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Case Report

Metastatic primary bifocal germinoma of the brain

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Abstract

Intracranial germ cell tumors are relatively rare. They can affect the pineal region of the brain or the suprasellar area, or both simultaneously, and can cause various complications as well as endocrinological disorders. These tumors are characterized by their aggressive behavior and the tendency to metastasize.

Intracranial germ cell tumors require an interdisciplinary approach in order to determine the most appropriate management. Radiotherapy and chemotherapy form the backbone of treatment strategies. Surgical methods are not the standard of care for this type of pathology, but they can provide histological confirmation in cases where tumor markers are not significant and can also be considered when seeking immediate symptomatic control.

This study presents a juvenile case of a bifocal primary brain germinoma in which a liver metastasis was found after initial brain surgery and radiation therapy. The complex treatment continued with liver metastasectomy and chemotherapy, with the result of a complete therapeutic response and no recurrence after more than seven years of follow-up.

Keywords

liver metastasis, pineal region, primary germinoma, suprasellar region, ventriculo-peritoneal shunt

Introduction

Germ cell tumors (GCT) arise from the gonadal tissue and most commonly affect the testicles in men or, significantly rarer, the ovaries in women. Non-gonadal origin is uncommon and usually affects structures of the midline: mediastinum, retroperitoneal space, and pineal and suprasellar regions of the brain.[1,6] Among non-gonadal GCTs, the most frequent are the cases with anterior mediastinal location.[1]

Tumors in the pineal region as a whole account for about 10% of all intracranial tumors. They are more common in children, and more than 50% of them are GCTs.[14] Primary intracranial germ cell tumors (ICGCTs) account for about 3%–4% of all pediatric brain tumors, while in the adult population their incidence reaches 0.3%–0.6%.[3,4]

ICGCTs are characterized by aggressive behavior because while growing, they have the potential to occlude the cerebrospinal fluid (CSF) channels and destroy neighboring nerve structures.[3] Another feature of these tumors is their tendency to metastasize. Metastases outside the CNS are rarely described and are usually seen after ventriculoperitoneal shunting.[14]

Case presentation

The subject of the present article is a clinical case of an 18-year-old male patient with a primary ICGCT. The patient had no additional comorbidity at the time of diagnosis. The initial symptoms included extreme thirst, increased diuresis, and weight loss, for which the general practitioner referred

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the patient to an endocrinologist. Diabetes insipidus was diagnosed, and treatment with desmopressin acetate 0.1 mg TID was initiated. A CT of the head was performed but did not reveal any space-occupying processes in the brain.

The diuresis gradually returned to normal, but other symptoms, such as staggering while walking, diplopia, and continuous weight loss, appeared over several months. Almost a year after the initial complaints, the patient was referred to a neurologist due to serious gait impairment and inability to walk without assistance. Vertigo, weakness in the lower extremities, and progressive diplopia were reported. The neurological examination revealed the following: no apparent signs of meningeal irritation; left eyelid ptosis; lower extremity paraparesis with normotony; normal reflexes for the upper extremities, but brisk reflexes for the lower extremities with evidence of spread to the neighboring roots; hypoactive abdomen wall reflexes; Babinski reflex evident on right leg; dysmetria; Romberg—unstable both with open and closed eyes; normal sensory activity; partial urine retention. An examination by a neuro-ophthalmologist revealed congestive eye papilla. Laboratory results were within reference ranges.

An MRI of the head ***(Figs 1, 2)*** *was performed, which revealed the presence of an epithalamo-mesencephalic (pineal) and a suprasellar tumor and additional obstructive hydrocephalus. Tumor markers β-hCG and α-fetoprotein (AFP) were within reference ranges, making them insignificant for differential diagnosis.*

The patient was admitted to the neurosurgery clinic. Upon admission, his general condition was slightly impaired, with a Glasgow Coma Scale score of 15 points. The patient had horizontal nystagmus, lower spastic paraparesis, severe cerebellar ataxia, and abnormal reflexes (Babinski positive in the right leg).

