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An Overview of Clinico-Pathological Correlates of CNS Germinoma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Germ cell tumors (GCTs) in the central nervous system (CNS), occurring in the first and second decade of life, mainly affect children and young adults typically. Ages from 10-19 years are the peak incidence. In patients younger than 20 years,3-5% of all or most intracranial tumors are caused by GCTs and are three times more common in males than females.

This condition can present with a vast constellation of signs, symptoms, and disorders based on the location, age of the patient, and tumor size. With raised intracranial pressure features, obstructive hydrocephalus is caused by pineal tumors. Suprasellar tumor's most common initial manifestation is diabetes Insipidus, pituitary dysfunction, and hypothalamic. Diagnosis and treatment for different germinomas are known by measuring the level of cerebrospinal fluid and serum of tumor markers. This article is part of students' projects to foster their research skills and integrated learning.

Keywords: Pineoloma; germ cell tumor; hormonal dysfunctions; diabetes insipidus; CNS tumor management.

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1. INTRODUCTION TO CNS GERMINOMAS

“In the brain, germinoma, also known as a pure germ cell tumor, is commonly found. During fetal development, germ cells migrate to the gonads typically and become sperm in male testes and eggs in female ovaries” [1]. “If these germ cells do not migrate to the correct location, they can become trapped in the brain and multiply in abnormal areas, causing dysfunction” [2].

A non-germinomatous tumor is the other germ cell type in the brain that secretes a chemical into the bloodstream and spinal fluid and requires intensive treatment compared to germinoma. Symptoms typically depend on where the germinoma develops in the brain. “Children with a germinoma in the pineal gland region can have the following symptoms; Hydrocephalus (swelling of the brain), Headache, Behavioral or cognitive changes, ataxia, and Visual changes” [2].

In Suprasellar or Pituitary gland region tumor cases, common clinical manifestations include Diabetes insipidus, delayed/ precocious puberty, stunted growth, and vision changes. Radiotherapy, chemotherapy and surgery are treatment options [2].

1.1 Anatomy of CNS Germinoma

Germinomas are usually located in the basal ganglia and thalamus, occurring between 10 to 19 years in young adolescents. In this age group, it might correlate with gonad development. Slow progression and insidious onset are features of basal ganglia germinomas. Significant symptoms are mental status change, cognitive declination, and progressive hemiparesis. In the clinical presentation, symptoms and signs are valuable for localization and contribute to identifying subtle lesions on the brain [3].

“Germ cell tumors (these include Germinoma, Dysgerminoma, Teratoma, Endodermal Sinus or Yolk sac Tumor, Embryonal Carcinoma, and Choriocarcinoma) [4] involve the gonads (testes and ovaries) and extragonadal regions (pineal gland, suprasellar area, anterior mediastinum, and sacrococcygeal)”. Elevated βhCG and Serum α-fetoprotein are used to confirm the diagnosis and guide the treatment.

Clinical presentations vary depending on tumor location. Pineal/ Suprasellar tumors produce upward paralysis, poor coordination, and headaches. Wheezing and cough are features of anterior mediastinal lesions. The presence of constipation and mass in the buttock or presacral region are seen in an infant with Sacrococcygeal tumors. Pelvic or abdominal mass present in young girls with ovarian tumors. Torsion of the testis and painless testicular swelling occur in testicular tumors. Chemotherapy is the optimal therapy, and radiation in some cases.

The highly malignant subtypes of GCT are Endodermal Sinus Tumors, Yolk-sac tumors, Embryonic Cell Carcinoma, and choriocarcinoma, which are heterogeneous on MRI and CT. Hemorrhage occurrence is the only distinguishing factor between choriocarcinoma and other tumors. Yolk sac tumor α-fetoprotein, both human chorionic gonadotropin, choriocarcinoma releases human chorionic gonadotropin, α-fetoprotein, and embryonic Cell Carcinoma is the helpful laboratory examinations of tumor markers for this purpose [1].

“When GCT is suspected, contrast material is instrumental in detecting CSF spread in the brain and spine, a common and early finding. Primary Central Nervous System (CNS) lymphoma, primitive neuroectodermal tumors, and glioma are differential diagnoses” [4].

