Metastatic melanoma	1
9	Metastatic RCC	1

In benign lesions six cases of **hemangioblastoma** are seen.

Table II:- Data of Hemangioblastoma cases.

Sr. no.	**Age/sex**	**History**	**Site**	**Radiological findings**
1	26years/female	Difficulty walking	Cerebellum	MRI brain: s/o neoplastic lesion.
2	49 years /male	Gait imbalance since 3 months	Cerebellum	MRI brain: p/o pilocytic astrocytoma or hemangioblastoma.
3	43 years /male	Headache, bilateral vision loss	Parasagittal parietal SOL	-
4	52 years /male	H/O fall down after giddiness	Parietal SOL	MRI brain: s/o right parietal av malformation
5	25 years /male	C/O headache, vertigo and altered sensorium	Cerebellum	MRI brain-. s/o malignant neoplastic etiology.
6	40 years /male	C/O convulsion and headache	para-sagittal sinus	MRI brain- s/o meningioma

As evident from above table X,here is male predominance; cerebellum and posterior fossa are most common site hence the common clinical presentation is ataxia; and radiological findings are suggestive of cystic lesion with mass effect.

Grossly it has characteristic reddish-brown and yellow coloration reflecting rich vasculature and high lipid content.

Upon microscopic examination- tumor consists extensive proliferation of capillary blood vessels surrounded by stromal large polygonal cells with abundant clear, pale and eosinophilic cytoplasm and central round to oval hyperchromatic nuclei.

In hemangioblastoma neoplastic stromal component resides ramifying vascular arcades and is recognized by a pale cytoplasm often rich in neutral fats and, as a consequence, vacuolated or clear in appearance in cytoplasm.

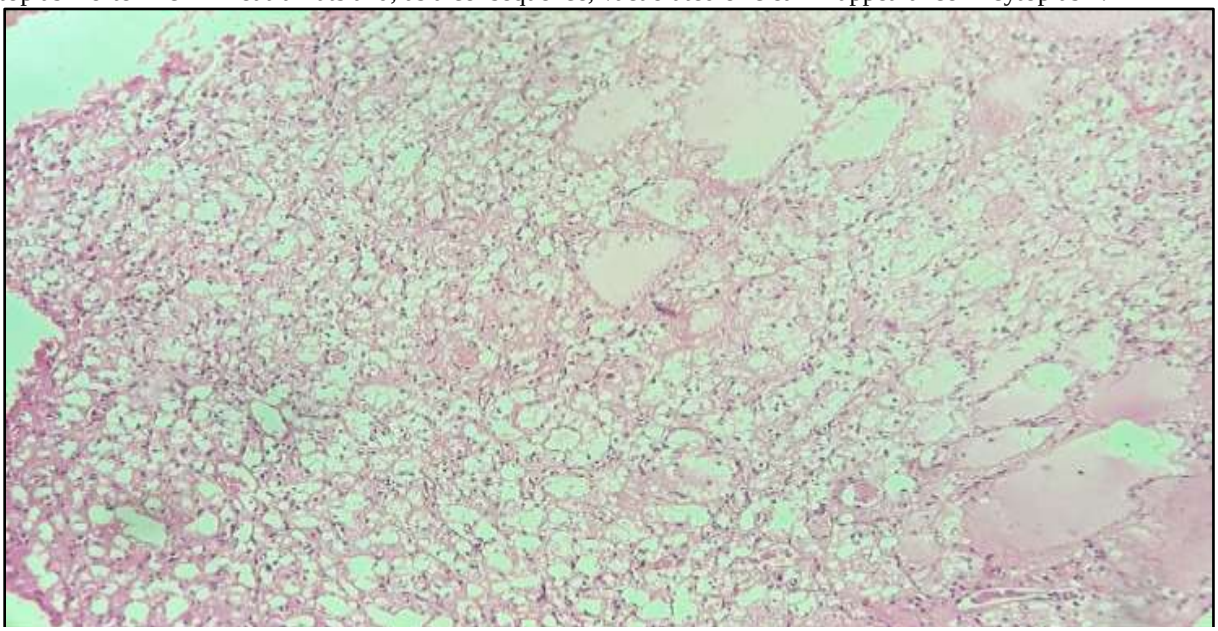

Figure I:- Hemangioblastoma; H & E stain (low power view).

Among **malignant clear cell lesions of CNS** most commonly encountered lesions are **oligodendroglioma (7 cases).**

Table III:- Data of oligodendroglioma cases.

Sr. no.	Age/sex	Clinical features	Site	Radiological findings
1	20 years/male	Headache, giddiness,	Parietal lobe	MRI brain: s/o solid cystic SOL
2	28 years /male	Hemiparesis and seizures	Fronto-parietal region	MRI brain:a well-defined space occupying intra-axial lesion
3	42 years /Female	Left sided weakness	temporo-parietal region	MRI brain: s/o recurrence right temporo-parietal SOL
4	55 years / female	Head ache	Parieto-temporal region	MRI brain- s/o high grade glioma
5	17 years /female	Headache and convulsion	Fronto-temporal region	MRI (brain): s/o oligodendroglioma
6	35 years / male	Headache	Left temporal lobe	NCCT scan of brain:s/o neoplastic etiology likely
7	24 years / male	Headache and convulsion	Left temporo-parietal region	MRI brain:p/o low grade glioma.

