Review Article

An Overview of Clinico-pathological correlates of CNS Germinoma.

ABSTRACT

Germ cell tumors (GCTs) in the central nervous system (CNS) typically affect children and young adults, predominantly occurring in the first and second decade of life the peak incidence is from 10-19 years of age. GCTs account for approximately 3-5% of all intracranial tumors seen in patients younger than 20 years of age. CNS germinomas are over three times more common in males than in females.

This condition can present with a wide constellation of signs, symptoms and disorders based on the location, size of the tumor and the patient`s age. Pineal tumors usually cause obstructive hydrocephalus with signs of increased intracranial pressure. Whereas the most common initial manifestation of suprasellar tumors is Diabetes Insipidus, Hypothalamic and Pituitary dysfunction. Measurement of serum and cerebrospinal fluid (CSF) levels of tumor markers have been known to aid in the diagnosis and treatment plan for different types of germinomas. 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

INTRODUCTION TO CNS GERMINOMAS

A germinoma, also known as a pure germ cell tumor, is a type of germ cell tumor commonly found in the brain. Germ cells typically migrate to the gonads during fetal development and become an egg in female ovaries or sperm in male testes [1]. If these germ cells don't migrate to the correct location, they can become trapped in the brain and multiply in abnormal areas, thereby causing dysfunction [2].

The other type of germ cell tumor of the brain is a Non-germinomatous tumor. It secretes chemicals into

the spinal fluid and bloodstream and requires more intensive treatment compared to germinoma.

Symptoms typically depend on where the germinoma develops in the brain. Children with 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 case of tumors located in the Suprasellar or Pituitary gland region, common clinical manifestations include: Diabetes insipidus, delayed/ precocious puberty, stunted growth and vision changes. Treatment options may include Surgery, Chemotherapy and Radiation therapy. [2]

ANATOMY OF CNS GERMINOMAS AND ENDOCRINOPATHIES

Germinomas are usually located in the basal ganglia and thalamus. They usually occur in young adolescents aged from 10 to 19 years. This may be correlated to gonad development in this age group. Basal ganglia germinomas usually have an insidious onset and slow progression. The most common symptoms are progressive hemiparesis, mental status change, and cognitive declination. In the clinical presentation, symptoms and signs are valuable for localization and contribute to the identification of 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). Serum α-fetoprotein and βhCG are usually elevated, which can be used to confirm the diagnosis and guide the treatment.

Clinical presentations vary depending on tumor location. Pineal/ Suprasellar tumors produce headaches, upward paralysis, and poor coordination. Anterior mediastinal lesions produce cough and wheezing. Sacrococcygeal tumors occur in infants, who may present with constipation and a mass in the buttock or presacral region. Ovarian tumors occur in young girls and present with an abdominal or pelvic mass. Testicular tumors produce painless testicular swelling or torsion of the testis. Optimal therapy includes chemotherapy and, in some cases, radiation.

Choriocarcinoma, Yolk-sac tumor, Embryonic Cell Carcinoma, and Endodermal Sinus Tumors are highly malignant subtypes of GCT. These high-grade tumors are heterogeneous on CT and MRI, and except for the occurrence of hemorrhage in Choriocarcinoma, there is no imaging peculiarity that could help in distinguishing them from other tumors. For this purpose, laboratory examinations of tumor markers are useful: Choriocarcinoma releases human chorionic gonadotropin, Yolk sac tumor α-fetoprotein, and Embryonic Cell Carcinoma both human chorionic gonadotropin and α-fetoprotein. [1]

When GCT is suspected, contrast material is particularly useful in detecting CSF spread in the brain and spine, a common and early finding. The differential diagnosis should include Glioma, Primary Central Nervous System (CNS) lymphoma, and primitive neuroectodermal tumors [4].

Unlike typical germinomas in pineal or suprasellar regions, thalamic and basal ganglionic germinomas show a higher tendency to cystic formation, hemorrhage, calcification, and progressive infiltration into the internal capsule, which may in turn cause Cerebral hemi atrophy. Cystic changes and hemorrhage are attributed to the more rapid enlargement of the germinomas in the basal ganglia and thalamus compared to those in the pineal body and suprasellar region [5].