In the neurosurgery department a two-stage procedure was conducted. At the first stage, a VP shunt was placed due to the excessive obstructive hydrocephalus. The shunt connected the right lateral ventricle with the peritoneal cavity via a valve system. Then at the second stage one month later, a complete resection of the epithalamo-mesencephalic tumor

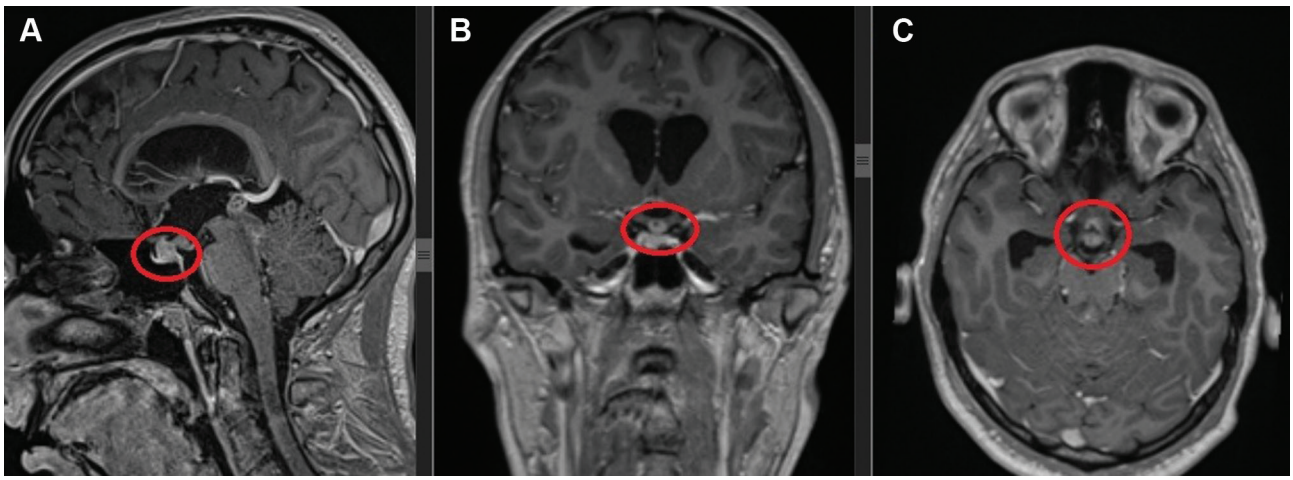

Figure 1. Bifocal ICGCT: MRI images of the tumor (shown in red circle) in the suprasellar region – sagittal (**A**), frontal (**B**), and axial (**C**) views.

