Navigating through the diagnostic labyrinth of rare bifocal intracranial germ cell tumors: a case report

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ABSTRACT

Background: Intracranial germ cell tumors (iGCTs) are a rare and heterogeneous group of neoplasms originating from germ cells within the central nervous system (CNS). These tumors are a subclass of CNS germ cell tumors (GCTs) that are typically observed in 1st to 2nd decades of life. They tend to occur in the midline, either at the pineal region or along the floor of the third ventricle/suprasellar region. Less commonly, both regions can be involved, presenting as bifocal tumors which usually carry a worse prognosis. Such bifocal lesions can be either two independent primary germinomas (GEs) (known as true bifocal GE) or it can be one primary GE with metastases (known as false bifocal GE). Bifocal presentation is mostly seen in GE, but some of the patients may have mixed GCT. Clinical features are mainly due to the mass effect and involvement of sellar and supra-sellar regions.

Case Presentation: A 21-year-old male presented with complaints of erectile dysfunction, lack of libido, headache, polydipsia, polyuria, diplopia, and recent onset blurring of vision over the past 6 months to 1 year. Radiological investigations revealed the presence of true bifocal iGCTs, which were confirmed to be β-human chorionic gonadotropin producing GEs upon histopathological and immunohistochemical analysis. The patient showed complete resolution of the tumor following treatment.

Conclusion: Intracranial GEs are highly radiosensitive tumors often characterized by insidious symptoms, leading to a significant delay in diagnosis, with patients often seeking medical assistance only when their daily activities are severely impaired. However, this delay could be mitigated by obtaining a thorough patient history and maintaining a high index of suspicion for intracranial GEs, particularly in the appropriate age groups. Our case report emphasizes the importance of a multidisciplinary team approach in facilitating timely and informed decision-making for optimal patient management.

Keywords: Germ cell tumor, intracranial GCT, intracranial germinoma, bifocal germinoma, true bifocal germinoma, mixed germ cell tumor, secreting germinoma.

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Background

Intracranial germ cell tumors (iGCTs) represent a rare and heterogeneous group of neoplasms originating from germ cells within the central nervous system (CNS). Despite their rarity, iGCTs pose significant diagnostic and therapeutic challenges due to their diverse histological subtypes, varied clinical presentations, and complex treatment algorithms. iGCT can be divided into two main categories: germinoma (GE) and non-germinomatous GCT (NGGCT). NGGCT is subdivided into four subgroups: teratoma, yolk sac tumor (YST), choriocarcinoma (ChC), and embryonal carcinoma (EC). The difference between GE from NGGCT has more practical inferences than theoretical arguments like GE is highly responsive to radiation therapy and chemotherapy (CX). GE rarely requires surgical intervention but NGGCTs often necessitate a surgical approach. There is another confusing subgroupe of iGCT, i.e., mixed germ cell tumors (GCT), which exhibits characteristics of multiple iGCT subtypes, predominantly categorized under NGGCT due to their diverse components. Typically, these include combinations of GE and TE, though some may contain elements like syncytiotrophoblastic giant cells or ChC which can be differentiated based on cerebrospinal fluid (CSF) study and histopathology (HP). Intracranial GCTs are predominantly diagnosed in East Asian populations, with incidence rates reflecting significant geographical variations: 3.4 per million per year in Korea, 2.7 in Japan, and 0.6 in the USA. Bifocal GEs, accounting for 6%–41% of all intracranial GEs, are an exceedingly rare occurrence and are more prevalent in males [1-3]. The origin of extragonadal GCTs) is not clearly understood, though there are a few hypotheses as in germ cell theory, embryonic cell theory, or misfolding during development. On computed tomography (CT), it presents as a hyperdense lesion compared to the

adjacent brain due to its high cellularity and enhancement. The presence of calcification in the pineal region is a helpful marker of an underlying tumor in the pediatric population as no calcification of the pineal is seen in children below the age of 6.5 years and calcification is seen in only about 10% of children between 11 and 14 years of age. Magnetic resolution imaging (MRI) demonstrates it as a ovoid or lobulated, soft tissue mass, engulfing the calcified pineal gland. Histopathological analysis and immunohistochemistry (IHC) are essential for accurately subtyping these tumors, crucial for determining appropriate treatment strategies.

