doi: 10.4183/aeb.2023.99

CASE REPORT

PINEAL GERMINOMA PRESENTED WITH PARALYSIS OF UPWARD GAZE AND DIABETES INSIPIDUS

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Abstract

Intracranial germ cell tumors (GCTs) include two categories: germinoma and non germinoma. The pineal gland and suprasellar are the most common site of involvement.

The patient is a 14-year-old boy who presented with paralysis of upward gaze, polyuria, polydipsia and diplopia. Examination of vertical eye movements was impaired. Puberty then progressed to stage 3 of Marshall - Tanner and had stopped. In laboratory studies, the patient had anterior hypopituitarism and diabetes insipidus (DI). In pituitary and hypothalamic MRIs, a mass-like enlargement of the pituitary stalk and pineal region was seen, but due to the small size of the lesions, stereotactic biopsy was not possible. During this time, the patient developed recurrent attacks of hydrocephalus. Serum and CSF β-subunit of Human chorionic gonadotropin levels were negative. Treatment was not started because different lesions could cause disease in this area. After one year, a biopsy was performed and the germ cell tumor was diagnosed. Chemotherapy was started and after treatment the vision disorder and diplopia disappeared, but DI and pituitary dysfunction remained. Treatment of intracranial germinoma is multidisciplinary. GCTs are very sensitive to radiation therapy. They are treated with combination of chemotherapy, radiotherapy, surgery, endocrine therapy and have a good prognosis.

Keywords: Germinoma, Diabetes insipidus, Diplopia.

INTRODUCTION

Germ cell tumors (GCTs) are divided into two categories: gonadal and extragonadal tumors. Extra gonadal tumors are typically in the midline, from the brain to the coccyx. The most common sites of GCTs outside the gonad are the anterior mediastinum, retroperitoneum, pineal gland, and suprasellar. In infants and young children, sacrococcygeal and intracranial GCTs are the most common (1).

Extragenital incidence of GCTs varies from 1.8 to 3.4 per million and is more common in men (2).

Intracranial germ cell tumors (IGCTs) make up 1% of all brain tumors in children and young adults. GCTs are the most common tumors in this group and the pineal gland is the most common site of tumor formation(3). Pineal GCTs are divided into germinomas and teratomas. Pineal GCTs are found in 3 areas A) Posterior third ventricle and pineal lesions. B) Anterior third ventricle, suprasellar, or intrasellar lesions C) Combined lesions in anterior and posterior third ventricle, apparently noncontiguous, with or without foci of cystic or solid teratoma.

The most common pineal gland tumors are actually germinomas (a form of teratoma). Germinomas may develop in the anterior hypothalamus or lower third ventricular floor, and most often present with clinical triad of diabetes insipidus (DI) and pituitary insufficiency and visual abnormality. Other neurological manifestations of germinomas include a tendency to infiltrate the anterior hypothalamus and metastasize to the spinal cord and CSF. Intracranial germinomas (IG) rarely have extracranial metastases; these include the skin, lungs, or liver (4).

Sometimes the lesions in this area are so small that we are unable to get a biopsy of this area. On the other hand, multiple tumors in this area are involved and the decision to treat is delayed. Therefore, knowing the history of known patients can help physicians in making treatment decisions.

CASE PRESENTATION

In December 2016, the parents of a 14-year-old boy noticed a change in their son's eyes. The

