



RARE INTRACRANIAL MULTIFOCAL NON-GERMINOMATOUS GERM CELL TUMOR IN AN 18-YEAR-OLD MALE: A CASE REPORT

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SUMMARY – Intracranial germ cell tumors are rare brain tumors that are distinguished based on their histology and selected tumor markers. Non-germinomatous germ cell tumors are a diverse group of such tumors having the poorest prognosis. Most commonly, they are located in the suprasellar and pineal regions. Since the exact treatment protocol has not yet been established, there is currently no standardized modality of management. We present a case of intracranial multifocal non-germinomatous germ cell tumor in an 18-year-old male, along with relevant literature review. We describe initial diagnostic and treatment procedures in a young adult presented with diplopia and ataxic gait. Neuroradiological findings and elevated alpha fetoprotein and beta chain of the human chorionic gonadotropin tumor markers indicated the possible mixed germ cell tumor. Chemotherapy regimen was adjusted accordingly, biopsy was not performed. The patient's clinical condition improved significantly and his alpha fetoprotein values decreased remarkably after initiation of chemotherapy. In conclusion, initial evaluation with neuroimaging, tumor markers, and cytology from cerebrospinal fluid is important as guidance to further treatment and prognosis. In selected cases, biopsy may not be indicated to start adjuvant chemotherapy. We emphasize the importance of specific treatment modality selection based mainly on tumor markers, regardless of the precise histologic classification.

Key words: *Non-germinomatous germ cell tumor, intracranial; Alpha fetoprotein; Beta human chorionic gonadotropin; Biopsy; Chemotherapy*

Introduction

The purpose of this article is to illustrate an unusual case of a patient with multifocal brain non-germinomatous germ cell tumor. This case is of value when

approaching similar examples of this rare condition, especially taking into account that diagnostic and treatment protocols did not include histopathologic diagnosis.

Intracranial germ cell tumors represent 0.5%-3% of pediatric central nervous system tumors in North America and Europe¹. This group of tumors is comprised of rare entities that can be gonadal and extragenital². Extragenital germ cell tumors typically arise in midline locations, such as anterior mediastinum,

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retroperitoneum, and midline brain regions. The most common intracranial locations are suprasellar and pineal regions, and in some cases (6%-13%) their simultaneous involvement is present³. Multifocal intracranial germ cell tumors can be treated as independent primaries, but may also result from the metastatic spread of suprasellar or pineal germ cell tumors and therefore suggest possible poorer prognosis⁴.

Intracranial germ cell tumor peak incidence is during the second decade of life with male preponderance 3:1 to 2:1, especially with tumors in the pineal region^{1,2,5}. Considering their histologic, etiologic and prognostic features, they are divided into germinomatous (GCT) and non-germinomatous germ cell tumors (NGGCT)¹.

Histologically, NGGCTs are divided into several subtypes including endodermal sinus tumor, embryonal carcinoma, and choriocarcinoma. These tumor masses are often mixed, with components of any combination of their subtypes⁶. Intracranial NGGCTs can also contain germinoma or teratoma, which can be additionally confusing and challenging in establishing their classification⁷. A biopsy is required for definitive histologic confirmation².

Serum and cerebrospinal fluid (CSF) beta chain of the human chorionic gonadotropin (β HCG) and alpha fetoprotein (AFP) tumor markers are used to distinguish between GCT and NGGCT. Any tumor with elevated AFP can be assumed to contain ele-

ments of NGGCT or immature teratoma. In cases of dramatic elevations of β HCG (>100 mIU/mL), a diagnosis of NGGCT is highly suggested. Patients with AFP >1000 μ g/L have poor prognosis⁶.

Neuroimaging techniques are useful in detecting the site and morphology of lesion; however, exact GCT type cannot be distinguished based on imaging alone⁸.

The patient clinical presentation varies by tumor location and size. Symptoms often include visual changes and hormonal imbalances (diabetes insipidus and panhypopituitarism in general).

Here, we present a case of intracranial bifocal NGGCT in an 18-year-old male and review of relevant literature dealing with this rare entity.