As evident from above table XI,

There is slight male predominance; Fronto-temporal region are most common site with seizures and headache the common clinical presentation is ataxia; and radiological findings are suggestive of heterogenous diffuse mass.

Upon microscopic examination- closely packed tumor cell having monomorphic nuclei, perinuclear clearing with chicken wire like vasculature and areas of calcifications. there is presence of perineural, perivascular and subpial aggregates (secondary structure of scherer). Out of seven cases four cases show features of microvascular

proliferation, areas of brisk mitotic activity and necrosis suggestive of anaplastic oligodendroglioma (WHO Grade III).

On microscopic examination oligodendroglioma gives fried egg appearance due to artifactual cytoplasmic dissolution during tissue processing, thus not seen in conventional frozen sections, intraoperative smears, or crush preparations.

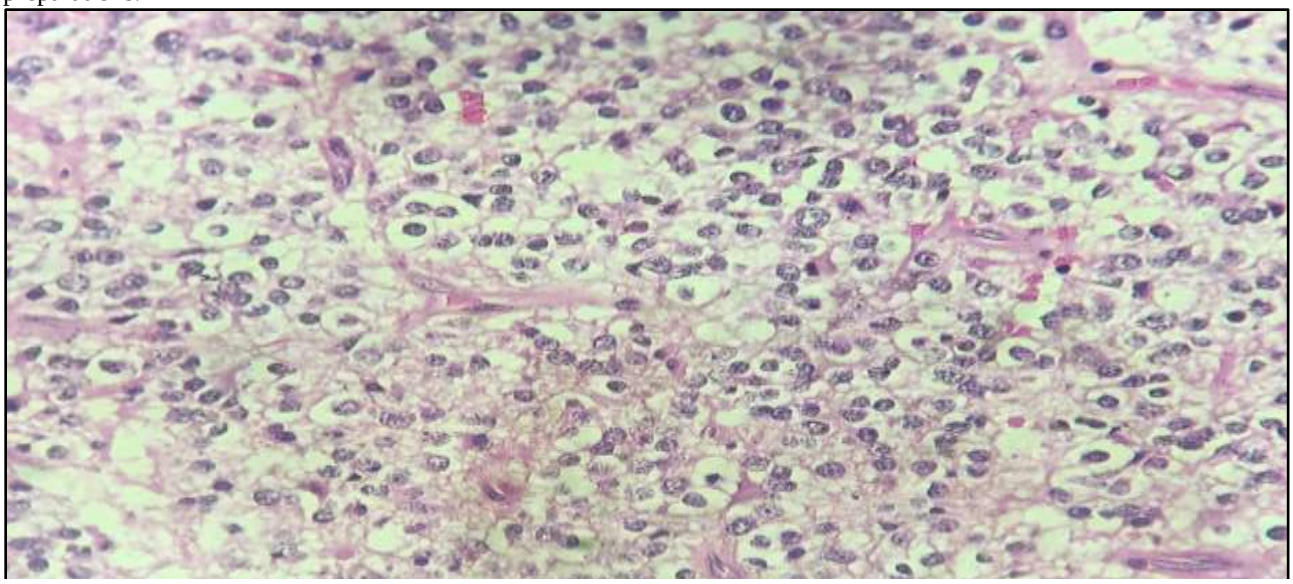

Figure II:- Oligodendroglioma WHO grade II; H & E stain (High power view).

Among malignant clear cell lesions of CNS another commonly encountered lesions are **pleomorphic xanthoastrocytoma (7 cases).**

Table IV:- Data of pleomorphic xanthoastrocytoma cases.

Sr. no.	Age/sex	Clinical features	Site	Radiological findings
1	44 years / female	Headache, giddiness,	Right frontal region	MRI s/o right frontal solid-cystic SOL
2	11 years / female	headache and vision loss	left parieto-occipital	-
3	30 years /male	Headache, convulsion,	Frontal region	MRI s/p/o infective etiology
4	21 years /male	Convulsion, right upper limb weakness	Left frontal region	MRI: p/o high grade glioma
5	33 years / female	Headache, B/L decrease vision, right L/L&U/Lparesis	Left Fronto-parietal region	MRI brain: p/o low grade glial tumor/ganglioglioma
6	8 years/ male	Right side weakness, convulsion,	Left temporal lobe	CT scan brain: s/p/o suprasellar neoplastic lesion.
7	57 years /male	Headache	Right Fronto-temporal region	MRI brain: possibly glioma/ pleomorphic xanthoastrocytoma.

As evident from table XII,

It is commonly located in cerebral region with seizures and headache the common clinical presentation; and radiological findings are suggestive of cystic mass with mural nodule.

Upon microscopic examination, pleomorphic xanthoastrocytoma shows spindle and bizarre multinucleated giant cells forms with latter having hyaline granular and vacuolated clear cytoplasm due to lipid accumulation.Three cases

also having greater than 5 mitoses per ten HPF and focal areas of necrosis along with epithelioid cellular morphology suggestive of high grade (Grade III) Pleomorphic xanthoastrocytoma.