“Basal ganglionic germinomas and thalamic show a higher tendency, unlike typical germinomas in the pineal or suprasellar region, for cystic formation, hemorrhage, calcification, and progressive infiltration into the internal capsule, which may in turn cause Cerebral Hemi atrophy. In the thalamus and basal ganglia, the rapid enlargement is caused by hemorrhage and cystic changes compared to those in the suprasellar and pineal regions” [5].

1.2 Sites Affected by Germinoma

“The brain is germinoma's primary location.

Germ cell tumors are found in different parts of the body, typically in deep midline locations like the pineal gland (45%) or suprasellar region (30%)” [4]. Germinoma has standard histology of about 5%-10% of patients whose tumor roots are from suprasellar and pineal locations [4]. 15% of the germinomas are usually unilateral in the thalamus and the basal ganglia. Most germ cell tumors originate outside the thalami and infiltrate the thalami from the posterior or anterior walls of the third ventricle. Hemiparesis is the most common presenting factor, caused by invasion of

the tumor of the internal capsule, followed by cognitive deterioration.

With the tendency to metastasize throughout the cerebrospinal fluid spaces, germinomas range from benign processes to highly malignant neoplasms histologically [5].

1.3 Classification of CNS Germinoma

CNS GCTs are categorized as either germinomatous or non-germinomatous germ cell tumors (NGGCTs) based on their laboratory and clinicopathological features and tumor markers. A Japanese Pediatric Brain Tumor Study Group proposed an alternative therapeutic classification base on stratification of the prognostic group of the histologic variants, as follows [4]:

- Good prognosis: Germinoma, pure and mature teratoma.
- Intermediate prognosis: Germinoma with syncytiotrophoblastic giant cells teratoma, teratoma with malignant transformation, immature teratoma, teratoma tumors, and mixed germinoma.
- Poor prognosis: mixed tumors of the yolk sac, yolk sac tumor, choriocarcinoma, embryonal carcinoma.

2. PATHOPHYSIOLOGY OF CNS GERMINOMA

2.1 Epidemiology

In the united state, between 2010 and 2014, 0.07, per 100,000 population had an overall incidence of GCTs (CNS), according to a report by CBTRUS. The incidence rate was lowest in African Americans (0.04 per 100,000) and 60% raised in Pacific/Asian Islanders than in non-Hispanic and whites [6].

Japan and other Asia countries have more people with primary CNS GCTs than North America and Europe. The proportion of GCTs among children with brain tumors in East Asia is 7.8% in Japan, 7.9% in China,9.5% in Korea and 14.0% in Taiwan, whereas it is about 4% in North America and Europe [6,7]. In the United States and Japan, a similar incidence was found in a study analyzing tumor registries of primary CNS GCTs.

In CNS GCTs, male predominance is noted chiefly. In the United States, the incidence in male patients and all ages combined with CNS germ cells was 3.7 times that in females, according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Sex is the primary determinant of the location of the tumor. In males, 70% of the tumors occur in the pineal area and 75% in females in the suprasellar areas. Incidence-rate ratio (IRR) of 3.1:1 for male-female was found in the United States and Japan CNS GCT registries. However, there was a significant difference depending on its site: In the non-pineal region of the CNS, the male-to-female IRR was 1.9:1 compared to the pineal region, which was a 16.0:1 ratio for malignant tumors.

71% of CNS GCTs cases are diagnosed before 20 years, but most cases are seen at birth and 34years. Ages 10-14 years have the highest incidence (0.28 per 100,000), while ages 10-14years have the peak incidence. The pediatric age distribution of CNS GCTs is categorized as follows [7,8]:

- 0-4 years: 9% of cases
- 5-9 years: 18% of cases
- 10-14 years: 39% of cases
- 15-19 years: 34% of cases.

2.2 Etiology

CNS GCTs' exact cause is idiopathic. In the developing embryo, primordial germ cells appear to give rise to GCTs which then migrate to the germinal ridges. These molecular pathways' aberration may potentially give rise to GCTs occur. The extracellular matrix is a crucial factor in cell migration; it greatly influences cell migration and adherence. Some other factors, such as Chemotropic factors, are another crucial factor that may also be involved in cell migration. Growth factor beta-1 has been shown in vitro studies to initiate primordial germ cell migration [9].