Case Report

An 18-year-old male presented with diplopia and ataxic gait. Pertinent physical examination revealed Parinaud's syndrome (upward gaze palsy), diplopia, and unsteady gait. There were no episodes of seizures. A computed tomography (CT) brain scan was done in the emergency department that showed two lesions, one suprasellar and one in the pineal region. The patient was then admitted to the neurosurgical unit for further diagnostic procedures.

Brain magnetic resonance imaging (MRI) confirmed the existence of two lesions (Fig. 1A). One was located in the suprasellar region (Fig. 1B). The mass

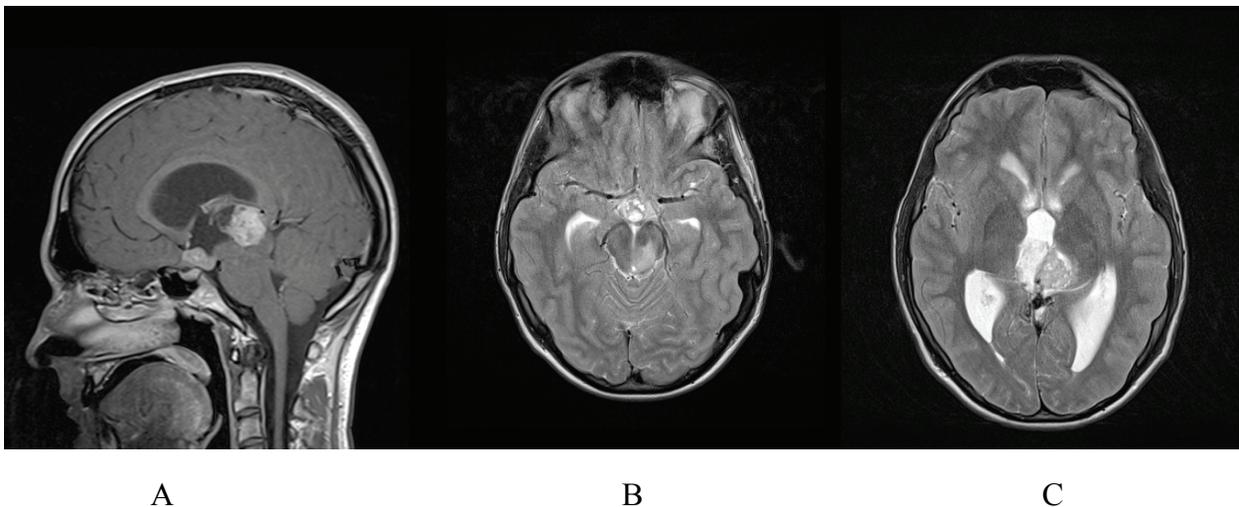


Fig. 1. Sagittal T1 sequence of the brain magnetic resonance imaging (MRI) showing bifocal tumor lesions in suprasellar and pineal regions (A); axial T2 brain MRI showing predominantly solid sellar region lesion (B); axial T2 brain MRI showing pineal region lesion with cystic and solid components and ventricular dilatation (C).

was spreading to the hypothalamus and floor of the third ventricle, and dorsally encompassed mammillary bodies. The pituitary stalk was compressed by the tumor. The pituitary gland morphology was normal. The mass had predominantly solid consistency with small zones of cystic degeneration with inhomogeneous contrast enhancing. Dimensions of the described lesion were 21 mm antero-posterior (AP), 16 mm cranio-caudal (CC), 14.1 mm latero-lateral (LL). The other lesion had a solid and cystic component and was located in the pineal region (Fig. 1C). More accurately, it was located in the left mesencephalic tectum and left side of the pineal gland spreading into the third ventricle. The tectal plate seemed to be compressed by the tumor. The mass was of mixed solid/cystic consistency with homogeneous contrast enhancement of its solid portion and no enhancement of the cyst. Its dimen-

sions were 28 mm AP and 24 mm CC and LL. The ventricular system was enlarged, and both foramina of Monro were dilated, but there were no signs of acute CSF obstruction or increased intracranial pressure (ICP).