SITES AFFECTED BY GERMINOMAS.

Germ cell tumors can be found in various parts of the body, but Germinomas occur within the brain, typically in deep midline locations like the pineal gland (45%) or suprasellar region (30%) [4]. 5% to 10% of patients have tumors arising in both the suprasellar and pineal locations, and the histology is most frequently a germinoma [4]. 15% of the germinomas occur in the thalamus and the basal ganglia and are usually unilateral. Most germ cell tumors originate outside the thalami and infiltrate the thalami from the posterior or anterior walls of the third ventricle. The most common presenting symptom is hemiparesis, caused by tumor invasion of the internal capsule, followed by cognitive deterioration. A high prevalence of intracranial germinoma in the far east is well documented, but the reason is unknown. Histologically, germinomas range from benign processes to highly malignant neoplasms with a tendency to metastasize throughout the cerebrospinal fluid spaces [5].

CLASSIFICATION OF CNS GERMINOMAS

CNS GCTs are broadly classified as germinomatous and non-germinomatous germ cell tumors (NGGCTs) on the basis of clinicopathological and laboratory features, including tumor markers. An alternative therapeutic classification proposed by the Japanese Pediatric Brain Tumor Study Group bases stratification on the prognostic grouping of the histologic variants, as follows [4]:

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

PATHOPHYSIOLOGY AND CLINICAL FINDINGS

EPIDEMIOLOGY

According to the CBTRUS report, the overall incidence of malignant CNS GCTs in the United States from 2010 to 2014 was 0.07 per 100,000 population. The CNS GCT incidence rate was 60% higher in Asian/Pacific Islanders than in whites and non-Hispanics, and was lowest in African Americans (0.04 per 100,000). [6]

Primary CNS GCTs are more common in Japan and other countries in Asia than in North America. In particular, CNS GCTs account for relatively high proportions of pediatric brain tumors in East Asia—7.8% in Japan, 14.0% in Taiwan, 7.9% in China, and 9.5% in Korea—whereas their frequency in North America and Europe is 4%. [6, 7] However, a study analyzing 4 tumor registries from Japan and the United States found a similar incidence of primary CNS GCTs in the two countries.

An overall male predominance is noted in CNS GCTs. Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program on CNS GCTs in the United States showed that the incidence of CNS germ cell tumors in males, all ages combined, was 3.7 times that seen in females. Location of CNS GCTs also varies by sex. In males, 70% of tumors occur in the pineal area; In females, 75% of CNS GCTs occur in the suprasellar areas. Likewise, CNS GCT registries in Japan and the United States found an overall male-to-female incidence-rate ratio (IRR) of 3.1:1, but with marked differences with GCTs in different sites: for malignant tumors of the pineal region, the male-to-female IRR was as high as 16.0:1, compared with 1.9:1 for tumors in a non-pineal region of the CNS. [7]

CNS GCTs are seen almost exclusively in individuals between birth and 34 years of age, with 71% of cases diagnosed before 20 years of age. The peak incidence is from 10-19 years of age with the highest incidence (0.28 per 100,000) at ages 10-14 years. The pediatric age distribution of CNS GCTs is 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

ETIOLOGY

The exact cause of CNS GCTs is unknown. GCTs appear to arise from primordial germ cells that migrate to the germinal ridges in the developing embryo. This process appears to be under the control of complex molecular events. Aberration in any of these molecular pathways may potentially give rise to GCTs.