Here, we report an unusual case of an adolescent male who presented with decreased visual acuity (VA), worsening headache with erectile dysfunction, and loss of libido. Imaging favors the presence of synchronously occurring true bifocal GEs in the pineal and suprasellar regions. The blood report raised the possibility of mixed germ cell tumor (MGCT) with ChC component. However, a biopsy and IHC confirmed the diagnosis of a rare form of iGCT, i.e., bifocal GEs with syncytiotrophoblasts, also known as HCG-secreting GEs. This case highlights the complexities of diagnosing the iGCT and how a multidisciplinary approach guided clinicians in the decision-making process for optimal treatment pathways.

Case Presentation

A 21-year-old male presented to the urology outpatient department in Apollo Multispeciality Hospitals, Kolkata, India with complaints of erectile dysfunction and lack of libido for the last 2-3 months, for which he was taking some over-the-counter ayurvedic medications with no obvious effect. He complained of worsening headaches for the last few months. On further inquiry, he revealed that his headache started almost a year back for which he was taking pain medication prescribed by a local physician. He also complained of diplopia for 6 months with recent onset blurring of vision, having started a month back. His complaints also suggested having polydipsia and polyuria for the last few months. There was no history of fever, loss of consciousness, or any other comorbidities. He was a college student and resident of Manipur, recently got married, and came to this hospital with the main complaint of erectile dysfunction and blurring of vision. On physical examination, his vitals and body mass index were within normal limits. He had slightly underdeveloped testicles and a scrotal sac corresponding to Tanner stage I with sparse, long pubic hair corresponding to Tanner stage II. He was advised of hormonal assay and scrotal USG. He was then referred to a general physician and ophthalmologist for consultation. His scrotal USG revealed mildly small-sized bilateral testis with microlithiasis and satisfactory color signal on Doppler imaging. Further neurological examination showed ataxic gait with hyperactive tendon reflexes. No sensory or motor deficit was observed during the examination. On ophthalmological examination, reduced VA was noted in both eyes (VA 3/10 in the left eye and 2/10 in the right eye). His photo-motor reflexes were slightly reduced in both eyes and spontaneous semi-mydriasis. For further work-up, an MRI Pituitary gland with contrast was advised. His hormone profile showed features of panhypopituitarism (Table). MRI Pituitary gland with contrast (Figures 1 and 2) revealed a well-defined solid lobulated lesion in the pineal region showing marked diffusion restriction and heterogenous enhancement. The pineal gland was not seen separately from the lesion. Few foci of intralesional calcifications were seen. On magnetic resonance spectroscopy the lesion showed choline:creatinine = 2.96, Choline: NAA = 11.8, indicative of neoplastic origin. The lesion was causing a significant mass effect on adjacent structures. Another similar-looking lesion was noted in the suprasellar region involving the infundibulum and stalk of the pituitary gland with a mass effect on optic chiasma. MRI features revealed the concurrent presence of GEs in pineal as well as suprasellar regions. The involvement of the pituitary stalk, infundibulum, and absence of any other metastatic lesion imposed the conclusion to be a “true bifocal GE” rather than metastasis from the primary pineal region tumor. MRI spine (Figure 3), contrast-enhanced CT whole abdomen and high resolution computed tomography chest revealed no evidence of metastasis. He was suggested to get admitted for further workup and treatment planning. But he refused due to some personal inconvenience.