Migrating cranially towards the diencephalic midline structures are primordial germ cells that have moved out of the yolk sac's endoderm instead of laterally to genital ridges. Fetal hypothalamus maturation coincides with primordial germ cell migration. Chemotrophic factors may be secreted from the fetal hypothalamus that attracts cells of primordial germ to the diencephalon [10].

The movement of the primordial germ cells into the mesenchyme of the mesentery may be an alternative event in the embryonic cell theory and

blood vessel formation stimulation; through the circulation, it reaches intracranial locations.

Once reaching their intracranial location through abnormal pathways, primordial germ cell undergoes congenital or acquired aberrant molecular events themselves or in the microenvironment surrounding them, leading to CNS GCTs formation [6,8,9].

The Neuroendocrine function surge of reproduction in the diencephalon may also be a contributing factor or a cause of CNS GCTs development, as demonstrated by the location of these tumors and their predominance in the pubertal age group [11,12,13].

2.2.1 Molecular pathology

The origin of CNS GCTs cells remains controversial. The germ cell theory proposes that these growths develop from primordial germ cells that have moved aberrantly throughout beginning development and consequently undergone deadly improvement. Proof in support of this concept consists of a genome-wide methylation profiling research of 61 GCTs that found pure germinomas are identified by global low DNA methylation, a unique epigenetic feature making them distinct from all other subtypes of GCT. At the migratory stage, the primordial germ cells (PGC) strongly resemble the methylation patterns, suggesting the tumor's cell origin.

On the other hand, the embryonic cell theory suggests that GCTs arise from an immigrational pluripotent embryonic cell. As proposed, germ cells come from pure germinomas; meanwhile, misplacement and misfolding of germ cells make NGGCTs into the mesoderm, entrapping the created cells in different brain locations [14,15]. Existing evidence recommends that GCTs develop from germinal aspects at numerous stages of growth.

Research of malignant testicular tumors has revealed that the short arm of chromosome 12 (I [12p] isochromosome is a usual, irregular chromosome [15,16]. Chromosomal contrast of CNS GCTs with gonadal growths using genomic hybridization evaluation has discovered the two to be identical. In adults, extragonadal germinomas onset is one of the usual irregularities duplicating the short arm of chromosome 12.

In children, cytogenetic abnormalities include loss of 1p and 6q, changes in sex chromosomes, and irregularities in 12p. Research in children exposed that a subset of individuals with pineal tumors demonstrated a gain of chromosomal produce at 12p.

The most common chromosomal abnormalities consist of gains of 1p, 8p, 12q, and losses of 13q and 18q [14,16,17]. Enhanced copies of the X chromosome are seen in CNS GCTs; one of the most constant genotype abnormalities is XXY, similar to that in Klinefelter disorder. Individuals with Klinefelter disorder are prone to develop intracranial GCTs, as are those with Down disorder and those with neurofibromatosis, type 1. Frequent modifications of the p14 genetics have been spotted, especially in pure intracranial germinomas, recommending that this genetics plays an essential function in the growth of these tumors. Mutations of the c-kit genetics have been found in 23-25% of intracranial germinomas. These anomalies are thought to promote the growth of intracranial GCTs [17].

“Genomic evaluation of GCTs has exposed distinctive messenger RNA and microRNA profiles, which may associate with histological distinction, and scientific results. In the future, these might act as unique therapeutic targets” [18].

3. CLINICAL MANIFESTATIONS

3.1 Tumors of the Pineal Region

The most common CNS GCTs presentation is seen in 34-50% of cases of Parinaud syndrome due to tectum compression. The syndrome includes the following ophthalmic manifestations [8,19,20]:

- Upward gaze paralysis
- Loss of light perception and Accommodation and light perception loss
- Nystagmus
- Convergence failure

Raised intracranial pressure features like papilledema, vomiting, nausea and headache may supervene. Development of seizures, ataxia, behavioral abnormalities, and somnolence may occur. In a pre-pubertal child, precocious puberty may develop.

Indicating involvement of the floor of the suprasellar area and the fourth ventricle are rare occurrences like anterior hypopituitarism and diabetes insipidus [19].