Important factors in cell migration include the extracellular matrix, which affects cell adherence and migration. Other factors, such as chemotropic factors, may also be involved in cell migration. In vitro studies have shown that tumor growth factor beta 1 may initiate the migration of primordial germ cells. [9]

Some primordial germ cells that have left the yolk sac endoderm migrate cranially towards the diencephalic midline structures rather than laterally to genital ridges. Maturation of the fetal hypothalamus coincides with the migration of primordial germ cells. The fetal hypothalamus may secrete chemotrophic factors that attract primordial germ cells to the diencephalon. [10]

The embryonic cell theory may be an alternative event in which the primordial germ cells migrate into the mesenchyme of the mesentery and stimulate blood vessel formation and may reach intracranial locations via the circulation. Once the primordial germ cells have reached their intracranial location through abnormal pathways, congenital or acquired aberrant molecular events occur in the primordial germ cell itself or in the surrounding microenvironment, leading to the formation of CNS GCTs. [6, 8, 9]

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

PATHOPHYSIOLOGY

The cell of origin of CNS GCTs remains controversial. The germ cell theory proposes that these growths develop from primordial germ cells that have actually moved aberrantly throughout beginning development and also 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 special epigenetic feature making them distinct from all various other GCT subtypes. The patterns of methylation strongly resemble that of primordial germ cells (PGC) at the migration stage, perhaps suggesting the cell of origin for these tumors. [13]

On the other hand, the embryonic cell theory suggests that GCTs arise from an immigrational pluripotent embryonic cell. It has actually additionally been proposed that pure germinomas occur from germ cells whereas mixed NGGCTs are a result of misfolding and misplacement of germ cells right into the side mesoderm, creating these cells to come to be entrapped in different locations of the brain. [14, 15] Existing evidence recommends that GCTs develop from germinal aspects at numerous stages of growth.

Researches of malignant testicular tumor have revealed that the most usual chromosomal irregularity is an isochromosome of the short arm of chromosome 12 (I [12p]. [15, 16] Chromosomal contrast of CNS GCTs with gonadal growths using genomic hybridization evaluation has actually discovered the two to be basically identical. In adult-onset extragonadal germinomas, one of the most usual irregularities is duplication of the short arm of chromosome 12.

In children, cytogenetic abnormalities consist of loss of 1p and 6q, changes in sex chromosomes, and also irregularities in 12p. A research in children exposed that a subset of individuals with pineal tumors demonstrated a gain of chromosomal product at 12p.

The most common chromosomal abnormalities consist of gains of 1p, 8p, as well as 12q and losses of 13q as well as 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 intracranial pure germinomas, recommending that this genetics plays an important 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 actually exposed distinctive messenger RNA and microRNA profiles, which may associate with histological distinction, and scientific result. In future, these might act as unique therapeutic targets. [18]

CLINICAL PRESENTATIONS

Pineal region tumors

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

- Paralysis of upward gaze
- Loss of light perception and accommodation
- Nystagmus

- Failure of convergence

Features of increased intracranial pressure may supervene. These include headache, nausea and vomiting, and papilledema. Somnolence, ataxia, seizures, and behavioral abnormalities may develop.

Precocious puberty may develop in a pre-pubertal child.

Diabetes insipidus and anterior hypopituitarism are rare occurrences and may indicate involvement of the floor of the fourth ventricle and suprasellar area. [19]

Suprasellar region tumors

Patients with suprasellar GCTs usually present with endocrine deficits. These include the following:

- Anterior hypopituitarism and Diabetes insipidus (DI)
- Thyroid and/or cortisol deficiency
- 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 may include diplopia, blurred vision, and diminished vision. Enuresis and psychiatric abnormalities may develop. In general, patients with symptoms of increased intracranial pressure and visual changes tend to present earlier in the disease course than patients with endocrine dysfunction.

Rare presentations of CNS GCTs include the following:

- Multiple lesions - GCTs in the pineal, sellar region, corpus callosum, and ventricles was 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, painless visual loss [21, 22, 23] therefore, biopsy for definitive diagnosis

may be required in patients with imaging studies suggestive of optic gliomas who have visual loss with hypothalamic-pituitary-adrenal dysfunction.

- 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]

DIAGNOSIS AND INVESTIGATIONS

Physical Examination

The clinical evaluation should include the following:

- General physical examination
- Check of growth parameters
- Careful neurological evaluation, with assessment for neurocutaneous stigmata
- Assessment of primary and secondary sexual characteristics
- Ophthalmologic exam

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

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

CSF cytology is made use of to find malignant cells. Measurement of serum as well as CSF degrees of tumor markers might aid in the diagnosis and treatment strategy. [15, 25, 27] Examination of the disease outside the CNS is normally not necessary.