After 1 month, he presented at the emergency department with a complaint of drowsiness. NCCT brain was done and revealed no significant interval change of the space occupying lesions (SOLs) with mildly increased hydrocephalus. Ventriculo-peritoneal shunting was done

Table 1. *Hormone profile of the patient.*

HORMONE	RESULT	BIOLOGICAL VALUE	UNITS
Prolactin	34.5	Males: 4-15.2	ng/ml
Thyroid stimulating hormone	3.02	Adults: 0.38-5.3	ug/ml
Leutinizing hormone	<0.2	1.2-8.6	mIU/ml
Follicle-stimulating hormone	0.53	Males:1.27-19.2	MIU/ml
Cortisol (serum)	1.4	6.7-22.6	mcg/dl
Adrenocortico-trophic hormone (plasma)	9.9	7.2-63.3	pg/ml

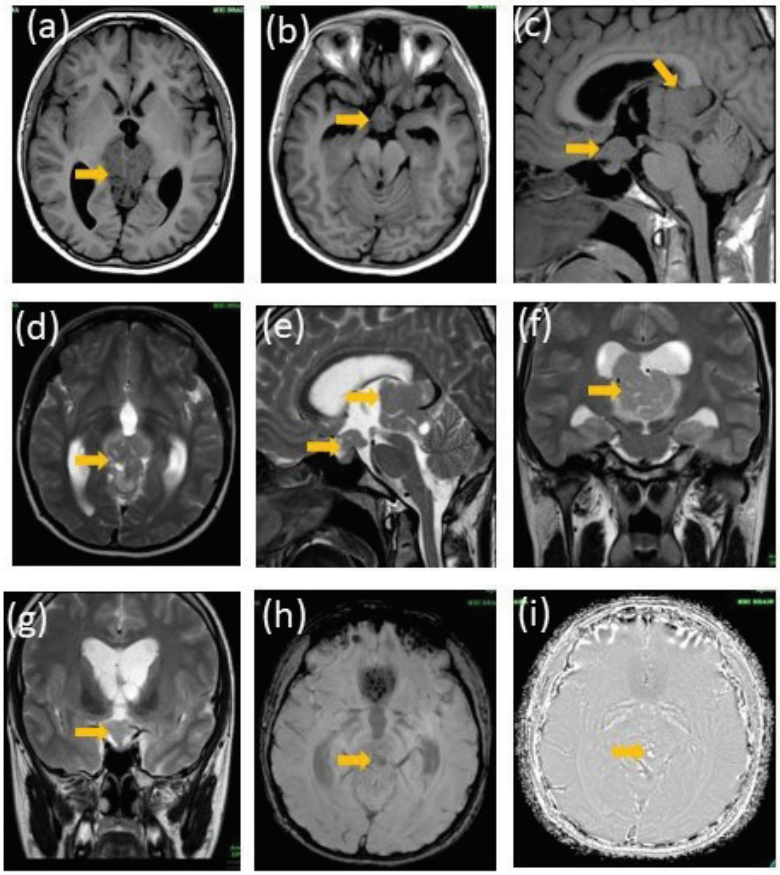

Figure 1. *MRI brain T1 weighted axial (a, b) and sagittal (c); T2 weighted axial (d);, sagittal (e) and coronal (f, g); axial SWI and SWI PHASE sequences (h, i). A suprasellar T1 hypointense and T2 iso-hyperintense SOL in axial (b), sagittal (c) and coronal (g) sections (yellow arrows) involving infundibulum and stalk of pituitary, causing mass effect on optic chiasma. A lobulated T1 hypointense and T2 iso-hyperientense pineal regian SOL involving tectal plates and compressing mid-brain (c, e) with few cystic non-enhancing areas within (d). Effacement of quadrigeminal cistern posteriorly, bilateral ambient cisterns laterally (c,d,e), partial effacement of aqueduct of sylvius and upstream dilatation of lateral and 3rd ventricles (a-g). Blooming on SWI sequences (h) with phase reversal (i), represents calcifications on axial section.*

