

Cerebral Germinoma as a cause of Abnormal Pubertal Development in a 16 years Old Boy

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Received date: 17 Feb 2016; Accepted date: 26 Apr 2016; Published date: 30 Apr 2016.

Citation: Guidoni E, Lucherini M, Coriolani G, Lotti F, Geronzi U, et al. (2016) Cerebral Germinoma as a cause of Abnormal Pubertal Development in a 16 years Old Boy. *Int J Endocrinol Metab Disord* 2(2): doi <http://dx.doi.org/10.16966/2380-548X.125>

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Abstract

Objective: To describe a case with a rare form of bifocal mixed germ cell tumor, interesting both pineal and sellar regions, with symptoms of increased intracranial pressure, neurological disorders, endocrine abnormalities with panhypopituitarism and a particular trend in pubertal development that probably progressed supported by β -HCG secretion by the tumor.

Methods: Brain MRI, biopsy and histological examination were performed, revealing the presence of a germ cells tumor compatible with dysgerminoma with a component of embryonal carcinoma. After initiation of replacement therapy for panhypopituitarism, the patient received chemotherapy and radiotherapy.

Results: Treatment showed tumor regression and the patient is currently on desmopressin, hydrocortisone, L-thyroxine and GH replacement therapies. He is currently followed at the adult's Unit, with no further relapses 7 years after the diagnosis.

Conclusions: The IGCTs are very rare; combined imaging, laboratory and histological diagnosis is needed for a correct diagnosis and to define the approach that will be used. One of the main challenges will be to minimize the side effects of treatment in order to improve the quality of life of these patients.

Keywords: Cerebral germinoma; Pubertal development; Intracranial germ cell tumors

Introduction

Intracranial germ cell tumors (IGCTs) represent 3-11% of paediatric brain tumors between 0 and 19 years [1,2]. The reported incidence of primary IGCTs in children is significantly higher in Asian countries (especially in Japan, Taiwan and Corea) compared with Western countries [3-5]. There is still no explanation for this geographic and ethnic difference.

IGCTs are more common in males and the peak of incidence is 10-12 years of age [1,6].

IGCTs are malignant neoplasms arising from remnants of primitive germ cells that have failed to migrate to the genital crest during embryonic life [7]. They show an evident predilection for the pineal region, the third ventricle and the suprasellar-hypothalamic area, which are located along the midline. Some IGCTs develop in unusual sites, including the basal ganglia, thalamus, fourth ventricle, spinal cord and corpus callosum [8-10].

Clinical presentation depends on the location and size of the tumor: pineal region tumors can determine increased intracranial pressure due to obstructive hydrocephalus with headache, vomit, somnolence and visual abnormalities. Suprasellar location can cause endocrine problems due to hypothalamic/pituitary axis dysfunction with diabetes insipidus, isolated growth hormone deficiency, delayed sexual development or precocious puberty and hypopituitarism. Other common symptoms include ocular signs due to the visual pathway infiltration by the tumor [1,11-13].

Histologically IGCTs are classified in two different types: pure germinomas, which account for approximately 50%-70% of cases, and non germinomatous germ cell tumors (NGGCTs) which include embryonal

carcinoma, Yolk sac tumor, choriocarcinoma, teratoma and mixed germ cell tumors. Mixed germ cell tumors, characterized by more than one histological component, represent about 25% of all paediatric IGCTs [1].

Germ cell tumors are also classified according to tumor markers secretion; the most common markers are β -human chorionic gonadotropin (β -HCG) and alpha-fetoprotein (AFP), which can be measured in both cerebrospinal fluid and serum. Pure germinomas are usually non secreting tumors, while choriocarcinomas classically produce β -HCG, teratomas and mixed germ cell tumors can secrete both β -HCG and AFP [1,14].

Other several immunohistochemical markers, such as CD30, CD117, OCT-4, β -HCG, AFP, placental alkaline phosphatase (PLAP), can be used to determine the histological composition of the tumors [15].

Diagnosis includes radiological exams (CT and MRI), measurement of tumor markers in blood and liquor and histological assessment [1,16].

The prognosis is closely related to the histological subtype. Pure germinomas are highly radiosensitive, whereas NGGCTs are less sensitive to radiotherapy and they have a worse prognosis [17,18]. The survival rate of patients affected by pure germinoma appears to be very high, with a 10-year overall survival rate of 90%, whereas the 10-year survival rate in NGGCTs is in the range of 30-80%, with many tumors relapsing within 18 months from diagnosis [19-22].

Also the treatment of intracranial GCTs differs according to histological subtype. Radiotherapy, with or without chemotherapy, is the gold standard for the treatment of pure germinomas, surgery is sometimes needed in case of obstructive hydrocephalus [23].