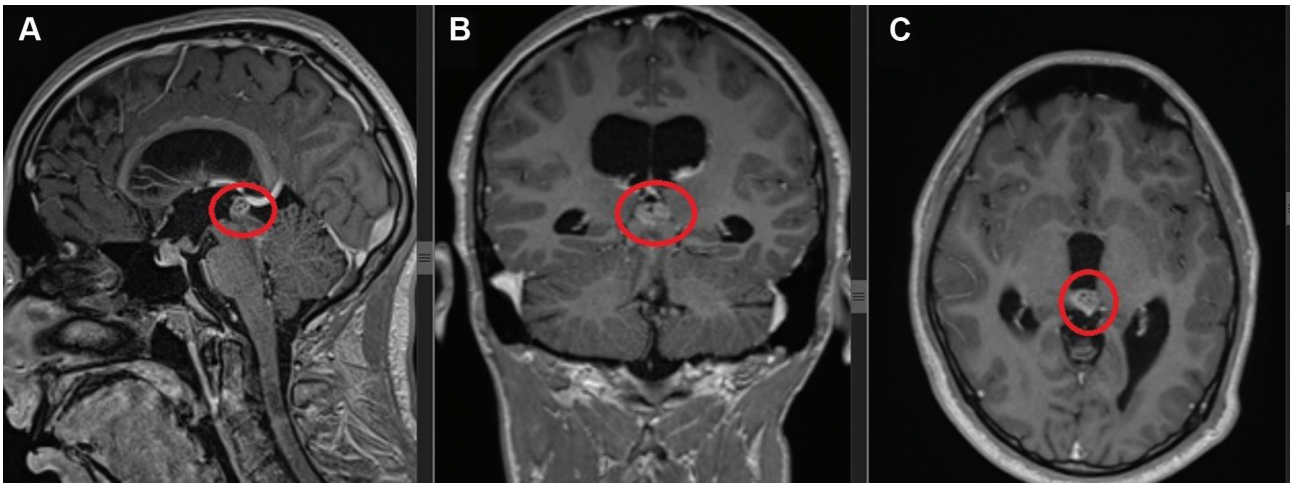

Figure 2. Bifocal ICGCT: MRI images of the tumor (shown in red circle) in the pineal region – sagittal (**A**), frontal (**B**), and axial (**C**) views.

was undertaken. The histological examination ***(Fig. 3)*** *reported a germ cell tumor (germinoma).*

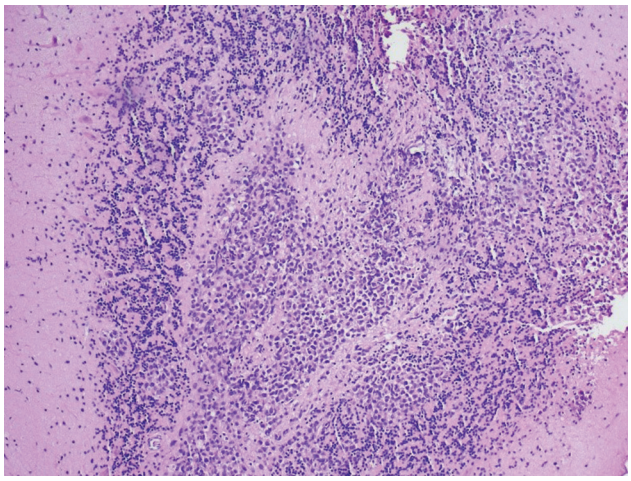

Figure 3. Hematoxylin and eosin (H&E) stained image of the histological specimen: a population of uniform-appearing cells forming sheets with intervening thin fibrous septa and septa and mature lymphocytes.

The postoperative control MRI examination of the neuroaxis did not reveal evidence of residual tumor tissue in the pineal region or additional lesions apart from the suprasellar one. A PET/CT scan was performed one month after the second surgical procedure, and it excluded extracranial dissemination of the process. Postoperative radiotherapy was conducted afterwards: initially the cranio-spinal axis was irradiated in 15 fractions of 2 Grays for a total of 30 Grays, and a boost dose was then administered in 5 fractions of 2 Grays for a total of 10 Grays. A control PET/CT two months after radiotherapy revealed no evidence of recurrence or metastatic lesions. Routine follow-up was accordingly initiated, during which restaging with PET/CT (once a year) and MRI of the brain (every six months) was regularly performed.

On a consecutive PET/CT examination 39 months after surgery, a solitary metastatic lesion was found in the 4th segment of the liver (a subcapsular hypodense metabolically active lesion measuring 35×23 mm and with a standardized uptake value (SUV) of 10.4 ***(Fig. 4)****. Abdominal ultrasound confirmed the presence of a formation about 3 cm in diameter on the diaphragmatic surface of the liver at the border between IVA and IVB segments. Tumor markers β-hCG and AFP were again insignificant. The patient was admitted to the surgery department, where a laparoscopic partial liver resection was performed with complete removal of the metastatic lesion. The histological examination confirmed the radiological diagnosis: metastasis from a malignant tumor with germinoma morphology. A control postoperative PET/CT scan three months after the abdominal surgery did not show any metabolically active lesions.*

Five months following the abdominal surgery, two mesenteric secondary affected lymph nodes (measuring 18×15 mm and with SUV of 7.5 and 8.5, respectively) were discovered in the small pelvis at the subsequent follow-up PET/CT scan. At the tumor board meeting a decision was taken to start chemotherapy.