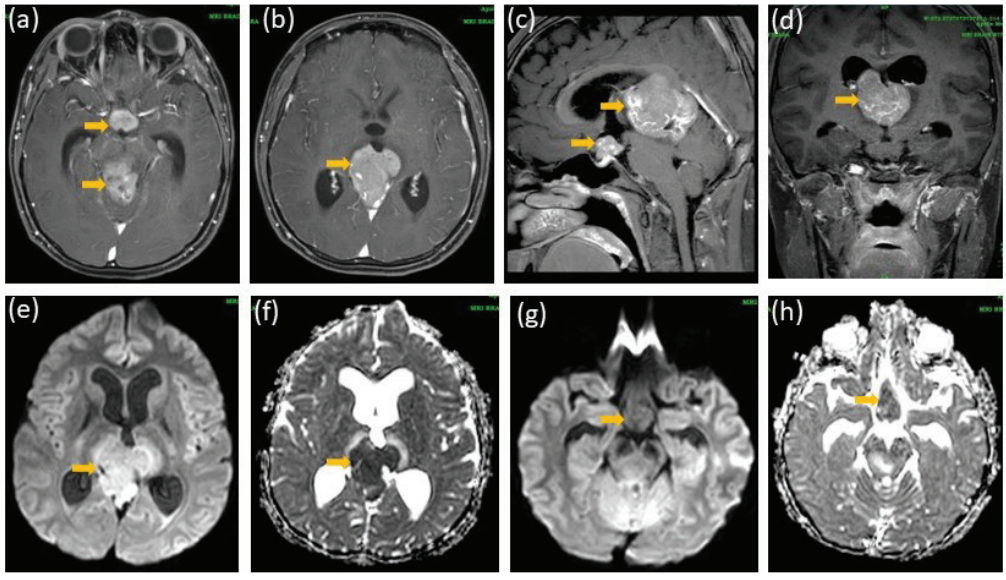

Figure 2. *Contrast enhanced MRI brain axial (a, b), Sagittal (c) and Coronal(d) images reveal heterogeneous enhancement of suprasellar SOL (a,c) and pineal region SOL (a-d). Diffusion weighted sequences (e,g) shows diffusion restriction with corresponding hypointensity on ADC sequences(f, h).*

to relieve the obstructive hydrocephalus. To determine further course of management, a navigation-guided biopsy was done to confirm the diagnosis. HP and IHC reports were awaited. Upon further workup, tumor markers β-human chorionic gonadotropin (bHCG) came positive (10.33 mIU/ml) and Alpha-fetoprotein (AFP) was negative (5 ng/ml), which suggested HCG HCG-producing iGCT. Clinicians infer this as a suspicion of a more aggressive GCT, i.e., MGCT with ChC component. Later histopathological evaluation showed a predominant GE component with small areas of syncytiotrophoblastic giant cells (Figure 4).

IHC done on paraffin block shows positivity for SALL 4, CD 117, and vimentin while immunostaining for cytokeratin (AE1/AE3), GFAP, Synaptophysin, CD 30 and glypican 3 are negative in large tumor cells. Immunostatin for CD 45, CD3, and CD 20 highlight the surrounding lymphoid, reactive T cell, and reactive B cell populations respectively. Thus, correlating the HP and IHC with radiological findings, a final diagnosis of bifocal intracranial GEs with syncytiotrophoblasts or secreting GEs was made.

A multidisciplinary team of our hospital considers cerebrospinal irradiation (CSI) as a treatment modality. He showed complete resolution of the tumors with a significant reduction of hydrocephalus (Figure 5).

Discussion

Intracranial GEs, also known as dysgerminomas or extra-gonadal seminomas are a subclass of central