Despite recent advances in chemotherapy and radiotherapy, due to its low sensibility to this therapy, neurosurgical treatment remains essential for the intracranial NGGCTs, providing tissue sampling, cerebrospinal fluid diversion and cyto-reduction [24]. In particular, the recent endoscopic endonasal transsphenoidal technique permits to approach sellar lesions [25].

Moreover, in case of endocrine dysfunctions replacement therapies are administrated.

We present this case in order to describe a rare form of bifocal mixed germ cell tumor, interesting both pineal and sellar regions, with symptoms of increased intracranial pressure, neurological disorders, endocrine abnormalities with panhypopituitarism and a particular trend in pubertal development that probably progressed supported by β -HCG secretion by the tumor.

Case Report

A 16-year-old boy was referred to our Clinic with complaints of bitemporal headache, morning vomiting, strabismus, visual disturbances (diplopia in the lateral sight), polyuria and polydipsia since several weeks.

The clinical examination showed: weight 50.5 kg (10th centile), height 167 cm (10-25th percentile), head circumference 53.2 cm (10-25th percentile), cardiorespiratory and abdominal examination was normal, with no hepato-splenomegaly. Superficial lymphonodes were intact, testicular volume was 15 ml left and 20 ml right, pubarche Tanner stage III. Convergent strabismus due to paralysis of the left lateral rectus, diplopia in the lateral sight, hyposthenia of the left arm, hypoesthesia on the left hemibody was present.

Brain MRI was performed: T2 sagittal scanning showed the presence of an expansive mass of 3 cm in diameter in the pineal region, herniating into the third ventricle, with compression on the aqueduct of Sylvius and secondary triventricular hydrocephalus (Figure 1); T1 weighted sagittal scanning with gadolinium revealed that the lesion showed a remarkable enhancement. Further lesions were present in the suprasellar region, the genu of corpus callosum, septum pellucidum and fornix (Figure 2).

Patient was admitted and an endoscopic third ventriculostomy (ETV) with biopsy was performed. Histological examination showed the presence of a germ cells tumor compatible with dysgerminoma with a component of embryonal carcinoma (CD 30+ e CD 117+) (Figures 3 and 4).

A tumor markers profile was also performed, showing elevated β -HCG levels of 15 mUI/ml in the serum (normal value <2,6) and 19,4 mUI/ml in the cerebrospinal fluid (normal value <15) with normal AFP levels of 2 UI/ml in the serum (normal value <15) and 3 UI/ in the cerebrospinal fluid (normal value <15).

Biochemistry revealed follicular stimulating hormone (FSH) 0.52 mUI/ml, luteinizing hormone (LH) 0 mUI/ml, prolactin (PRL) 33.1 ng/ml, testosterone (T) 1030 ng/dl, estradiol 24.1 pg/ml, inhibin B <5 pg/ml. The LHRH stimulation test did not show any increase in FSH and LH levels. Urinary specific weight and osmolarity were extremely low.

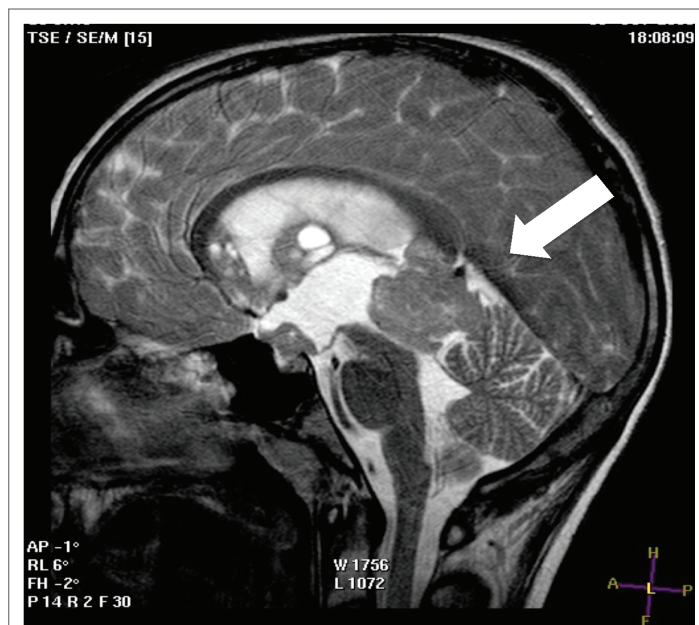


Figure 1: T1 weighted sagittal scanning with gadolinium revealed the presence of an expansive mass of 3 cm in diameter in the pineal region, herniating into the third ventricle, with compression on the aqueduct of Sylvius and secondary triventricular hydrocephalus.