Foamy or vacuolated cells in pleomorphic xanthoastrocytoma are due to intracytoplasmic lipid accumulation, although the latter is not a uniformly conspicuous feature.

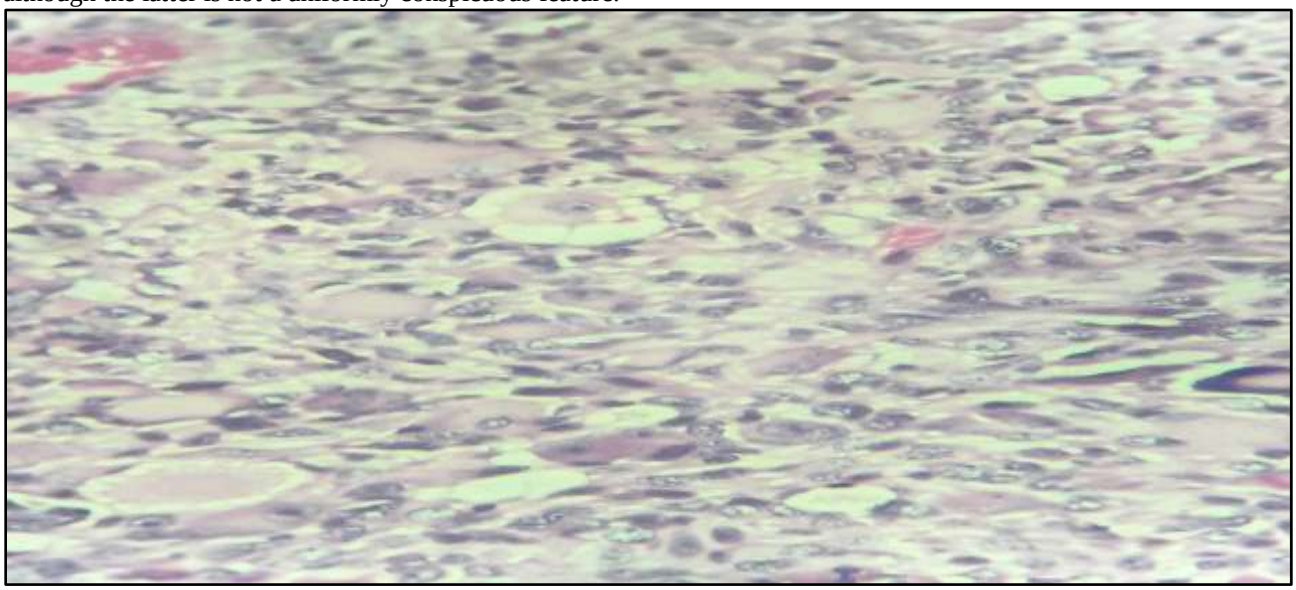

Figure III:- Pleomorphic xanthoastrocytoma grade II; H & E stain (High power view).

Among other CNS tumors five cases of **central neurocytoma** are seen in present study.

Table V:- Data of central neurocytomacases.

Sr. no.	Age/sex	Clinical features	Site	Radiological findings
1	28 years /male	Headache	Intra-ventricular	MRI brain: S/o intraventricular ependymoma or central neurocytoma
2	20 years /male	Headache	Third ventricular fossa	MRI brain: p/o neurocytoma
3	19 years/ female	Headache, giddiness, vomiting	Intraventricular	MRI:p/o choroid plexus papilloma
4	36 years / female	Headache & blurring of vision	Left lateral ventricle	MRI: s/o (central neurocytoma)
5	28 years /male	Headache with giddiness	Intraventricular SOL	MRI s/p/o central neurocytoma

As evident from above table XIII,

Central neurocytoma is commonly located in third or lateral ventricular region hence symptoms of raised intracranial pressure like headache, giddiness and vomiting seen as common clinical presentation.

Upon microscopic examination, tumor shows compact cohesive sheets of round to oval monomorphic tumor cells with mild hyperchromatic nucleus, granular chromatin pattern and scant cytoplasm. There is also evidence of sheets of tumors showing perinuclear clearing, tumor cells with neurocytic differentiation and at places rossettoid pattern with fibrillary background, delicate plexiform vasculature and Homer wright rosettes.