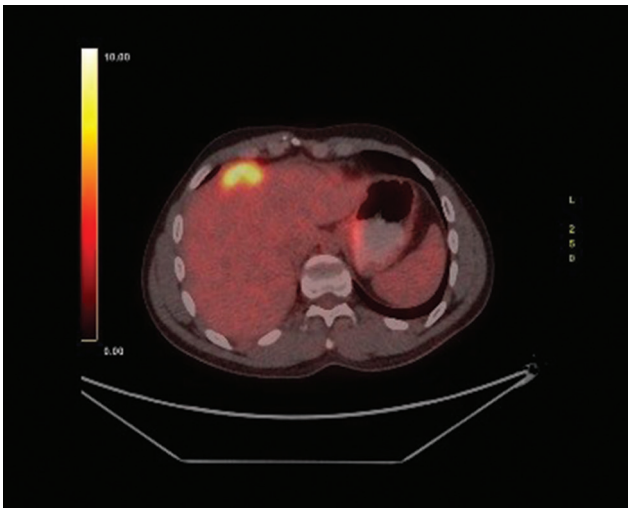

Figure 4. PET/CT image of a solitary hepatic metastasis in the 4th segment of the right hepatic lobe.

Three cycles of BEP chemotherapy were then performed according to local guidelines (bleomycin 30 mg on days 1, 8, and 15; etoposide 100 mg/m^2 on days 1, 2, and 3; and cisplatin 20 mg/m^2 on days 1, 2, and 3 with the additional administration of the colony-stimulating factor pegfilgrastim on day 3 of every 21-day cycle). During the third cycle of chemotherapy, a CT of the head was performed with contrast matter, which revealed no recurrent intracranial lesions. Three months after chemotherapy, a restaging PET/CT scan showed no data of metabolically active lesions, which was consistent with complete metabolic response according to the PERCIST criteria. Then the follow-up procedures were restarted with regular restaging.

The most recent cranial MRI, obtained five years post-initial treatment, demonstrated no evidence of recurrent disease ***(Fig. 5)****. Additionally, whole-body PET/CT scans performed one year after chemotherapy, and subsequently on an annual basis for over seven years following the initial neurosurgical intervention, consistently revealed no recurrent or metastatic lesions. Furthermore, tumor markers, including β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP), remain within normal reference ranges.*

Discussion

Germ cell tumors of the brain are most commonly found in male patients, predominantly in their second decade of life. The male-to-female ratio is 1.8:1 in germinomas and 3:1 in non-germinomatous GCTs.[3] The peak age of diagnosis is between 10 and 12 years of age, with 90% of cases being diagnosed before the age of 20.[3,9]

In more than two-thirds of ICGCT cases, the tumor is localized in the area of the pineal gland and the posteri-