3.2 Tumors of the Suprasellar Region

Suprasellar GCTs patients usually may have endocrine deficits like:

- Diabetes insipidus (DI) and Anterior hypopituitarism
- Deficiency of the cortisol and/or thyroid
- Growth failure from growth hormone deficiency
- Delayed puberty from gonadotropin deficiency
- Regression of sexual development or sexual dysfunction
- Posterior pituitary dysfunction (vasopressin deficiency)
- Precocious puberty may develop in a pre-pubertal child (due to tumor-induced hypothalamic injury or secretion of human chorionic gonadotropin by the tumor) [20].

Visual disturbances like blurred vision, diminished vision, and diplopia may be present. Enuresis and psychiatric abnormalities may develop. Generally, patients with endocrine dysfunction present later than patients with symptoms of visual changes and raised intracranial pressure.

3.3 Rare Presentations of CNS GCTs Include the Following

- Multiple lesions - GCTs in the pineal, sellar region, corpus callosum, and ventricles were reported in an 18-year-old man who presented with psychosis [19].
- Wide skull base extension - This was reported in a 15-year-old girl with radiologic evidence of central skull base and suprasellar tumor extending into the cavernous sinus, intra-orbital region, ethmoid sinus, sphenoid sinus, and pituitary fossa [20].
- Optic pathway - Intracranial germ cell tumors may occur primarily in the optic nerve and/or optic chiasma with progressive and painless visual loss [21,22,23]. In patients with optic gliomas having visual loss with hypothalamic-pituitary-adrenal dysfunction detected via imaging studies, the definitive diagnosis is a biopsy.
- Midbrain outflow tremor (Holmes tremor): “Holmes tremor is a hyperkinetic movement disorder that presents as mild to severe tremors, dystonia, and cerebellar deficits; it has been reported in patients with germinoma” [24].

4. DIAGNOSIS AND INVESTIGATIONS

4.1 Physical Examination

The clinical evaluation should include the following:

- General physical examination.
- Check of growth parameters.
- Neurocutaneous stigmata assessment with Careful neurological evaluation.
- Primary and secondary sexual characteristics assessment.
- Ophthalmologic exam.

The diagnostic workup for central nervous system (CNS) germ cell tumors (GCTs) should include the following: [25,26]

- MRI studies of the brain and also spinal column
- Measurement of the tumor markers β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) in both product and cerebrospinal liquid (CSF).
- Tissue verification by biopsy.
- Brain and spine MRIs are essential for medical diagnosis, assessing the level of intracranial condition, and spotting metastatic conditions. Postoperative MRI of the brain is vital to examine residual tumors.

CSF cytology is used to find malignant cells. Measuring serum and CSF tumor markers might aid the diagnosis and treatment strategy [15,25,27]. Examining the disease outside the CNS usually is unnecessary.

As a result of the diversification of germinomas and the reality that just a small biopsy specimen might be acquired, central pathology evaluation is essential to accomplish precise medical diagnosis, which is necessary for suitable treatment preparation.

4.2 Imaging Studies

4.2.1 Computed tomography of the brain

The germinomas' pattern is homogenous and hyperdense compared to brain cells; with pineal gland tumors, calcification of the gland might be seen. Mature teratomas have blended thickness,

with large cysts and areas of calcification with distinctive growth margins.

4.2.2 Magnetic resonance imaging

MRI of the brain and spine with and without gadolinium is the basic imaging research study. Leptomeningeal transition is present at medical diagnosis in 10-15% of clients. Showing iso intensity or slightly low signal intensity on T1-weighted images of germinomas homogeneity and Iso intensity or high intensity on T2-weighted images [28].