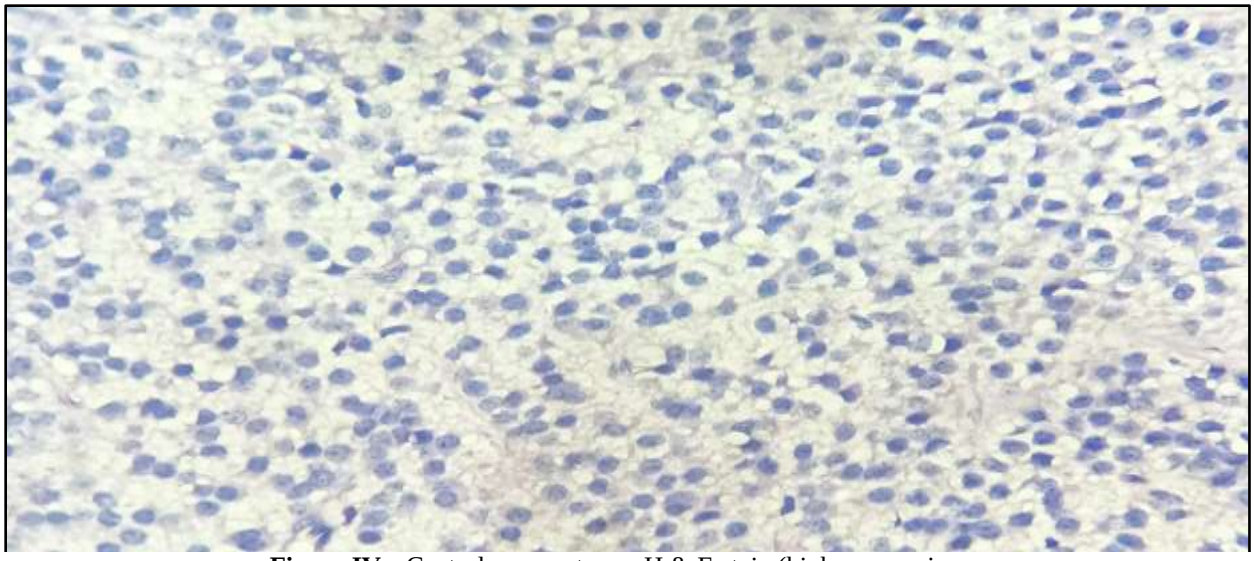

Figure IV:- Central neurocytoma; H & E stain (high power view.

Total 39 cases **ependymoma** observed during study. Among which three cases of clear cell ependymoma and one case of Anaplastic ependymoma are seen.

Table VI:- Data of clear cellependymomacases.

Sr. no.	Age/sex	Clinical features	Site	Radiological findings
1	48 years /Female	Drowsiness and altered sensorium	Corpus callosum	-
2	12 years / female	Headache, altered sensorium	Intraventricular SOL	MRI brain: P/o neoplastic lesion ependymoma.
3	18 years /female	Convulsion	Right parieto-occipital cystic SOL	-
4	22 years / male	Convulsion and headache	Intraventricular SOL	MRI s/o central neurocytoma

Ependymoma is commonly located with ventricular lining and Headache convulsions are common clinical presentation.

Upon microscopic examination, clear cell ependymoma shows well circumscribed tumor having round to oval cell with clear cytoplasm perivascular pseudo rosettes (marked by black box), true ependymal rosettes (marked by red box) along with branching capillary network often suggests an oligodendroglioma, but there sharp demarcation from adjacent brain tissue which favors ependymoma.

Another case show tumor with multinodular growth pattern with small aggregates of tumor cells haphazardly disposed in a voluminous, hypo vascular fibrillary meshwork. Tumor cell nuclei are hyperchromatic with moderate pleomorphism. At places clear cell change is also seen. Foci of dystrophic calcification and cystic spaces are also seen. There is formation of ependymal rosettes and foci of hemorrhage and necrosis. There is also evidence of extensive microvascular proliferation and atypical mitoses.

Following possibilities may be considered:
1. Anaplastic ependymoma WHO grade III.
2. Atypical central neurocytoma WHO grade-III.

So Immunohistochemical examination was performed which is negative for Synaptophysin, positive for GFAP and perinuclear dot like positivity for EMA hence confirming diagnosis of anaplastic ependymoma.

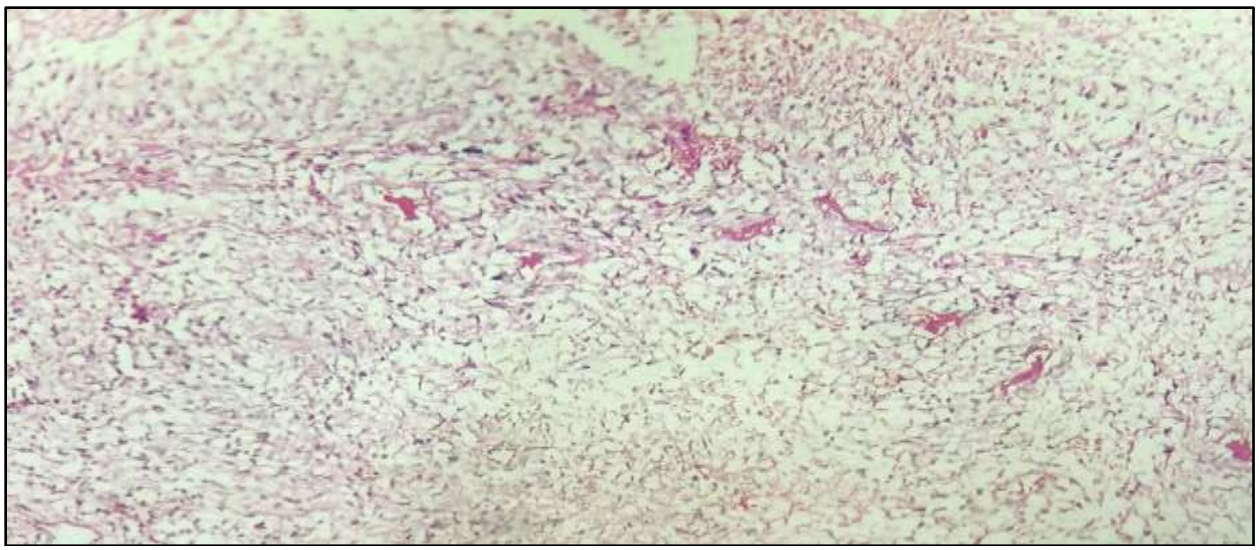

Figure V:- Clear cell ependymoma; H & E stain (low power view).