As a result of the diversification of germinomas and also 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.

Imaging Studies

Computed tomography of the brain

Germinomas show a homogeneous pattern and are hyperdense compared to brain cells; with pineal gland tumors, calcification of the gland might be seen. Mature teratomas have blended thickness, with large cysts as well as areas of calcification with distinctive growth margins.

Magnetic resonance imaging

MRI of the brain and also spine with and also without gadolinium is the gold basic imaging research study. Leptomeningeal transition is present at medical diagnosis in 10-15% of clients. Germinomas are homogeneous and show isointensity or slightly low signal intensity on T1-weighted images, and Iso intensity or high intensity on T2-weighted images. [28]

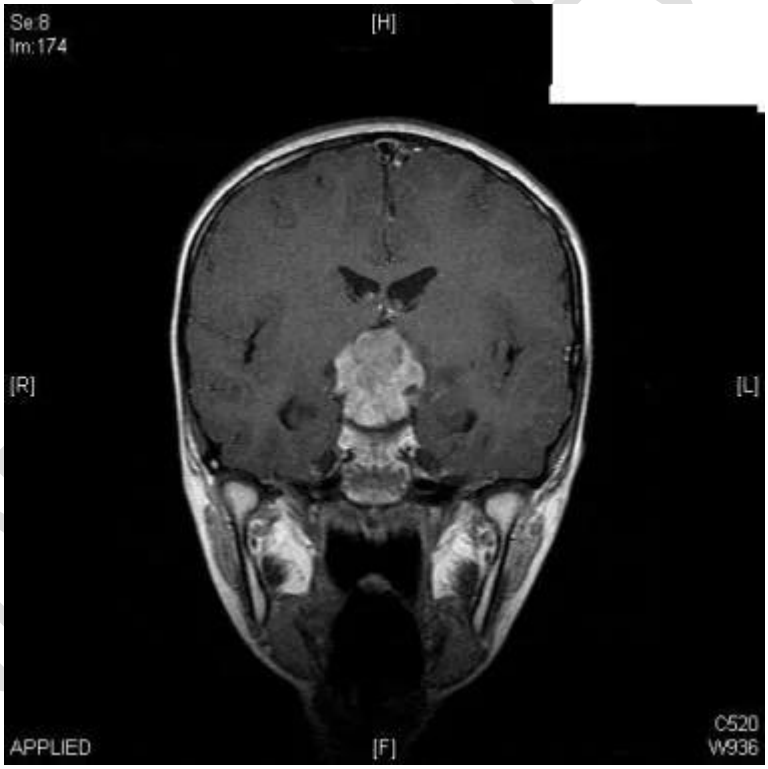

Fig 1: MRI of the brain - T1 weighted-image- coronal view- showing a heterogeneously enhancing, multicystic mass in the suprasellar region.
Source: Link