Cervical, thoracic, and lumbar spine MRI was performed with and without contrast. There was no evidence for drop metastasis or any signs of mass lesion or pathologic enhancement in the spinal system (Fig. 2). Thoracic, abdominal and pelvic CT scan did not show any abnormalities. Ultrasound of the testes was normal, excluding gonadal lesions. Semen cryopreservation was also performed.

To distinguish if the mass was pure extragonadal GCT or NGGCT, we obtained serum β HCG and AFP (Table 1). Initial values of the patient's serum AFP levels were elevated to 492.7 kIU/L (normal

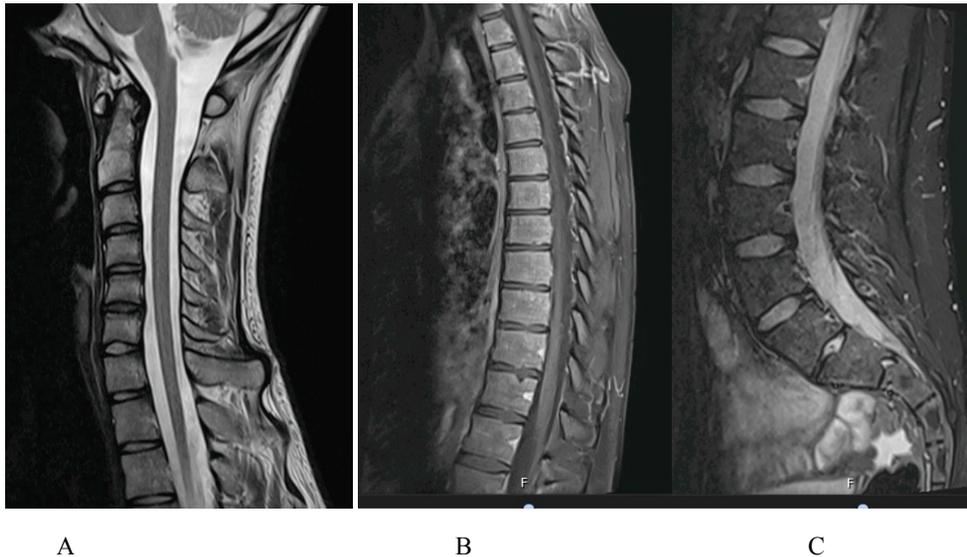


Fig. 2. Sagittal magnetic resonance imaging of cervical (A), thoracic (B) and lumbosacral (C) spine showing no leptomeningeal tumor spread.

Table 1. Specific tumor markers in different histopathologic tumor types

Tumor type	Tumor marker	
	β HCG	AFP
Germinoma (syncytiotrophoblastic)	+	-
Endodermal sinus tumor	-	+
Choriocarcinoma	+	-
Mixed germ cell tumor	+/-	+/-
Immature teratoma	+/-	+/-

β HCG = human chorionic gonadotropin; AFP = alpha fetoprotein

Table 2. Changes of specific tumor marker values in relation to chemotherapy

Tumor marker	Days prior to chemotherapy			After first chemotherapy cycle	Unit	Normal range
	6	1	1			
Alpha fetoprotein	492.7	1113.8 (blood)	2176 (CSF)	248 (blood)	µg/L	≤5.8
Human chorionic gonadotropin	54.3	75.3 (blood)	476 (CSF)	negative (blood)	IU/L	0-2

CSF = cerebrospinal fluid

Table 3. Pretreatment hormone values

Hormone	Value	Unit	Normal range
TSH	10.623	mIU/L	0.58-3.6
T3	1.05	nmol/L	1.3-2.3
T4	44	nmol/L	68-126
LH	<0.3	IU/L	1.7-8.6
FSH	<0.3	IU/L	1.5-12.4
Total testosterone	50.3	nmol/L	Age 18-49: 8.6-29.0
Prolactin	3507	mIU/L	86-324
Free cortisol	<11	nmol/L	0-245
Growth hormone	0.85	ng/mL	0-10
IGF-1	82	ng/mL	146-494

TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; LH = luteinizing hormone; FSH = follicle stimulating hormone; IGF-1 = insulin-like growth factor 1

range ≤5.8), and βHCG level was noted to be 54.3 IU/L (normal range, 0 to 2) (Table 2).