Two cases of **chordoma** are seen during present study located at clivus of occipital bone.On microscopic examination, chordoma shows tumor cells arranged in lobular architecture with cells having eosinophilic to clear cytoplasm giving bubbly appearance (marked with black arrow) with vesicular nuclei and myxoid stroma (marked with red arrow) and one focal area of necrosis.The physaliphorous cells characteristically seen in chordoma have bubbly vacuolated to clear cytoplasm due to glycogen accumulation.

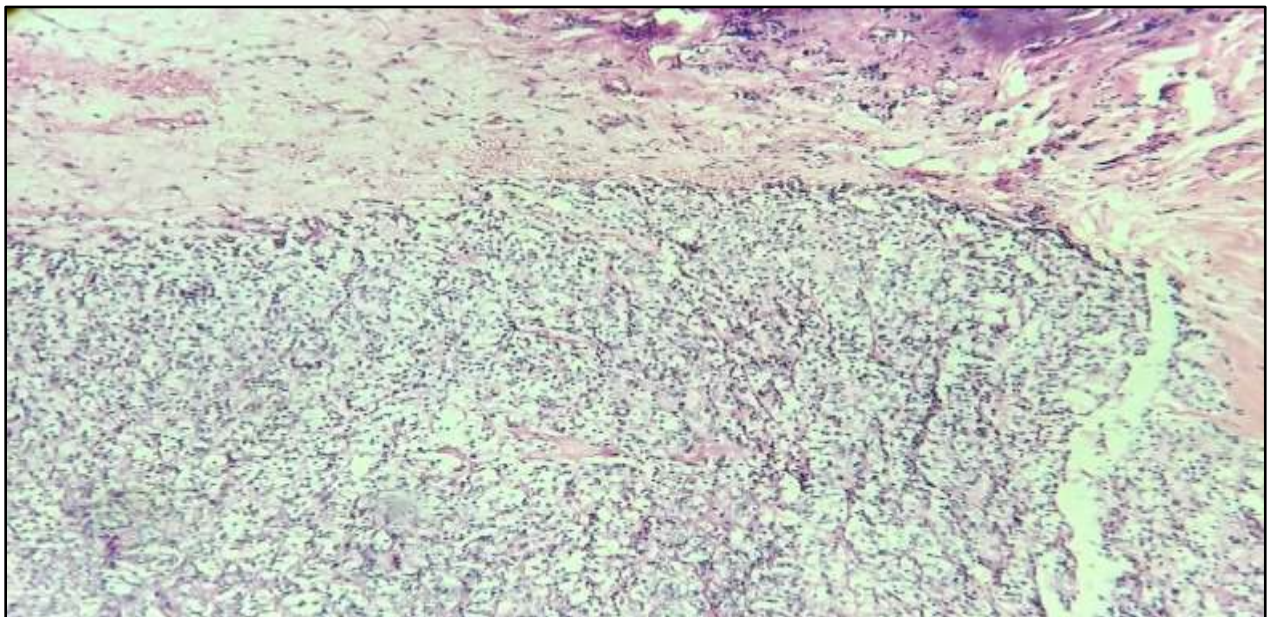

Figure VI:- Chordoma; H & E stain (low power view).

Among malignant clear cell lesions of CNS, two cases of **metastatic clear cell lesions** were observed.one case was of 45-year male with c/o headache and weakness for 1 year.

And radiological findings were suggestive of frontotemporal lobe space occupying lesion.