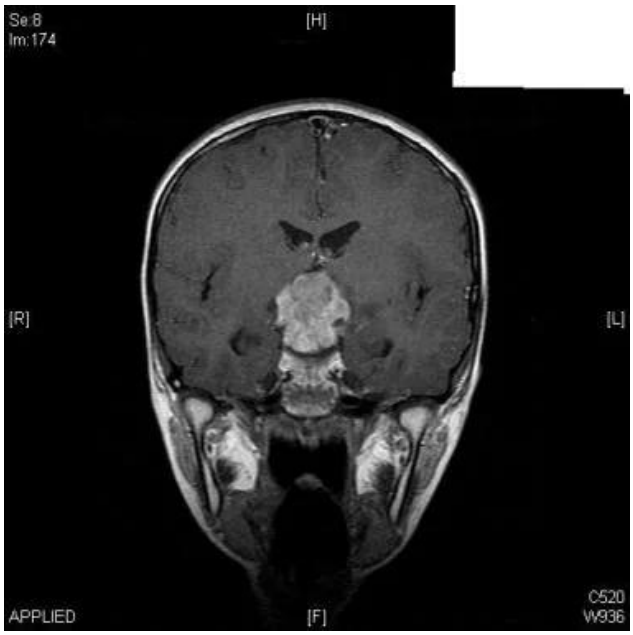

Fig. 1. MRI of the brain - T1 weighted-image- coronal view- showing a heterogeneously enhancing, multicystic mass in the suprasellar region. Source: Link

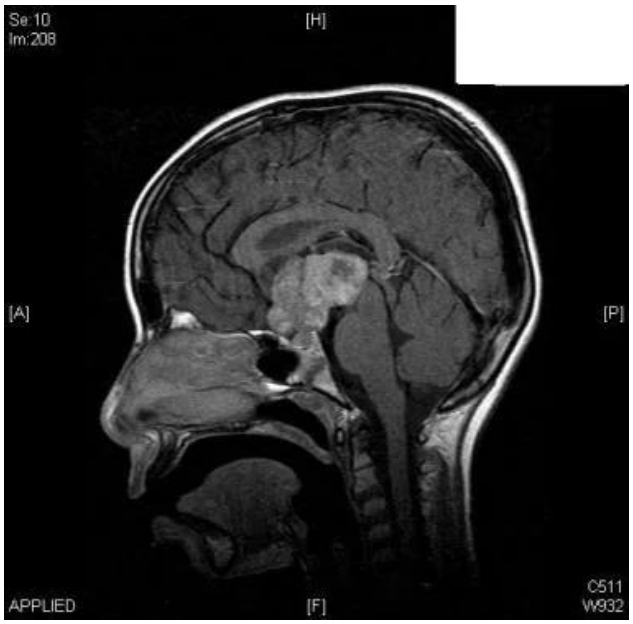

Fig. 2. MRI of the brain - T1-weighted image, sagittal view of post-gadolinium - The optic chiasm severely compressed by a suprasellar lesion encases the posterior aspect of the optic nerves bilaterally, and with significant compression of the brain stem, it causes superior displacement of the third ventricle. Source: Link

4.2.3 Positron emission tomography

The utility of positron emission tomography (PET) scans has been investigated by several studies. In a retrospective review of 10 patients, the detection of germinomas by 18F-fluorodeoxyglucose PET(FDG-PET) was reported. In a tumor, contour definition to planning for biopsy or surgery 11C-methionine PET (MET-PET) can help [29,30]. Limited information is available on the value of 18F-fluoroethyl choline PET/MRI for the diagnosis of intracranial GCTs and follow-up by assessing for residual tumor.

4.3 Biopsy

As recommended, the histological confirmation of pineal and the suprasellar tumor is done through surgical biopsy, either by open or stereotactic/endoscopic biopsy. Less mortality and morbidity have been achieved through modern endoscopic techniques. Pineal tumors are less accessible to surgical biopsy than the suprasellar tumor.

In non-germinomatous GCT, adequate specimen size is significant as a false representation of the actual tumor type occurs if specimen size cannot capture important tumor components.

Surgery is unnecessary for tissue diagnosis in patients with CSF levels of AFP or β-hCG >50-100 IU/ml and elevated serum [27]. Diagnosis without tissue verification should be considered in such patients because high postoperative mortality has been reported after resectioning secreting tumors [30].

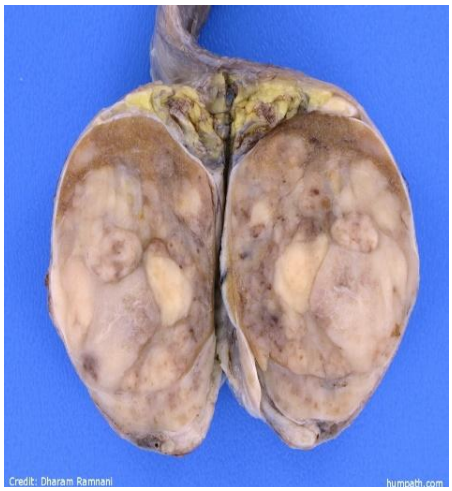

Fig. 3. Gross image of Germinoma
Source: https://cancerworld.info/wp-content/uploads/2017/06/Germinoma-Germ-Cell-Tumors-Symptoms-Treatment-Prognosis-1.jpg