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patient were seen by an ophthalmologist, but the examination showed nothing positive except vertical ocular movement paralysis, and the patient was referred to a neurosurgeon. Brain magnetic resonance imaging (MRI) without contrast was requested for the patient; the MRI showed the pituitary gland was smaller than normal (a small pituitary gland according to the patient's physiological age). About 20 days later, the patient developed diplopia, polydipsia, and polyuria. Symptoms of polydipsia and polyuria occurred suddenly and the symptoms were so severe finally the patient was referred to the endocrinology department. On physical examination the patient's height, weight, blood pressure, heart rate, sublingual temperature and number of breaths were 153 cm, 63 kg, 110/70 mm Hg, 88 beats per minute, 37°C and 17 times per minute respectively. The vertical movements of the eyes were impaired but the horizontal movements were normal and the pupils of both eyes were mid-sized, the pupil reflex to light and the corneal reflexes were normal. Deep tendon reflexes and limb strength were normal and Babinski reflex was negative. Cerebellar tests were normal. On examination, pubertal development was in stage 3 Marshall and Tanner and the testicular volume was about 10 cc. The patient did not have a male beard or mustache, nor did his tone of voice change, other examinations were normal. Table 1 summarizes the patient's tests before and after intervention. The 24-hour urine output was 9 liters and the 24-hour fluid intake was 10 liters. A water deprivation test was performed and a diagnosis of central DI was made. Treatment for DI was started. In order to investigate the cause of hypogonadotropic hypogonadism, central DI and decrease in IGF1 (insulin growth factor1), increase in prolactin and paralysis of upward gaze, contrast MRI was requested. A mass like enlargement of pituitary stalk and pineal area was reported in MRI. The most important differential diagnoses were histiocytosis X and GCTs, brain metastases, another differential diagnosis was lymphoma. Stereotactic biopsy was also not possible due to the small size of the lesion on MRI. Bone marrow aspiration and biopsy and CT scans of different parts of the body to find a lesion available for biopsy were all negative. The presence of lytic bone lesions was negative for the diagnosis of histiocytosis X. Repeated serum laboratory tests were negative for serum alpha-fetoprotein (AFP) and β-hCG (The β-subunit of human chorionic gonadotropin) and cerebrospinal fluid β-hCG. Due to the lack of specific pathology, treatment was not started for the patient. During this period, he developed secondary adrenal and thyroid insufficiency. Seven months after the onset of the disease, he was hospitalized with a diagnosis of hydrocephalus (due to headache, nausea and vomiting) and a brain shunt was implanted. Again, CSF was tested for β-hCG and cytology but the results were negative. He went to the emergency room again nine months later with dizziness and headache and was diagnosed acute hydrocephaly, due to shunt malfunction he was admitted and shunt reversion was performed and treated with vancomycin and ceftriaxone. Finally, one year later, a stereotactic biopsy was performed under MRI guidance and the diagnosis of germinoma was made (Fig. 1). After definitive diagnosis, because there was no suitable radiotherapy device in the patient's place of residence, his physician preferred chemotherapy to radiotherapy.

Treatment with cisplatin and etoposide was

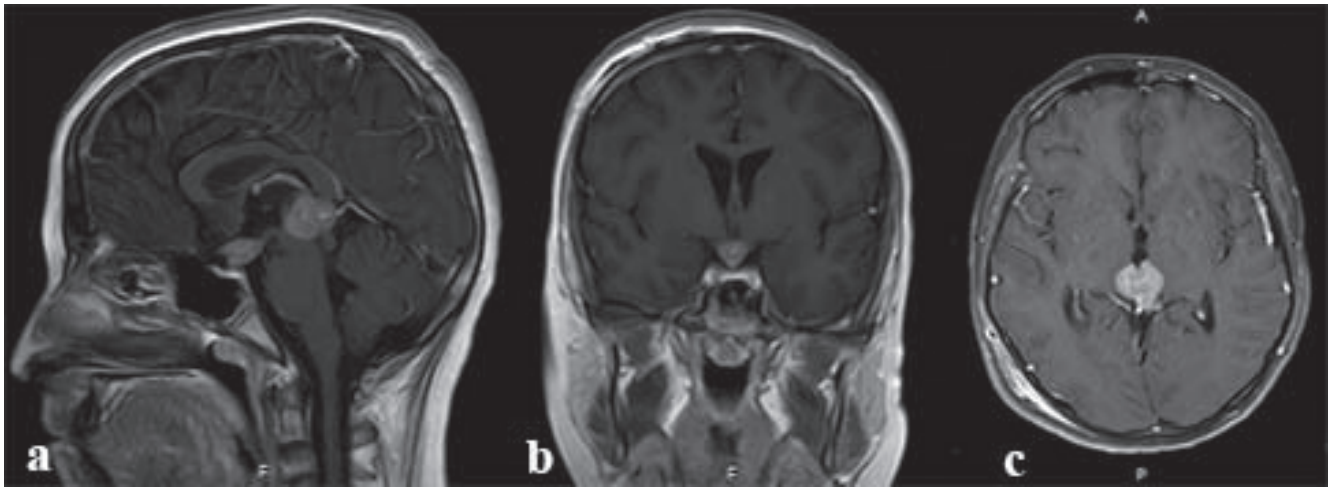

Figure 1. Brain MRI of germ cell tumor, one year after the onset of the disease. a - Sagittal post contrast image reveal a well-defined lobulated margin iso-signal in size of 17 * 22 mm is noted in pineal region which shows homogenous enhancement and similar lesion in size of 12 * 8.5 mm is present in the suprasellar cistern with post contrast homogenous enhancement. b- Coronal image show suprasellar mass. c- Axial image show pineal mass.

started. Brain MRI also returned to normal. The patient's laboratory tests after treatment are also listed in Table 1. Despite the normalization of MRI, hypopituitarism continued and puberty did not begin, therefore, the testosterone enanthate 50 mg/IM/monthly, injected and continued for 9 months, then gradually the amount of drug was increased to 200 mg/IM every 3 weeks. The patient currently weighs 70 kg and the patient's height is 166 cm and is being treated with levothyroxine, nasal spray of desmopressin, prednisolone, testosterone ampoules and carbamazepine tablets. In 2022, no signs of tumor recurrence were observed on MRI.