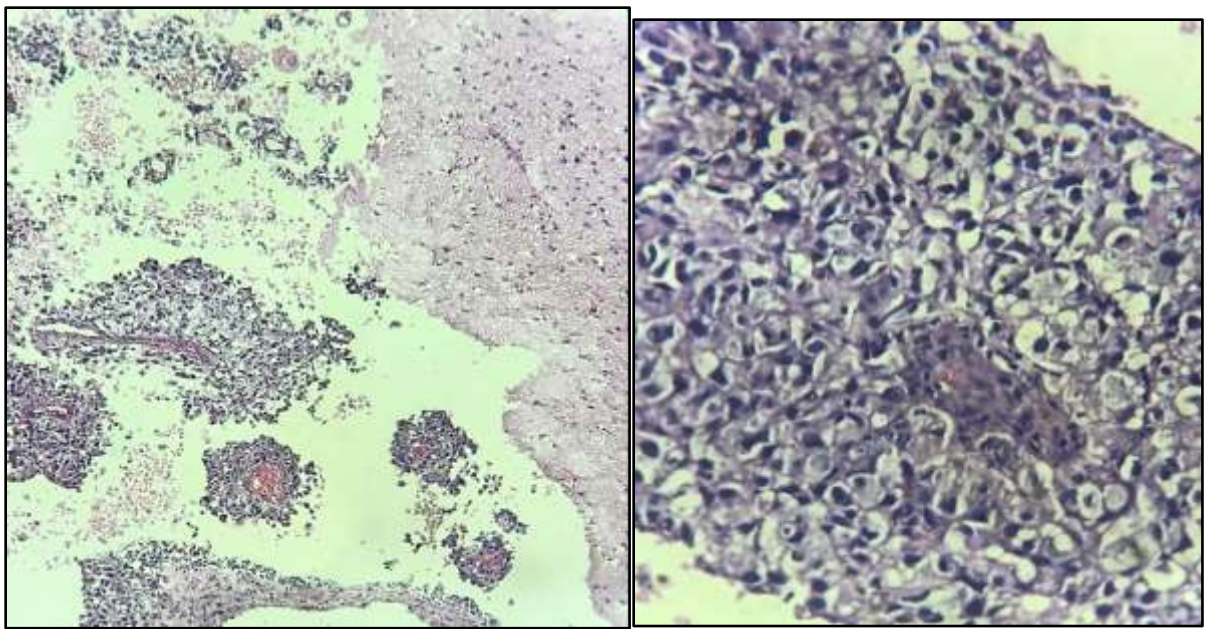

Figure VII:- Metastatic melanoma in brain (a) low power view;(b) High power view;H & E stain.

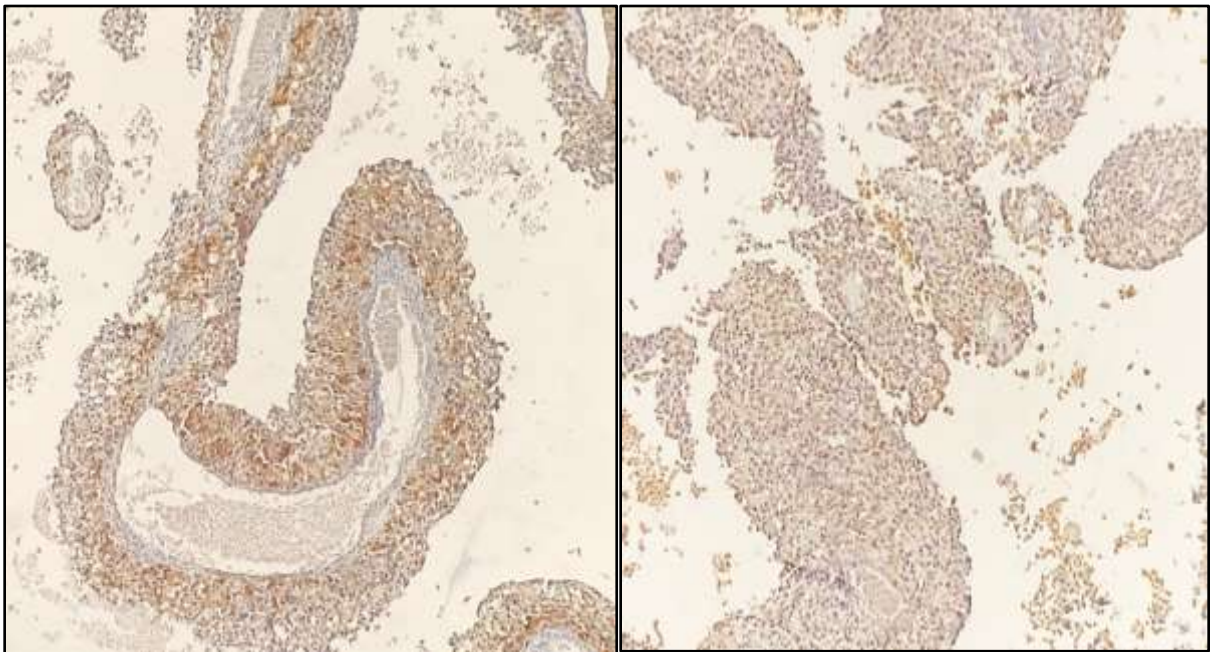

Figure VIII:- (a) S100 cytoplasmic positivity (b) HMB 45 cytoplasmic positivity in metastatic melanoma in CNS

Another case of 52-year-old male having right frontal space occupying lesion presented with complain of headache. His radiological findings were suggestive of frontal lobe space occupying lesion with possibility of neoplastic etiology.