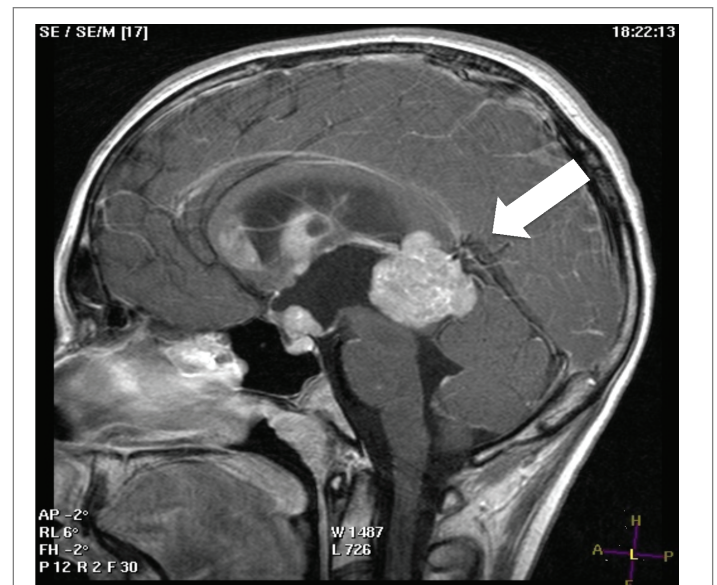


Figure 2: T1 weighted sagittal scanning with gadolinium revealed that the lesion showed a remarkable enhancement. Further lesions were present in the suprasellar region, the genu of corpus callosum, septum pellucidum and fornix.

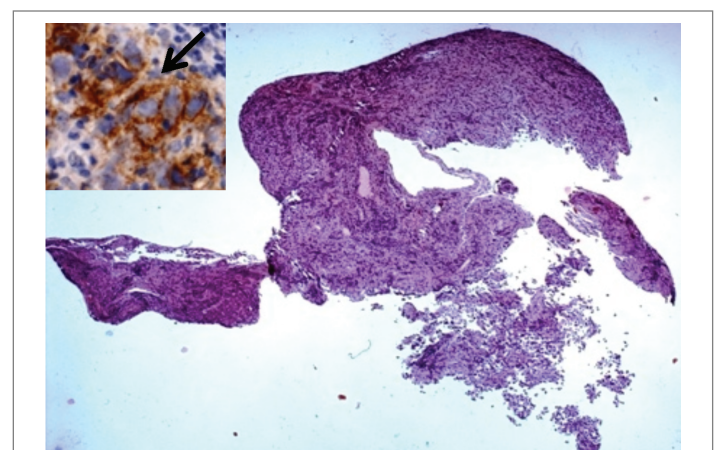


Figure 3: Mixed germ cell neoplasm at scanning power. Detail of CD117-positive, brown stained dysgerminoma tumor cells (arrow), admixed with embryonal carcinoma cells, which are, instead, negative for CD117, Haematoxylin and eosin, Original magnification \times 25. Insert: Immunohistochemistry-streptavidin-biotin method; Chromogen: diaminobenzidine; Original magnification \times 200.

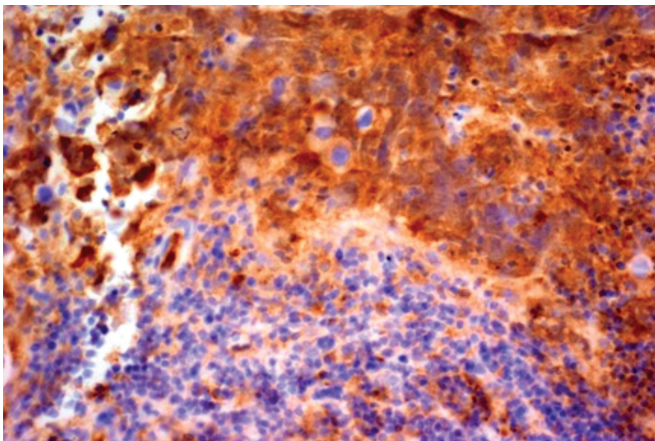


Figure 4: Component of embryonal carcinoma immunopositive for CD30. At the bottom of the figure, dysgerminomatous cells are not labelled by CD30 antibody. Immunohistochemistry-streptavidin-biotin method; Chromogen: diaminobenzidine; Original magnification $\times 200$.

Thyroid stimulating hormone (TSH) levels were low (0.02 $\mu\text{UI/mL}$), as free thyroxine (FT4) levels (6.5 pg/mL). GH-IGF-1 axis investigations revealed the presence of GH deficiency, but replacement treatments were postponed at the end of chemo-radiotherapy.

As the patient had panhypopituitarism, glucocorticoid replacement therapy with hydrocortisone was started (12 $\text{mg/m}^2/\text{d}$), followed by levothyroxine replacement (75 $\mu\text{g/d}$), testosterone enanthate (150 mg i.m. monthly) and desmopressin (1 puff twice daily).