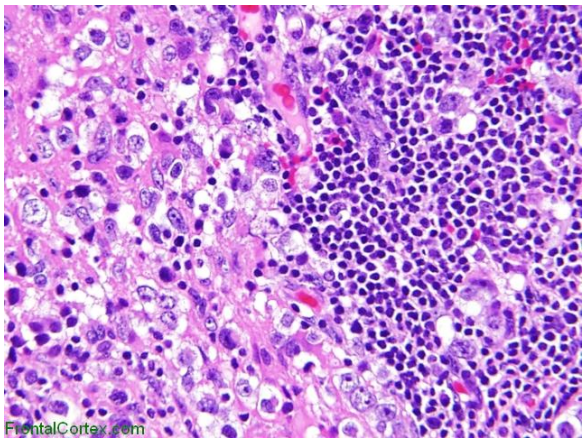

Fig. 4. Histology showing Germinoma (Tumor cells and lymphocytes) in the pineal region
Source: https://www.bing.com/images

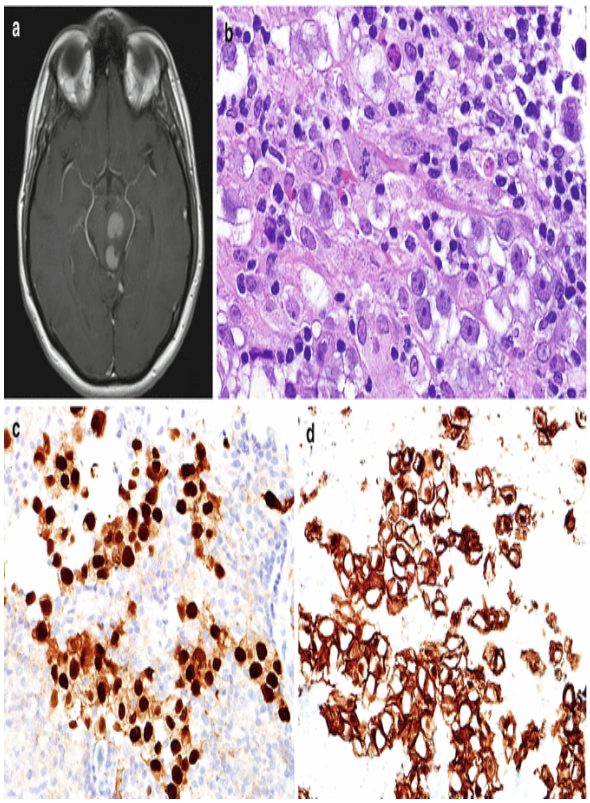

Fig. 5. Germinoma involving the midbrain. On occasion germinomas may involve the midbrain in a more diffuse form or a in a multinodular fashion, which may cause diagnostic confusion (a). Mitotic activity and apoptosis are frequent in germinomas (b). Additional immunohistochemical features of germinoma include OCT4 (c) and KIT expression (d)
Source: basicmedicalkey.com