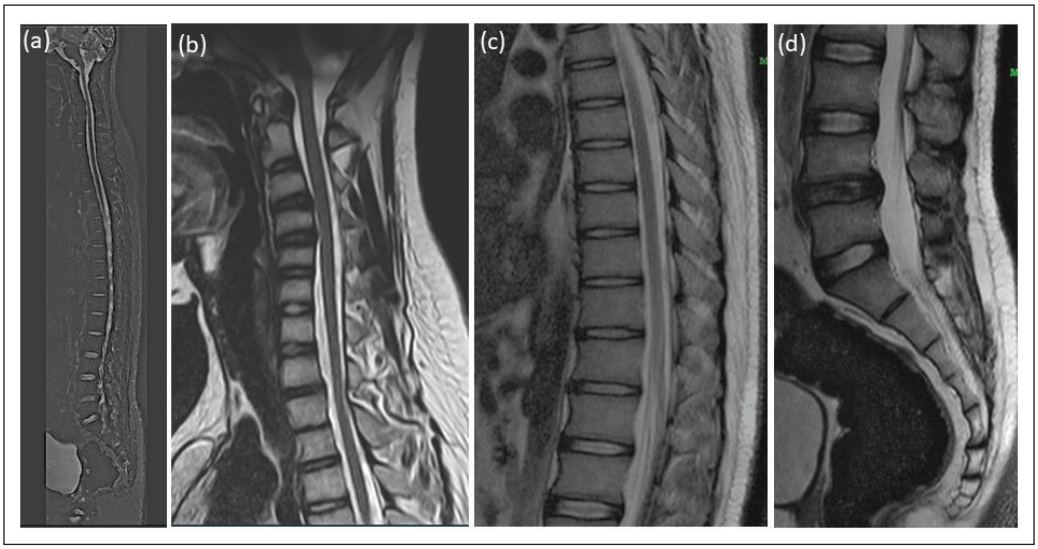

Figure 3. *Pre-treatment MRI whole spine screening (a-d). Sagittal sections whole spine(a), cervical spine(b), dorsal spine(c) and Lumbo-sacral spine(d) showing no evidence of signal intensity change to suggest metastasis. Mild disc bulges at C3-C4, C4-C5(a,b) and L3-L4 vertebral levels (d).*

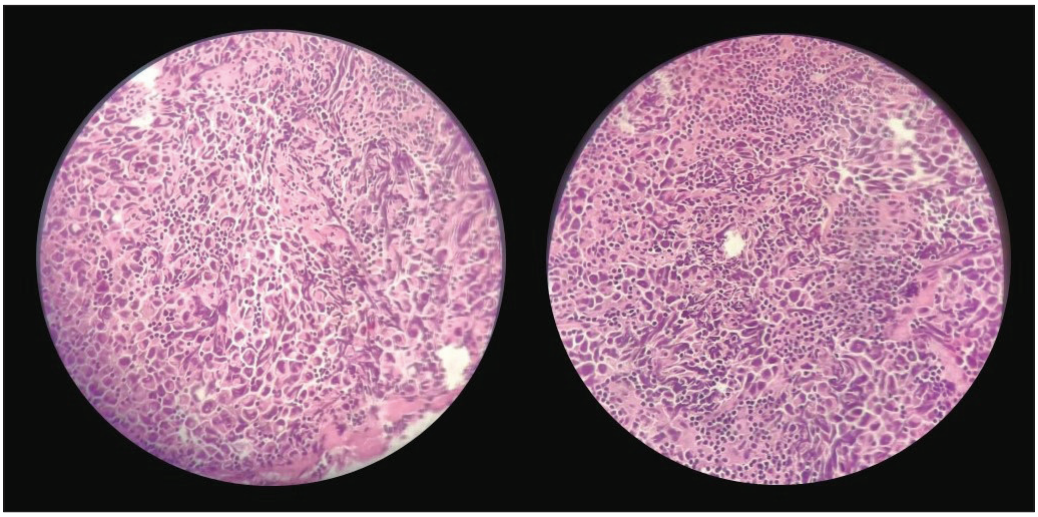

Figure 4. *HP slides showing predominantly monomorphic large germ cells with enlarged centrally located vesicular nucleus, prominent nucleolus and moderate clear cytoplasm arranged in sheets, divided into lobules by fibrous septa with lymphocytic infiltrates. Features suggesting GCT with predominant GE component and small areas showing syncytiotrophoblastic giant cells.*