On his laboratory analysis prior to chemotherapy, the patient was noted to have sodium 151 mmol/L (134-144), blood sugar 3.7 mmol/L (3.9-5.9), bilirubin 40 µmol/L (7-30), thyrotropin stimulating hormone (TSH) 10.632-14.12 mIU/L (0.35-4.9), triiodothyronine (T3) 1.05 nmol/L (1.3-2.3), thyroxine (T4) 44 nmol/L (68-126), free thyroxine (FT4) 6.16 pmol/L (9-19), luteinizing hormone (LH) <0.3 (1.7-8.6), follicle stimulating hormone (FSH) <0.3 (1.5-12.4), prolactin (PRL) 3507 mIU/L (86-324), prolactin after sedimentation 2832 mIU/L (63-245), insulin-like growth factor 1 (IGF-1) 82 ng/mL (146-494), total testosterone (T) 50.3 nmol/L (8.6-29), tumor markers AFP 492.7-1113.8 µg/L (<7), βHCG 54.3-75.3 IU/L (negative), and lactate dehydrogenase (LDH) 180 U/L (<241). Free cortisol and growth hormone (GH) were

normal (Table 3), as well as 24-hour urine volume.

One day prior to chemotherapy, CSF obtained *via* lumbar puncture showed the following values: total cell count 289/3x10⁶/L (<15), red blood cells 736/3x10⁶/L, AFP 2176 µg/L, βHCG 476.53 IU/L, lactate 1.10 mmol/L (1.2-2.1), and total proteins 1.84 g/L (0.17-0.37), LDH 95 U/L (<30). Cytologic fluid analysis was negative for tumor cells.

The patient was on daily therapy with oral hydrocortisone 20 mg in the morning and 10 mg in the evening and oral levothyroxine 50 µg daily. On days 1 to 5, chemotherapy with etoposide 75 mg/m² iv; ifosfamide 1200 mg/m² iv with mesna protection (3x800 mg iv); and cisplatin 20 mg/m² iv was started. On day 2 of the second chemotherapy cycle, AFP decreased to 248 µg/L and neurological symptoms improved (visual field disturbance due to diplopia). On day 5 of the second chemotherapy cycle, the patient developed diabe-

tes insipidus with 8 L of 24-hour urine volume, which was successfully treated with intranasal vasopressin and fluids. On the same day, his testosterone level declined significantly (0.5 nmol/L) and was treated accordingly.

A total of four cycles of chemotherapy were planned, as well as irradiation therapy, depending on further tumor marker values and the patient's clinical condition.

Discussion

We describe the diagnosis and management of a rare case of intracranial multifocal midline lesions in an 18-year-old male. The patient presented with typical but nonspecific signs of a midline mass lesion effect, without any signs of rapid deterioration. Therefore, thorough clinical and neuroradiological examination, as well as blood tests was performed.

The preferred initial evaluation method for diagnosis of these lesions is MRI (although CT is also sensitive in detecting these lesions)⁹. Neuroradiologically, these tumors appear isointense or hypointense on T1 sequences and hyperintense on T2 sequences. They are contrast enhancing, and homogeneous if there are no cystic components, and heterogeneous if there is a cyst present¹⁰.

Our patient had two separate lesions, one in the sellar region and the other in the pineal region. Both lesions had heterogeneous MRI appearance with cystic components. The sellar region lesion had multiple cystic zones and the pineal mass was partially solid and partially cystic.

An entire spinal axis MRI is mandatory for staging of intracranial GCTs since 15% of patients will have leptomeningeal spread².

Excluding biopsy, the most important laboratory parameters in establishing the histopathologic diagnosis are serum and CSF tumor markers, AFP and β HCG¹¹. Due to their highly elevated values in our patient, a diagnosis of NGGCT (endodermal sinus tumor/choriocarcinoma) or mixed syncytiotrophoblastic germinoma/NGGCT was clear.