DISCUSSION

Germinomas are the most common type of germ cell tumor. GCTs are divided into three categories in terms of prognosis: benign, malignant and intermediate. Benign tumors include dermoid, epidermoid, and teratomas. Malignant tumors include choriocarcinoma, endodermal sinus tumor, and embryonic carcinoma and finally intermediate tumors includee germinomas and immature teratomas (5). Germinomas make up 66% of all IGCTs and 3-11% of all pediatric intracranial tumors. The most common site of IG is in the pineal gland and neurohypophysis regions (84%). Their peak incidences

Table 1. Lab data before and after treatment of intracranial germ cell tumor

Variable	First Lab data (2017 January)	Lab data 5 months after chemotherapy (2018-December)	Lab data (2021-May)	Normal reference range
Hemoglobin g/dL	12.6	13.2	14	13-17
FBG mg/dL	90	89	88	60-99
Creatinine mg/dL	0.8	0.8	1	0.86-1.4
IGF1 ng/mL	85	89.6	86.3	190-950 111-970
FSH mUI/mL	0.15	0.61	-	*1-14*
LH mUI/mL	0.1	<1	-	*0.7-7.4*
Testosterone ng/mL	0.4	0.14	*4.59*	*2-6.9*
Estradiol pg/mL	<22	-	-	*36.7-146.8*
Prolactin *ng/mL*	43	53.8	*41.9*	*4-18.4*
T4 µg/dL	6.33	6.4	*10.2*	*4.5-12*
T3 ng/dL	148	133	*160*	*80-200*
TSH Miu/L	0.38	0.016	*0.9*	*0.3-4*
TT3RU	24.2	32.4%	*30.7*	*22.5-37*
ACTH pg/mL	22	-	-	*7.2-63.6*
Cortisol µg/dL	16.9	<0.5	*2.96*	*3-21*
Na mEq/L	143	137	*141*	*136-145*
K mEq/L	5.3	4.2	*4.7*	*3.5-5.1*
AST U/L	32	-		*Up to 40*
ALT U/L	40	-	*45*	*Up to 40*
ALKP	338	-		*80-306*
Alb g/dL	4.8	4.4	*4.5*	*3.5-4.5*
Ca mg/dL	10.3	9.5	*9.3*	*8.4-10.2*
PO4	5.1	4.5	*3.8*	*2.7-4.9*
25 OHVit D ng/dL	12.6		*32*	*30-100*
Serum ßHCG IU/L	1	-		*0-3*
LDH IU/L	355	-		*100-500*
ACE IU/L	93	-	-	*8-65*
AFP IU/mL	2.82	-	-	*0-4*
CSF ßHCG mg/dL	<2	-	-	-
CSF LDH	0.871	-	-	-
Urine SG	1004	1020	*1030*	-

ACE= Angiotensin-Converting Enzyme, ACTH=Adrenocorticotropic Hormone, Alb=Albumin, AFP= Alfa feto Protein, ALKP=Alkaline Phosphatase,ALT= alanine aminotransferase, AST= aspartate aminotransferase, ßhcg=Beta Human Chorionic Gonadotropin, Ca=calcium, CSF= Cerebrospinal fluid ,P=Phosphorus, Cr=Creatinine, FBG= Fasting Blood Glucose, IGF1= insulin-like growth factor-1, FSH= Follicle-Stimulating Hormone, K=Kalium,LDH= Lactate Dehydrogenase, LH= luteinizing hormone,Na=Natriun, ῀ SG= Specific Gravity, Tes= Testosterone,T4= thyroxine, T3=Triiodothyronine, ,T3RU= T3 Resin uptake TSH= thyroid-stimulating hormone.