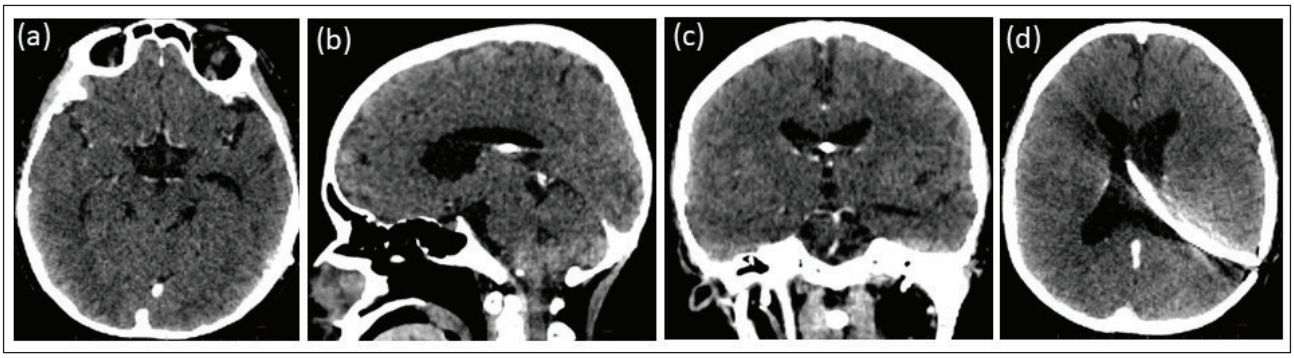

Figure 5. *Post-treatment CECT brain axial sections (a, d), Sagittal (b) and Coronal (c) reformats showing complete resolution of suprasellar SOL (a, b) and pineal region SOL (b, c). CECT brain axial section reveals partial resolution of hydrocephalus with VP shunt in situ (d).*

nervous system GCTs that are rare and typically observed in the age group of 10-20 years. They tend to occur in the midline, either at the pineal region or along the floor of the third ventricle/suprasellar region. Less commonly, both regions can be involved, presenting as bifocal tumors which usually carry a worse prognosis [4,5]. Such bifocal lesions can be either two independent primary GEs (known as true bifocal GE) or it can be one primary GE with metastases (known as false bifocal GE) [5]. Bifocal presentation is most commonly seen in GE, but some of the patients may have mixed GCT [3]. The clinical presentation varies according to the location and size of the tumor. Suprasellar region tumor causes features of pan-hypopituitarism, i.e., hypogonadotropic hypogonadism and delayed development of secondary sexual characteristics. Another characteristic finding is the presence of central diabetes insipidus, i.e., polydipsia and polyuria. Mass effect on the optic chiasma can lead to reduced VA. Obstructive hydrocephalus caused due to compression on the cerebral aqueduct is a characteristic feature in the case of pineal region GEs, which results in the typical symptoms of headache, vomiting, diplopia and Parinaud's syndrome due to midbrain involvement. In this case, the patient also had a similar clinical history (Table 1). These symptoms, often insidious, led to a significant delay in diagnosis, with the patient only seeking help when daily activities became severely impaired like in our case. The long latency between symptom onset and overt tumor progression remains a puzzle. However, post-puberty hormonal influences by the tumors make the symptoms more recognizable.

Diagnosis of this type of CNS tumor entity is usually supported through clinical, radiological, and biological markers. According to Tonn J-C, Westphal M, Rutka J, et al., an ovoid or lobulated T1/T2 isointense or slightly hyperintense soft tissue mass, which shows vivid and homogeneous enhancement on contrast studies with evidence of cystic areas, hemorrhage, and central calcification (engulfed pineal gland) are characteristic features of GE. In this case, the similar MRI features are found (Figures 1 and 2). Characterization of the tumors is possible using MRI. Thickened pituitary stalk and extension into the hypothalamus with an origin at the hypophysis suggests "True bifocal tumors" whereas tumor originating at the floor of the third ventricle and extending to the neurohypophysis, without involving the pituitary stalk with high-intensity signal on T1W MRI in the posterior pituitary favors false bifocal lesions or metastasis [6]. In our patient presence of a suprasellar lesion involving the infundibulum, stalk of the pituitary gland, and loss of T1 bright spot in the posterior pituitary along with pineal gland SOL which showed signal intensities like GE confirms the presence of true bifocal GE. Also, the leptomeningeal seeding or drop metastasis should be ruled out before irradiation by imaging the entire spinal cord, because it has a much poorer prognosis and the management approach differs in such cases. In our case, MRI spine showed no such confusion. The positivity of AFP or ßHCG in the blood or CSF confirms the germinal and secreting nature of the tumor. Biochemical markers, particularly serum and CSF levels of AFP and β-HCG assist in differentiating germinomatous from non-germinomatous tumors, as pure GEs are typically non-secretory. Elevated β-HCG levels (10.33 mU/ml), as seen in this patient, might suggest the presence of syncytiotrophoblastic giant cells or indicate a MGCT [7]. An arbitrary value of 5-10 mIU/ml is used to distinguish GE with syncytiotrophoblasts and mixed GCT with ChC components. As in our case, β-HCG was in the borderline range, there was confusion in the definitive diagnosis. However, the HP proved it to be secreting GEs/GEs with the mere presence of syncytiotrophoblasts. Also, SALL 4 is a novel diagnostic marker for primary GCTs with 100% sensitivity for GE, EC, and YSTs of the CNS. An immunohistochemical panel, including SALL4, AFP, and CD30, will help to solve this diagnostic difficulty. GE will show SALL4+/AFP-/CD30-, whereas EC will show SALL4+/AFP +/CD30+ profile, and YST will show SALL4+/AFP+/CD30− profile.[8]