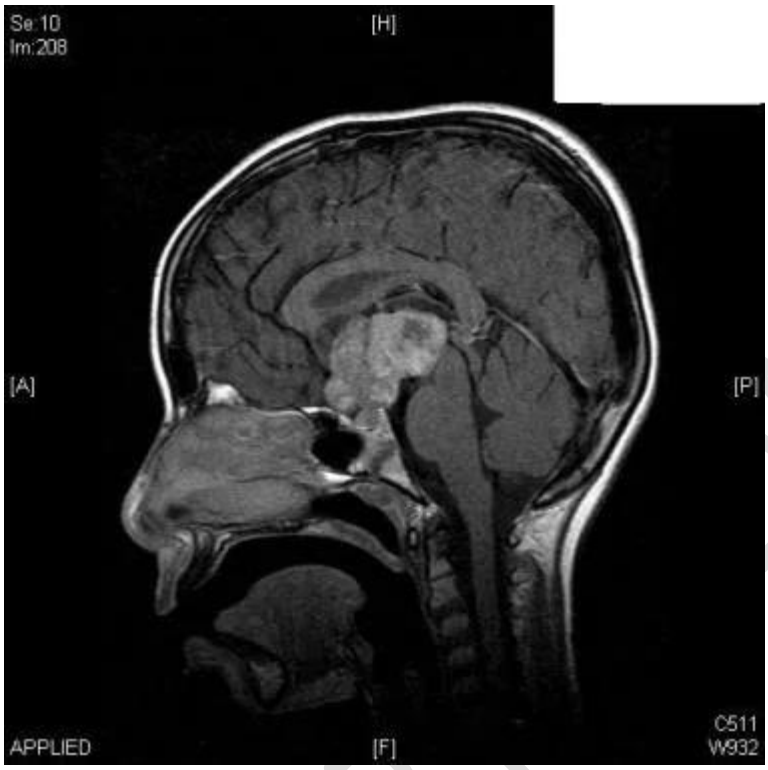

Fig 2: MRI of the brain - T1-weighted image - post-gadolinium sagittal view- A suprasellar lesion that severely compresses the optic chiasm encases the posterior aspect of the optic nerves bilaterally and causes superior displacement of the third ventricle, with significant compression of the brain stem.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

Positron emission tomography

Several studies have investigated the utility of positron emission tomography (PET) scans. In a retrospective review of 10 patients, it was reported that 18F-fluorodeoxyglucose PET(FDG-PET) was able to detect the presence of germinomas while 11C-methionine PET (MET-PET) can help define tumor contour to plan for biopsy or surgery. [29, 30] Limited information is available on the value of 18F-fluroethylcholine PET/MRI for the diagnosis of intracranial GCTs and follow-up by assessing for residual tumor.

Biopsy

Currently, the recommendation for all patients with pineal and suprasellar tumors is to undergo surgical biopsy for histological confirmation, which is accomplished by means of endoscopic/stereotactic biopsy or open biopsy. Advances in endoscopic techniques have led to less morbidity and mortality with this procedure. Suprasellar tumors are generally more accessible to surgical biopsy than are pineal tumors.

Adequate specimen size is important because in non-germinomatous GCT, a specimen that is too small may miss a tumor component and thus may not be representative of the actual tumor type.

Only patients with elevated serum or CSF levels of AFP or β-hCG >50-100 IU/ml [27] do not warrant surgery for the sole purpose of tissue diagnosis. Diagnosis without tissue verification should be considered in such patients because high postoperative mortality has been reported after resection of secreting tumors. [30]

MANAGEMENT OF GERMINOMAS

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

Over the last 35 years, CNS germinomas have become one of the paediatric brain tumours with the best outcomes with a greater than 85% overall survival over 5 years. This is in part due to the fact that germinomas are very responsive to chemotherapy and radiation. Some of the major challenges going forward will be to find ways to minimize the adverse effects of our treatments particularly with regard to radiation and to improve the quality of life of patients who develop neurologic, neurocognitive and/or endocrine deficiencies. [4, 31]

The most common treatment modality in published cases is Craniospinal irradiation. In the cases reviewed, limited Radiation treatments (whole ventricle or focal) combined with Chemotherapy regimens yield comparable outcomes where there is no spinal dissemination. Outcomes do not appear to be altered by biopsy in cases with negative tumour markers and characteristic imaging appearances.
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.

RADIATION THERAPY

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

Full-dose Craniospinal Radiation (CSI) was traditionally employed for patients with pure germinomas. Side effects of CSI may be significant. Studies comparing CSI with reduced-volume radiation, whether whole-brain or whole-ventricular, have shown no significant difference in the pattern of relapse in germinomas. Therefore, CSI is no longer used for localized germinomas.