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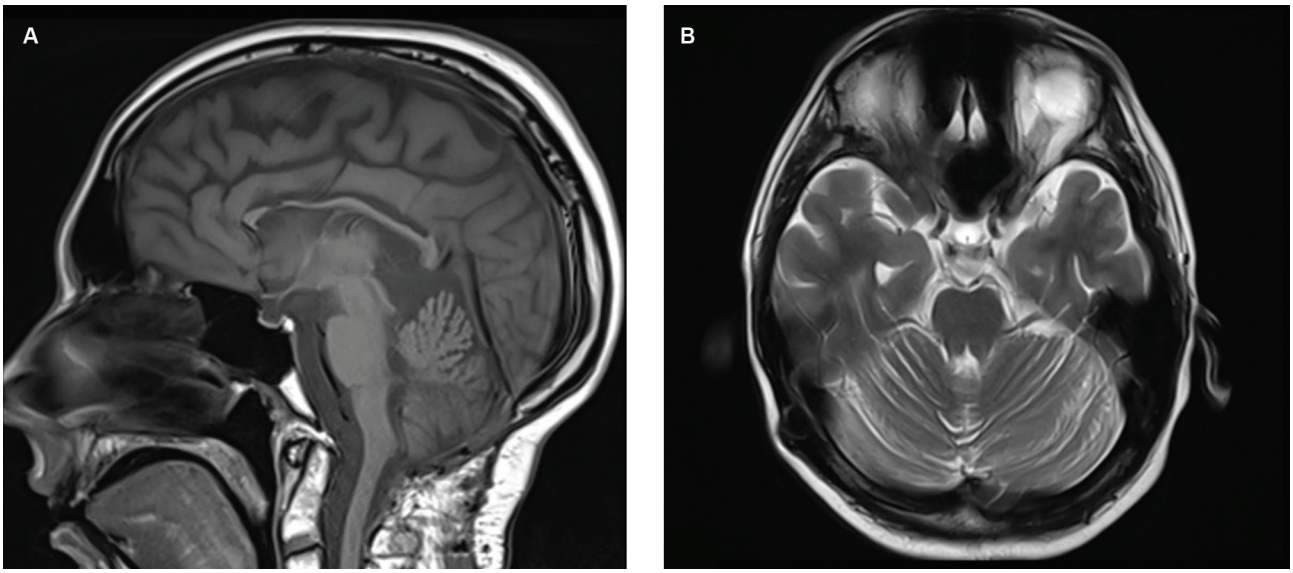

Figure 5. MRI images five years post-initial treatment demonstrating no recurrent disease – sagittal (**A**) and axial (**B**) views.

or part of the walls of the third ventricle. The suprasellar area is the second most commonly affected location. Cases with simultaneous occurrence in both regions are usually described as bifocal (or multifocal), and they account for about 5-10% of ICGCTs.[3]

Histologically, ICGCTs and germ cell tumors with gonadal localization are identical. GCTs of the central nervous system (CNS) can be classified as germinomas and non-germinomatous tumors. Germinomas account for about two-thirds of all cases, while non-germinomatous tumors are rarer and can represent various histological types: yolk sac tumors, choriocarcinoma, embryonal carcinoma, teratoma, or mixed lesions. Germinomas are histologically very similar to seminoma of the testes or dysgerminoma of the ovaries.[14]

The pathogenesis of CNS germinomas is still not fully defined. Currently there are two theories trying to explain their origin. One states that ICGCTs probably arise from pluripotent stem cells during an aberrant embryonic neural tube development. A more recent theory proposes a mechanism involving an abnormal primordial germ cell migration to the fetal genital ridge.[14]

ICGCTs are malignant tumors, as was previously mentioned, and because of their local growth and/or metastasis, they can exhibit especially aggressive behavior. Metastasizing is often achieved through direct invasion of the neighboring brain tissue or by way of the cerebrospinal fluid channels into the subarachnoid and subependymal spaces. Clinical manifestations vary according to the location and size of the tumor lesions.[3]

Often the first sign of the presence of ICGCTs are various endocrinological disorders like growth retardation, precocious puberty, weight loss, hypocorticism, hypothyroidism, and others.[6,14] In some cases central diabetes insipidus can develop with the accompanying characteristic polyuria and polydipsia.[6,14] A suprasellar ICGCT should always be considered in terms of differential diagnosis in young patients with clinical manifestations of diabetes insipidus. With the tumor growth, the optic chiasm may be compressed, causing visual disturbances like diplopia and impaired visual acuity.[6] If the cerebrospinal fluid channels become blocked, an obstructive hydrocephalus can occur, resulting in increased intracranial pressure and corresponding clinical features (headache, vomiting, ataxia, and somnolence). Parinaud's syndrome is often seen in pineal ICGCTs.[14]

Diagnosis is usually established with the help of imaging techniques. MRI of the brain is the method of choice for detecting intracranial tumors. CT of the head with contrast matter can be complementary, especially when intracranial hemorrhage is to be excluded.[14]