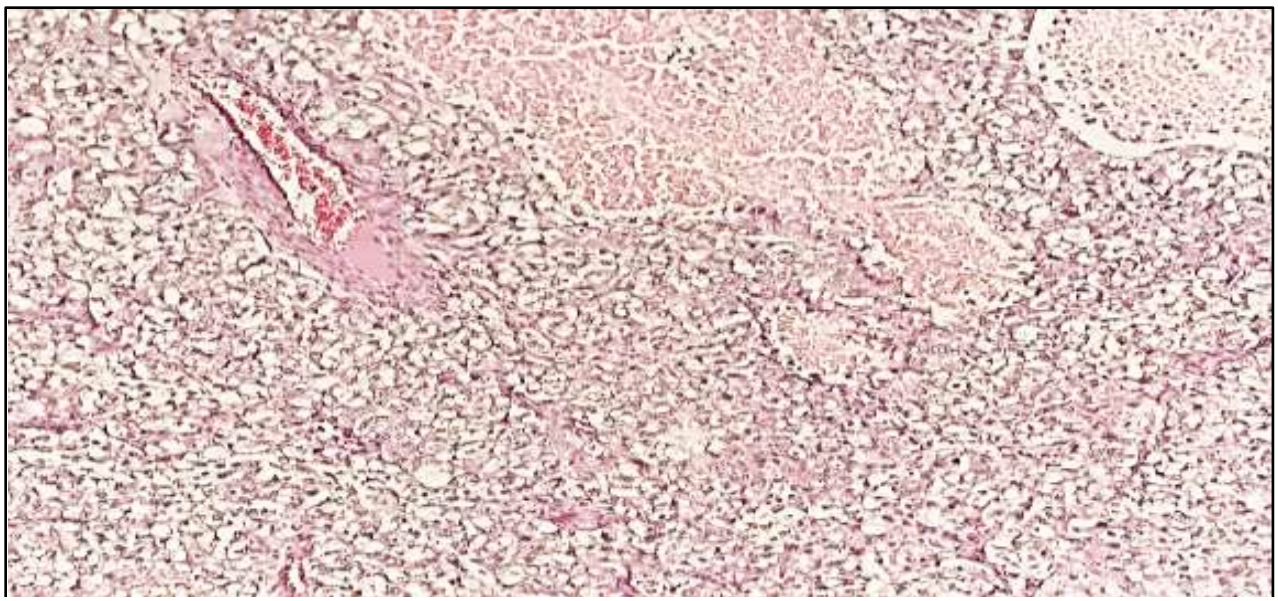

Figure IX:- Metastatic clear cell RCC in brain; H & E stain (low power view).

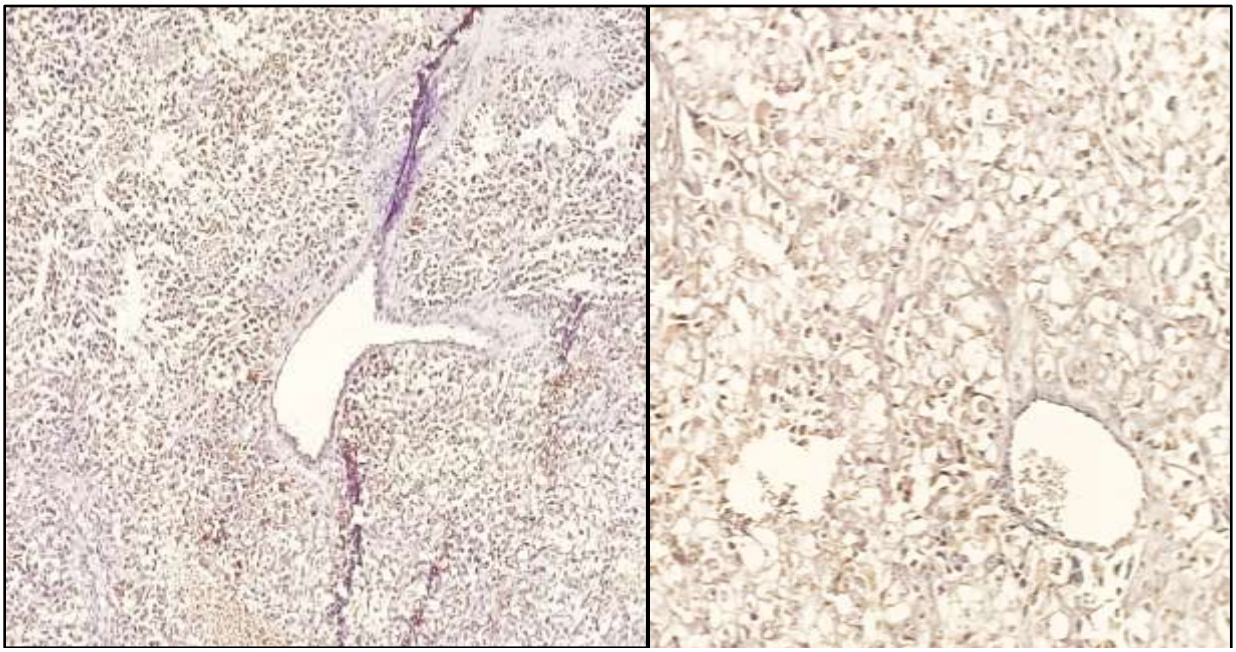

Figure X:- (a) CK 7 diffuse focal positivity, (b) vimentin focal diffuse positivity in metastatic clear cell RCC.

Discussion:-

Not infrequently, clear cell changes are encountered in various non neoplastic benign and malignant neoplasms, the sources and nature of which are difficult to determinate on the basis of the conventional morphological study.

Clear cell tumors in Central nervous system can be correctly identified by giving attention to clinical presentation, location, radiographic findings, and histomorphological features, immunohistochemistry analysis wherever necessary.