Any tumor with elevated AFP (>10 μ g/L) can contain elements of endodermal sinus tumor or immature teratoma. On the other hand, β HCG in males and non-pregnant females can be present in tumors with syncytiotrophoblastic germinoma, choriocarcinoma, or in immature teratoma components. Pure endodermal sinus tumor does not produce β HCG, therefore it is ex-

cluded. Syncytiotrophoblastic germinomas and choriocarcinomas do not produce AFP, so they are excluded as well. Therefore, a histopathologic differential diagnosis of mixed germ cell tumor (with syncytiotrophoblastic germinoma/choriocarcinoma and endodermal sinus elements) or immature teratoma was considered in our patient. Since the tumor markers in case of immature teratoma can be variable (negative or increased)¹², this diagnosis was found to be less likely (Table 1).

A multifocal midline intracranial tumor with negative or low β HCG levels (5-100 mIU/mL) and negative AFP levels (\leq 10 ng/mL) is pathognomonic for germinoma, and NGGCT is excluded in this case¹¹.

Accordingly, we decided not to perform surgical biopsy for confirmation of diagnosis. Although histologic examination is needed to establish a definitive diagnosis and staging of a suspected intracranial GCT, chemotherapy can be initiated without biopsy in selected cases. Therefore, these two lesions were treated as NGGCT and chemotherapy was immediately initiated. A biopsy specimen would have been mandatory if the serum and CSF AFP and β HCG tumor marker values had been normal. This is to distinguish between pure germ cell tumor and mature teratoma since their therapeutic approaches are different⁷.

Serum AFP >1000 μ g/L has been identified as a poor prognostic indicator⁶, but a significant portion of these tumors have mixed components¹³. Therefore, tumor markers should not be used for risk evaluation without tissue diagnosis¹⁴. Tumor markers AFP and β HCG both from serum and from CSF can aid in the diagnosis of NGGCTs, and are of great clinical importance¹⁵. Both should be obtained in the absence of clinical contraindication⁷. In our patient, AFP values were increasing rapidly prior to chemotherapy. After the first chemotherapy cycle, AFP decreased to its half initial value.

When sellar mass is present, it is an imperative to obtain detailed hormonal evaluation. This includes serum TSH, T3, T4, LH, FSH, prolactin, IGF-1, growth hormone, testosterone, and 24-hour urinary free cortisol. We followed this protocol in our patient.

Immediate neurosurgical intervention is indicated only in case of increased ICP due to obstructive hydrocephalus or rapid visual field impairment from suprasellar mass. Since this was not the case in our patient, urgent decompressive surgery was not indicated.

Considering the pitfalls of procedures used to obtain tissue for analysis, it is worth discussing its ne-

cessity. Generally, surgical approach to such midline lesions, especially multifocal, of similar morphology and location, is associated with a threat of potential neurosurgical complications that exceed the benefits of resection. For suspected intracranial GCT, with elevated both AFP and β HCG, biopsy might be of lesser value than previously thought. Biopsy samples are often too small to provide an accurate histopathologic diagnosis, as GCT is often heterogeneous and subject to sampling error. Therefore, the histopathologic diagnosis can be misleading¹⁴. When tissue diagnosis is not reliable, treatment should be based upon the outcome associated with the most malignant histology and worst prognosis⁹. This was an additional reason why we did not opt for biopsy. Gross tumor resection in our patient was not recommended either.

Considering the very high and rapidly increasing AFP values, we targeted the chemotherapy regimen based on the presumption of an endodermal sinus tumor component. These tumors are more sensitive to platinum-based compounds including cisplatin or carboplatin along with etoposide. Studies have shown that neoadjuvant therapy before initiation of radiation therapy results in long-term survival (60%-70% of cases)¹⁴. Furthermore, as long as the chosen treatment modality is successful it seems that biopsy may not be mandatory to guide chemotherapy. Pursuing a presumptive chemotherapeutic protocol, our patient's clinical state improved significantly, and his AFP values decreased remarkably.