are in the second decade of life and infancy. It is more common in boys (4). In general, pineal tumors present with hydrocephalus and central midline mass on MRI. Parinaud syndrome is a manifestation of pineal tumors. In half of patients with Parinaud syndrome, manifestations such as paralysis of upward gaze, pupillary areflexia (to light), paralysis of convergence, and a wide-based gait can be seen. Gait disturbances can also occur because of brainstem or cerebellar compression. Other neurological symptoms that may be seen in pineal tumors include: spasticity, ataxia, nystagmus, syncope, vertigo, cranial nerve palsies other than pair VI and VIII, intention tremor, scotoma, and tinnitus. Most IGCTs present with clinical triad of DI and pituitary insufficiency and visual abnormality. Due to pituitary insufficiency, most patients with germinomas either do not enter puberty or, if they do, the progress to puberty stops, but in some cases there are reports of precocious puberty (especially in boys). Chorionic tissue in germinomas may have sufficient β-hCG secretion to cause precocious puberty (3, 4). Precocious puberty can occur in boys with ICGTs because of luteinizing hormone-like effects of β-hCG in the central nervous system. β-hCG has a similar effect to luteinizing hormone and therefore can cause precocious puberty (5). In our patient, puberty had started, but with the onset of the disease, the puberty process stopped and did not improve after treatment. Germinomas are associated with elevated β-hCG, but are inconsistent. They are usually measurable in CSF. High level germinomas β-hCG may have a poor prognosis. Lactate dehydrogenase and placental alkaline phosphatase (PLAP) are high in germinomas(5). PLAP levels in cerebrospinal fluid (CSF-PLAP) measurements were effective in differentiating GCTs from other brain tumors, with high specificity and sensitivity and also effective at the time of GCT recurrence (6, 7).

Diagnostic methods for GCTs are different. In some countries, a histological sample must be evaluated, which is often obtained by gross total resection rather than a biopsy is taken.

Other countries use tumor markers and radiological evidence to diagnose of GCT. Tumor markers used include AFP (typically increased in yolk sac tumors) and β-hCG (typically increased in choriocarcinoma) and CSF-PLAP. An increase in these three tumor markers in serum or cerebrospinal fluid (CSF) above the defined threshold indicates the diagnosis of germ cell tumor. But in cases where the tumor markers are negative, a surgical biopsy is used for diagnosis (6-9).

However, treatment of intracranial germinoma includes surgery, chemotherapy, radiotherapy and endocrine therapy. In fact, it is multidisciplinary (10). Radiotherapy is the preferred treatment for germ cell tumors, because they are very sensitive to radiation therapy. The success rate of radiotherapy is more than 90%, while that of chemotherapy is about 84%. Due to the high chance of recurrence following chemotherapy alone and to prevent high doses of radiation, most physicians use chemotherapy followed by radiation therapy. Surgery is often used for biopsy to determine the pathology and treatment of hydrocephalus. Surgery is determined by the patient's age and the location of the tumor. For example, a multicenter study was performed on pituitary germinomas. This study used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (2004-2016). The most common treatment in pediatrics was radiation + chemotherapy (47%), while the most common treatment in adults was radiation + gross total resection + chemotherapy (23%) followed by radiation + gross total resection (19%). The most common treatment in children was chemotherapy plus radiotherapy. But the most common treatment in adults was surgery plus chemotherapy plus radiotherapy (11).

However, surgery for intracranial germ cell tumors is rarely required. Occasionally years after successful intracranial germ cell tumor therapy, these patients develop testicular germ cell tumor. Therefore, long-term follow-up of these patients is necessary (4).

In some patients, DI improves after treatment of the primary tumor, but for the most patients, DI persists. In our patient, IGF1 levels remained low after chemotherapy and gonadotropin levels did not increase. Before the onset of testosterone, our patient was about 3 cm taller than onset of the disease and after the initiation of testosterone he was about 6 cm increase hight, which seems to be a relative growth hormone deficiency. Levels of other thyroid hormones and corticosteroids remained low, and the patient is now in good general condition.

In conclusion, the most common site of ICGCT are in the pineal gland and neurohypophyseal regions in children. They often present with clinical triad of DI and pituitary insufficiency and visual abnormality. Hydrocephalus is also found in these tumors. Sometimes pituitary and hypothalamic lesions are not seen on MRI without contrast and contrast must be used. Serum or CSF, β-hCG biomarkers may or may not be high. Placental alkaline phosphatase levels in CSF measurements were effective in differentiating germ cell tumors from other brain tumors. Treatment of intracranial germinoma is

multidisciplinary. Germ cell tumors are very sensitive to radiation therapy. They are treated with combination of chemotherapy, radiotherapy, surgery, endocrine therapy and have a good prognosis.

Conflict of interest

The authors declare that they have no conflict of interest.

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