The mainstay of treatment in case of intracranial GE is radiotherapy as it offers a long-term cure rate of almost

85% (range 79%–90%) [9]. Overall, the prognosis is good and offers over 90% of 5-year survival with CX and radiotherapy. In false bifocal GEs and true bifocal GEs with metastases, craniospinal irradiation is recommended for include in management, whereas limited radiotherapy can be considered in true bifocal GEs with no metastases [6]. Usually, a worse prognosis is noticed in bifocal lesions than in single lesions, so it is beneficial to treat them as a disseminated disease due to failure rates of localized radiotherapy fields. Several studies recommended CSI or whole ventricle irradiation with CX for adult patients with bifocal intracranial GEs to prevent spinal recurrences [4,9,10]. In our case, the multidisciplinary team of our hospital decided to give CSI.

Conclusion

To conclude, biopsy confirmation is not always necessary to diagnose a case of iGCTs. Proper imaging and CSF study are enough to clinch the diagnosis of this rare entity. However, it becomes essential when radiological findings are inconclusive or when differentiating between various types of GCTs is required for treatment planning. As in our case the histopathological data along with radiological diagnosis and hormonal work finally helped the clinicians to decide the proper modalities of treatment.

What is new?

Intracranial GEs are rare kinds of highly radiosensitive tumors often characterized by insidious symptoms, leading to a significant delay in diagnosis. This case report emphasizes the importance of proper imaging and CSF study along with multidisciplinary team approach in facilitating timely and informed decision-making for optimal patient management.

List of Abbreviations

BHCG	Beta human chorionic gonadotropin
ChC	Choriocarcinoma
CSF	Cerebrospinal fluid
CSI	Cerebrospinal irradiation
EC	Embryonal cell carcinoma
GCT	Germ cell tumor
GE	Germinoma
IGCT	Intracranial germ cell tumor
MGCT	Mixed Germ cell tumor
MRI	Magnetic Resolution Imaging
NGGCT	Non germinomatous germ cell tumor
VA	Visual Acuity
YST	Yolk Sac Tumor

Conflict of interests

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent of publication

Written informed consent was obtained from the patient.

Ethical approval

The need for ethics approval was waived by the institution ethics committee. Name of the ethics committee -Institutional Ethics Committee, Apollo Multispeciality Hospitals, Kolkata, Kolkata-700054.

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Summary of case

1	Patient (Gender/Age)	21 years/ Male
2	Final diagnosis	Bifocal iGCTs
3	Symptoms	Headache, vomiting, diplopia and Parinaud's syndrome, pan-hypopituitarism i.e. hypogonadotropic hypogonadism and delayed development of secondary sexual characteristics, polydipsia and polyuria.
4	Medications	CX and radiotherapy
5	Clinical procedure	Hormonal assessment. MRI and CT imaging.
6	Specialty	Neuro-onco-radiology