Complications such as central diabetes insipidus and panhypopituitarism occur frequently¹⁶ and should be treated with supplemental hormonal therapy.

All patients with any type of NGGCT component should receive a combination of chemotherapy and radiotherapy to achieve optimal outcome. Furthermore, any signs of CSF spread require craniospinal treatment⁷ and radiation therapy will be included in our patient's long-term management. The exact formulation of future radiation therapy has yet to be determined and will be based on his outcome after chemotherapy.

To summarize, distinction of a true germinoma *versus* NGGCT is crucial. NGGCT is more difficult to treat, as it is considerably less sensitive to radiation. Even though NGGCT has a worse prognosis than pure germinoma, it usually shows good response to selected chemotherapy regimens. Pure germ cell tumors are sensitive to radiation therapy with long-term progression-free survival rates being high.

Largely due to the fact that NGGCT is less common than pure germinoma, there are insufficient scientific data to predict treatment outcome and to establish a standard management protocol.

As a result, in the absence of randomized studies, the current standard of care for patients with intracranial NGGCT is neoadjuvant chemotherapy, followed by craniospinal irradiation.

The rarity of multifocal brain NGGCT requires reporting each such case to contribute to the body of scientific data on this entity. This is especially important if an individual treatment protocol has resulted in good outcome. Based on the above, we feel that our case report is important due to a number of its characteristics. First, the patient was slightly older than the average demographic group for the described pathology. Second, he presented with two separate brain lesions, and lastly, he was successfully treated without histopathologic confirmation.

Randomized controlled studies are difficult to perform in these cases due to the low incidence of intracranial NGGCT. Case series and case studies are essential to establish a standard protocol for the management of these rare diseases.

Although the exact histopathologic tumor classification is of prognostic as well as academic value, it seems that its practical importance might ultimately be less relevant. Therefore, our efforts could potentially be aimed towards the specific treatment modality selection, based mainly on tumor markers, in the absence of precise histologic classification.

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Sažetak

RIJETKI INTRAKRANIJSKI MULTIFOKALNI NE-GERMINOMATOZNI TUMOR ZAMETNIH STANICA KOD 18-GODIŠNJEG MLADIĆA: PRIKAZ SLUČAJA

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Intrakranijski tumori zametnih stanica su rijetki tumori mozga koji se razlikuju na temelju histologije i tumorskih biljega. Ne-germinomatozni tumori zametnih stanica su raznolika podskupina tih tumora s najlošijom prognozom. Najčešće su locirani u supraselarnoj i pinealnoj regiji. S obzirom na to da točan protokol liječenja još nije utemeljen trenutno ne postoji standardizirani način liječenja. Predstavljamo slučaj intrakranijskog multifokalnog ne-germinomatoznog tumora zametnih stanica kod 18-godišnjeg mladića, popraćen relevantnim pregledom literature. Opisali smo početne dijagnostičke i terapijske postupke provedene kod mladića koji se prezentirao diplopijom i ataksičnim hodom. Neuroradiološki nalazi i povišeni tumorski biljezi, alfa fetoprotein te beta lanac humanog korionskog gonadotropina, upućivali su na mogući miješani tip tumora zametnih stanica. Propisana je odgovarajuća kemoterapija, a biopsija nije učinjena. Nakon početka kemoterapije bolesnikovo kliničko stanje se iznimno popravilo te su mu se vrijednosti alfa fetoproteina značajno snizile. Zaključno, početna neuroradiološka obrada, nalaz tumorskih biljega i citologija iz likvora važni su čimbenici u određivanju smjera liječenja i predviđanju prognoze. U određenim slučajevima biopsija ne mora biti indicirana kako bi se započelo s kemoterapijom. Naglašavamo važnost odabira specifičnog načina liječenja prvenstveno na temelju nalaza tumorskih biljega bez obzira na preciznu histološku klasifikaciju.

Ključne riječi: *Ne-germinomatozni tumor zametnih stanica, intrakranijski; Alfa fetoprotein; Beta humani korionski gonadotropin; Biopsija; Kemoterapija*