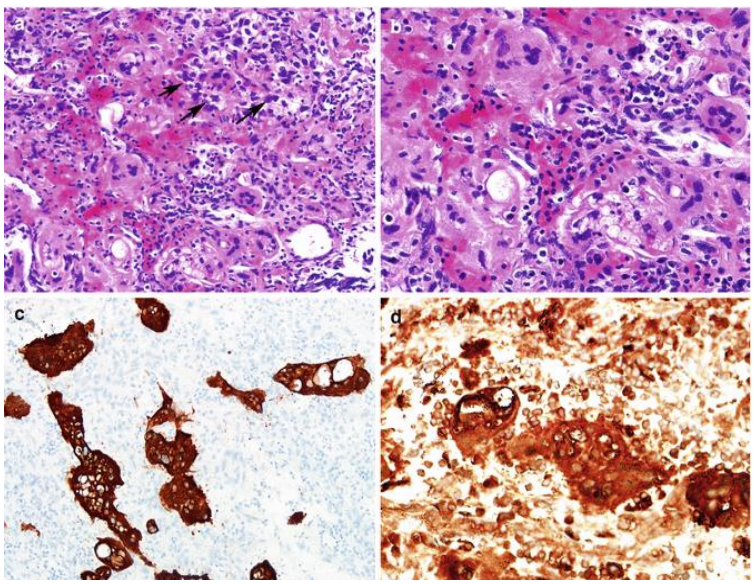

Fig. 6. Syncytiotrophoblast giant cells in germinoma. A subset of germinomas contain variable numbers of syncytiotrophoblast-like giant cells (a, b) which may be associated with B-HCG elevations. Cytokeratin (c) and B-HCG (d) expression may be detected by positive immunohistochemistry markers. [SALL4, OCT4, CD117 (KIT) and HESRG]
Source: basicmedicalkey.com

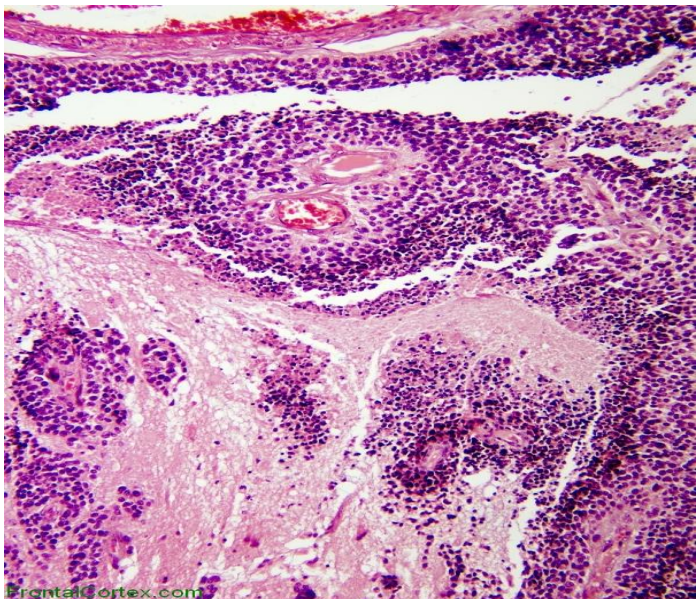

Fig. 7. Disseminated Germinoma in the leptomeninges
Source:http://frontalcortex.com

5. MANAGEMENT OF GERMINOMAS

Pediatric and Young adult CNS germinomas have favorable cure rates. However, long-term follow-up data are limited because of the rarity of this tumor.

The best outcome amongst pediatric brain tumors in the last 35years is in CNS germinoma, with more than 85% overall survival over five years because germinomas respond to radiation and chemotherapy. In the future, finding ways to minimize the adverse effects of these treatments, particularly regarding radiation, and improving the quality of life of those that develop neurocognitive, endocrine deficiencies, and neurologic might be challenging [4,31].

Craniospinal irradiation is a widespread published treatment modality. With no spinal dissemination, chemotherapy regimens with limited radiation treatments (whole ventricle or focal) have yielded similar outcomes in the cases reviewed. In cases with characteristic imaging appearances and negative tumor markers, biopsy does not seem to alter the outcome.

Biopsy to confirm the diagnosis is not necessary for pfeatures like diabetes insipidus, classic appearance of germinoma.Patients who present with a classic appearance of germinoma, negative tumour markers and diabetes insipidus probably do not require a biopsy to confirm the diagnosis.

5.1 Radiation Therapy

Germinomas are highly responsive to radiation therapy in more than 90% of patients with a 5years survival and a complete response rate. Non-germinomatous GCTs (NGGCTs) are less radiosensitive than pure germinomas, with overall 5-year survival of 30-50% [31].

Patients with pure germinomas were traditionally treated with full-dose Craniospinal Radiation (CSI), but it had a significant side effect. Therefore, localized germinomas are no longer treated with CSI.

To reduce the radiation therapy dose, chemotherapy and whole-ventricular irradiation are the most effective therapy currently. A study reviewed the outcome in the pediatric patient where ventricular clinical target volumes were excluded from temporal ventricular horns because radiation exposure to the temporal ventricular horns and hippocampi may lead to long-term poor cognitive function. Clinical outcomes were excellent, with no temporal ventricular horn failures and no death in the exclusion, which resulted in significant dose sparing to the hippocampi and temporal lobes. To confirm the benefits, long-term neuropsychological studies are required [31,32].