1. Total 33 cases of clear cell tumors of CNS were encountered in our study out of 215 cases.
2. Among benign tumor, most common tumor showing clear cells is **hemangioblastoma**. Among malignant lesions, **oligodendroglioma** (7 cases) and pleomorphic xanthoastrocytoma (7 cases) are commonly encountered tumors having clear cells.

3. Other encountered clear cell neoplasms in CNS are central neurocytoma (5 cases), clear cell ependymoma (4 cases), chordoma (2 cases) and metastasis (2 cases).
4. In most of instances, morphologic features direct toward definitive diagnosis. First step is identifying whether the lesion is infiltrative or not. Presence of infiltration in normal surrounding brain parenchyma with presence of secondary structures of Scherer (perineuronal satellitosis, perivascular satellitosis, subpial aggregation, and infiltration of white matter tracts) are good indicators of infiltration and likely oligodendroglial in nature.
5. In **oligodendroglioma** clear cell changes are due to **artifactual change** during tissue processing hence it is not seen during frozen section/crush preparations.
6. The presence of pseudo rosettes and ependymal rosettes is consistent with non-infiltrative tumor borders diagnosis towards ependymal differentiation.
7. In the presence of whorls and intranuclear inclusions, clear cell meningioma is the most likely diagnosis.
8. In **meningioma** clear cell features are due to abundant **intracellular glycogen** accumulation. Rare Clear cell meningioma variant is WHO grade II tumor and associated with high recurrence rate.
9. Also, presence spindle and bizarre multinucleated giant cells forms with latter having hyaline granular and vacuolated **clear cytoplasm (due to lipid accumulation)** directs diagnosis toward **pleomorphic xanthoastrocytoma**. It is commonly seen in children and despite of high pleomorphic features it is WHO grade I tumor and have very good prognosis.
10. In case of numerous thin-walled capillaries with vacuolated stromal cells diagnosis is points towards hemangioblastoma.
11. In our study, in most of the instances morphological architectural pattern of tumors along with clinico-radiological investigations had directs to arrive at final diagnosis.
12. **Camelo-Piragua S. at El** also described approach to clear cell tumors CNS with the help of clinicopathologic and radiologic features to help guide the general pathologist in the diagnosis of clear cell tumors of the CNS. This study also provided an algorithmic approach towards these tumors with immunohistochemistry markers to arrive at an appropriate diagnosis.[7]
13. **Kar at al** also described histomorphological approach to arrive at diagnosis of various clear cell lesions based on location and biological behavior.[8]
14. Often, clear cell tumors in CNS show similar morphologic features, and then, ancillary studies are required to arrive at accurate diagnosis. So,recommended IHC markers used for differentiation of clear cell CNS tumors are GFAP, S-100, EMA, keratin, vimentin, and synaptophysin.
15. In our study, two cases of metastatic clear cell tumors were seen.
16. One of them on microscopic examination, shows normal cerebral tissue as well as tumor tissue. Tumor show predominantly papillary arrangement of tumor cells with extensive areas of coagulative tumor necrosis. Individual tumor cells show marked pleomorphism with hyperchromatic nuclei, prominent nucleoli and brisk mitotic activity. The tumor cells show moderate to abundant eosinophilic cytoplasm. Some of the tumor cells show clear cell changes. There are also tumor cells showing brownish melanin like pigment.

So, depending upon microscopic findings following possibilities may be considered:

1. Metastatic Melanoma
2. Metastatic Papillary adenocarcinoma
3. Anaplastic Ependymoma

- So, Immunohistochemistry is performed for final confirmation.
  - CK and EMA: focally weak positive,
  - VIM: Diffuse strong positive,
  - GFAP: Negative
  - **S-100: +VE,**
  - **HMB 45: diffuse strong positive**
- So, on the basis of IHC findings final diagnosis of metastatic melanoma was considered.
- In another case, microscopic examination was showing tumor tissue with areas of hemorrhage and necrosis along with normal cerebral tissue. The tumor is composed of malignant large polygonal clear cells arranged in diffuse, perivascular and papillary patterns. So, the overall histology was suggestive of malignant clear cell tumor with features favoring metastatic origin.
- Further workup with immunohistochemistry was performed.
  - HMB 45: Negative
  - Cytokeratin: Negative

- Epithelial membrane antigen: Focal moderate Positive
- **Vimentin: Focal moderate Positive**
- **CK-7- Positive**
- Thyroglobulin – Negative

➢ So final diagnosis was Metastatic malignant clear cell tumor -Renal cell carcinoma - clear cell papillary type.

Conclusion:-

Clearing of cytoplasm or clear cell changes are seen in various entities of different locations due to diverse reasons. So whenever clear cell is encountered, algorithmic approach is required to further proceed. In most of the instances morphologic features like architectural pattern, pleomorphism, necrosis and mitosis directs us to reach at diagnosis along with clinical and radiological findings. Knowledge of the non-neoplastic and neoplastic conditions displaying clear cell change at each anatomic site helps to approach the differential diagnosis of each condition in a more logical and rigorous manner.After morphologic evaluation, special stains and immunohistochemistry can be performed to reach at a final diagnosis; the different special stains and immunomarkers necessary are different according to type and location of the tumor, which can easily give the clue to diagnosis.

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