Tumor markers have an essential role in establishing the diagnosis and in post-therapeutic monitoring.[6] Oncoproteins, such as β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP), are secreted by ICGCTs into the blood and cerebrospinal fluid.[6,14] Increased values of AFP are linked with non-germinomatous histology, while β-hCG can be secreted both by germinomas and non-germinomatous lesions.[11] Other biomarkers, such as fetal isoenzyme of alkaline phosphatase (PLAP) and octamer-binding transcription factor 4 (OCT4), among others, are recently explored for their diagnostic and prognostic values.[6,14]

Treatment of ICGCTS is complex and can include radiation therapy, chemotherapy, and surgery. It is essential to say that treatment strategies for germinomas and non-germinomatous tumors are different, so the establishment of a correct diagnosis is crucial for the right management of the disease.[3] Currently the obtaining of biopsy material via surgical methods is not compulsory in cases where tumor markers and imaging techniques correspond to the picture of ICGCT.[9,14] In some cases, however, the histological ver-

ification of the process is still necessary, especially when the tumor markers are in reference values.[3]

Surgical techniques can also be applied in cases of obstructive hydrocephalus in order to relieve intracranial pressure via a CSF diversion shunt, but the risk of intraperitoneal seeding should be carefully considered.[14] In selected instances surgical methods can be used to achieve prompt local symptom control. The aim of surgery in these cases is the maximal volume reduction of the tumor formation. However, complete surgical resection is not a standard practice in ICGCT management.[9] Another option is the so-called second-look surgery for residual lesions after initial induction chemotherapy, but its role is still controversial in ICGCT treatment.[14]

Previously, radiation therapy alone of the craniospinal axis was the standard of care for intracranial germinomas, both locally and metastatically.[14] However, higher doses and volumes of radiotherapy are generally needed to achieve effective results. The risk of long-term side effects of radiation therapy has therefore prompted various scientific groups to initiate clinical trials and investigate the effectiveness and safety of combining chemotherapy with lower volumes and dosages of radiation therapy.[9] Currently, consecutive chemoradiotherapy is the standard treatment strategy for most cases of intracranial germinomas, with excellent results in terms of event-free survival (EFS) and overall survival (OS).[14]

In recent years, complex treatment has led to a significant improvement in prognosis, especially in juvenile brain GCTs, where the 5-year survival rate reaches over 90%.[2,5,7,8,10-13]

If relapse occurs, the treatment strategy depends on the initial treatment protocol. Chemotherapy may be administered to patients who only received radiation therapy; patients who first received chemotherapy may be qualified for either radiotherapy or a combination of chemotherapy and radiation.[9] Cisplatin–etoposide or cisplatin–etoposide–ifosfamide are preferred chemotherapy regimens; in cases where cisplatin is contraindicated, carboplatin can be used in its place.[9]

As already discussed, ICGCTs can lead to a variety of concomitant endocrinological disorders.[3,9,14] They are usually irreversible and can be further worsened by chemo- and radiotherapy.[9] To alleviate and control these disorders, some patients must remain on hormone replacement therapy for life.[3]

As a result of surgery, chemo- and radiotherapy adverse events may also appear, which require corresponding management. Patients should be strictly monitored for recurrence.[9] These features of germinomas require systematic clinical, paraclinical, and imaging control for a long period of time after treatment has achieved satisfactory results.[9] MRI is usually performed 2-3 times in the first 3 years, followed by yearly follow-up examinations.[9] It is very important that post-treatment follow-up be performed by a multidisciplinary team, including surgeons, radiation oncologists, medical oncologists, endocrinologists, and radiologists.

Conclusion

Primary germinomas of the CNS are rare tumors that affect primarily young males. Correct diagnosis of this condition is crucial to determine proper treatment strategy. Treatment is complex and may include surgery, radiation therapy, and/or chemotherapy. This method works well for long-term management of intracranial germinomas. After initial therapy, patients should undergo regular follow-up by a multidisciplinary team with clinical examinations and MRI re-evaluations.

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Competing interests

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