No evidence of dissemination may obviate the need for craniospinal irradiation, but good quality long-term follow-up data are required to demonstrate the benefits of combined focal radiotherapy and chemotherapy regimes

Currently, effective therapy uses whole-ventricular irradiation and chemotherapy to reduce the radiation therapy dose. Because radiation exposure of the temporal ventricular horns and hippocampi may lead to long-term poor cognitive function, reviewed the outcome in paediatric

cases in which the temporal ventricular horns were excluded from ventricular clinical target volumes. Exclusion resulted in significant dose sparing to the hippocampi and temporal lobes, while clinical outcomes remained excellent, with no deaths and no temporal ventricular horn failures. However, long-term neuropsychological studies are required to confirm the benefits. [31, 32]

Radiation therapy to include the whole ventricles appears to be essential in controlling disease. Higher rates of recurrence have been documented in patients who received radiation therapy to the localized tumour alone.

CHEMOTHERAPY

In patients with germinomas, chemotherapy has been added to the treatment regimen to permit the use of a lower radiation dose, thereby reducing the long-term morbidity associated with radiation therapy while maintaining the excellent survival rates. Germinomas are chemo sensitive, especially to platinum-based agents. The current recommendation is to proceed with neoadjuvant therapy prior to lower-dose and lower-volume radiation therapy.

Patients with NGGCTs have an inferior outcome compared with patients with germinomas. Combined therapy with neoadjuvant and adjuvant chemotherapy with radiation therapy is intended to improve outcome. The increase in survival seen with combination therapy has made chemotherapy an integral part of treatment for NGGCTs. [33, 34]

SURGERY

Currently the recommended practice is to acquire a tissue biopsy sample, with the exception of patients who have a characteristic elevation in tumour markers and in whom surgical intervention may lead to significant sequelae.

Surgical treatment of CNS GCTs varies according to the tumour type. Germinomas carry a relatively excellent prognosis and management has therefore focused on reducing morbidity. Partial and gross total resection of germinomas has no proven benefit and may lead to neurological or endocrinological deterioration. Therefore, most neurosurgeons limit surgical intervention to biopsy and instead treat these patients with radiation and chemotherapy.

Conflicting results may occur, in particular with small surgical samples that may not be representative, such as histological diagnosis of pure germinoma and raised alpha fetoprotein levels, in which case the patient should be treated more aggressively than those with pure germinoma with normal CSF/serum marker levels. [35]

In patients who have had an incomplete response to initial chemotherapy, second-look surgery may be performed to remove the residual tissue and permit its histological verification. The remaining tissue may contain malignant elements; however, it may consist of fibrosis, necrosis, or a mature teratoma—the so-called growing teratoma syndrome. The growing teratoma

syndrome is characterized by enlarging tumour mass during or after chemotherapy in the presence of normal or declining tumour markers. Surgical resection of the tumour is considered curative

COMBINATION IMMUNOTHERAPY

Combination immunotherapy was more likely to result in a single or multiple endocrinopathy compared to anti-PD-1 monotherapy (27% vs 9% and 7% vs 0% respectively, $P < 0.01$). Endocrinopathies occurred after a median of 8 weeks from treatment commencement (range: 12-225 days), [36, 4] with combination immunotherapy resulting in significantly earlier onset compared to ipilimumab. Combination immunotherapy has a greater risk of development of endocrinopathy compared to anti-PD-1 monotherapy. Regular biochemical profiling of patients, particularly within the first twelve weeks, results in early detection of endocrinopathy to minimise morbidity.

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

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

CONCLUSION

Many patients with unrecognized CNS GCTs may have had a long history of complications such as movement disorders, enuresis, anorexia, and behavioral and psychiatric complaints including obsessive-compulsive disorder, tics, and psychosis. Diagnosis in such cases has been delayed from 7 months to 3 years.

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

Total surgical resection of CNS GCTs has been hampered by the deep-seated location of these tumors. Therefore, craniospinal irradiation has been the standard adjuvant therapy. Advances in diagnostic imaging, surgical and anesthetic techniques, and radiation therapy and the addition of chemotherapy have improved the outcome in patients with these tumors.

Trials to determine the best regimen for radiation therapy are ongoing. Currently, patients with localized or multifocal disease may receive 24 Gy to the whole-ventricular system and a 21-Gy boost to all measurable disease.

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