In controlling disease, radiotherapy to the whole ventricles appears to be essential. The Patients who had radiotherapy to the localized tumor

alone had higher rates of recurrence documented.

5.2 Chemotherapy

To permit lower radiation doses to a patient with germinomas, chemotherapy has been added to the treatment regimen to reduce long-term morbidity associated with radiotherapy with an excellent survival rate. Germinomas are chemosensitive, especially to platinum-based agents. Neoadjuvant therapy prior to low dose and low volume radiotherapy is the current recommendation.

Germinomas patients have a better outcome than NGGCTs patients. Combined therapy with neoadjuvant and adjuvant chemotherapy with radiation therapy is intended to improve outcomes. Chemotherapy is an integral part of NGGCTs treatment because of the increased survival of combination therapy [33,34].

5.3 Surgery

Excluding patients with a characteristic elevation in tumor markers, acquiring a tissue biopsy sample is the recommended practice, and in whom surgical intervention may lead to significant sequelae.

The CNS GCTs tumor type determines the surgical treatment. The main focus on germinomas is reducing morbidity since it has excellent management and prognosis. There is no proven benefit for gross or partial resection, as it may cause endocrinological or neurological deterioration. Therefore, most neurosurgeons limit surgical intervention to biopsy and treat these patients with radiation and chemotherapy.

In raised fetoprotein levels and histological diagnosis of pure germinoma, small surgical samples may not represent the tumor well, as it gives a conflicting result. Hence this category of patient should be treated more aggressively than patients with pure germinoma and normal CSF/serum marker levels [35].

Second-look surgery may be performed in a patient who has had an incomplete response to initial chemotherapy to remove the residual tissue and permit histological verification, as this residual tissue may contain malignant elements consisting of necrosis, mature teratoma, and fibrosis (Growing teratoma syndrome -GTS). GTS is characterized by enlarging tumor mass during or after chemotherapy in the presence of standard or declining tumor markers. Surgical resection of the tumor is curative.

5.4 Combination Immunotherapy

Compared to anti-PD-1 monotherapy (27% vs. 9% and 7% vs. 0%, respectively, $P < 0.01$), combination immunotherapy was projected to result in single or multiple endocrinopathies. After a median of 8 weeks from the beginning of treatment (range: 12-225 days), there was endocrinopathies occurrence, [36,4] with combination immunotherapy resulting in significantly earlier onset compared to ipilimumab. Anti-PD-1 monotherapy poses less risk in endocrinopathy development than Combination immunotherapy (higher risk). To minimize morbidity and achieve endocrinopathy early detection, patients' biochemical profiling must be regular, especially within the first twelve weeks.

Endocrine immune-related adverse events (endocrinopathies) are increasingly prevalent, with immune checkpoint inhibitors used to treat metastatic melanoma and other malignancies. There are no evidence-based guidelines for the screening or management of such patients.

Although CNS germinomas have favorable cure rates, late recurrences, subsequent malignancies, and stroke significantly affect long-term survival. Close attention to long-term follow-up with assessing stroke risk factors is recommended [36].

6. CONCLUSION

Unrecognized CNS GCTs in many patients may have complications with a long history, such as psychiatric complaints, enuresis, movement disorders and anorexia, and behavioral including psychosis and tics. Delays from 7 months to 3 years occur in such diagnoses.

In germinomas, normal AFP and detectable hCG levels are typical imaging study findings in most patients with bifocal (pineal and neurohypophyseal) GCTs. However, some bifocal non-germinomatous germ cell tumors (NGGCTs) may have similar radiographic features, detectable hCG levels, and standard or modestly elevated AFP [36].

The deep-seated tumor location hampers the chance of CNS GCTs' total surgical resection. Hence the standard adjuvant therapy has been craniospinal irradiation. Therefore, the standard adjuvant therapy is craniospinal irradiation. Surgical and anesthetic techniques, diagnostic advancement, radiotherapy, and chemotherapy have improved the patient's tumor outcome.

There are ongoing trials to determine the best radiation therapy regimes. 24 Gy is currently administered to patients with multifocal or localized disease to the whole ventricular system, and a 21-Gy boost to all measurable diseases [36].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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