After clinical-pathological-instrumental stadiation, antineoplastic treatment was started, according to the protocol of the Italian Society of Paediatric Oncology (SIOP CNS TGC '96). Chemotherapy was performed for 4 cycles: cycle 1 and 3: cisplatin (changed in carboplatin because of ear toxicity) and etoposide, cycle 2 and 4: ifosfamide and etoposide. Chemotherapy was followed by conventional radiotherapy to the craniospinal axis (2550 cGy), including whole ventricular irradiation (1950 cGy) and a boost to the pineal region (900 cGy). Overall, on the site of the primitive lesion a dose of 54 Gy was reached and at the level of ventricles, site of metastases, the dosage was 44 Gy.

Treatment caused tumor regression, confirmed by brain MRI performed 2 months after the end of treatment.

At the age of 17, the patient showed complete pubertal development, weight at 50th percentile, height at 10-25th percentile.

At the last evaluation performed in our department, at the age of 18, weight was at 25-50th percentile and height at 10-25th percentile. The patient continued on desmopressin, hydrocortisone, L-thyroxine and GH replacement therapies. He is currently followed at the adult's Unit, with no further relapses 7 years after the diagnosis.

Discussion

The germ cell tumors are rare cancers with frequent intracranial location. The mostly affected sites are the pineal and suprasellar regions. 5%-25% of patients present synchronous lesions in both locations [1,26].

Bifocal IGCTs, by definition limited to the pineal and neurohypophyseal regions, should not be considered as metastatic disease but as independent primary tumors [27].

The tumors of the pineal region cause obstruction of the aqueduct of Sylvius and foramen of Monro, resulting in hydrocephalus and signs

of intracranial hypertension; the main manifestations of suprasellar IGCTs are endocrine diseases and visual defects. In particular, the most common initial symptom is diabetes insipidus (50%), followed by visual disturbances (17%). Visual defects are represented by decreased visual acuity and visual field defects (especially bitemporal hemianopia); their incidence is about 78% throughout the course of the disease [12].

The alterations due to hypothalamic-pituitary axis deficiency may appear either at the onset, at overt symptomatology, during chemo-radiotherapy or during follow-up.

Our case represents a rare form of bifocal mixed germ cell tumor, interesting both pineal and sellar regions. The patient had symptoms of increased intracranial pressure due to hydrocephalus, neurological disorders caused by compression by the tumor and endocrine abnormalities with panhypopituitarism, requiring hormone replacement therapy.

Pubertal development of our patient showed a particular trend. Secondary sexual characteristics development was already advanced at the time of our first observation, probably sustained by the hypothalamic-pituitary-gonadal axis physiological activation. The tumor situated in the pineal region has led to panhypopituitarism, with pituitary-gonadal axis suppression confirmed by lack of FSH and LH response to LHRH stimulation test, resulting in arrest of pubertal development progression.

Clinically it was difficult to detect this pubertal arrest because of secondary sexual characteristics progression, in particular pubic hair and penile growth.

Probably this progression has been supported by β -HCG secretion by the tumor.

The β -HCG is a molecule produced by the placenta syncytiotrophoblastic cells; it may also be secreted in some forms of germ cell tumors. β -HCG producing germinomas account for about 18% of all germinomas [28].

Because of its similarity with LH, β -HCG is able to bind the LH receptor on Leydig cells and stimulate T synthesis and secretion, which inhibits LH pituitary secretion by negative feed-back [29].

In our patient serum T level was very high at diagnosis.

Treatment caused tumor regression and suppression of abnormal T secretion, thus stopping the progression of pubertal development, reinstated with replacement T therapy.

Correlation with the serum tumor markers, β -HCG and AFP is an essential consideration in the diagnosis of IGCTs [14,30]. Detection of β -HCG is not a marker of metastasis or tumor size, but its presence indicates the activity of syncytiotrophoblastic elements within the tumor [31].

It is known that secreting tumors have a worse prognosis compared to non-secretory germinomas, with a higher recurrence rate and shorter survival [31,32].

NGGCT is diagnosed as IGCT with any malignant germ cell component or any AFP or β -HCG secreting tumor.

The cut-off level of elevated β -HCG for the diagnosis of NGGCT differs in each study (50–100 IU). Tumors with high β -HCG concentrations are considered to have worse prognosis by some researchers [14,28,33,34].

However, many other studies have shown that an elevated β -HCG level is not particularly associated with poor prognosis when there is no evidence of dissemination through the liquor [35-39].

Conclusions

The IGCTs are very rare and require particular attention in the diagnosis of neurological and endocrinological symptoms. The neuroimaging characteristics of IGCTs are similar enough to limit diagnostic certainty, therefore histological examination and measurement of specific tumor markers are needed for a complete diagnosis [10]. Only a combined imaging, laboratory and histological diagnosis should define the approach that will be used [40].

One of the main challenges will be to minimize the side effects of treatment in order to improve the quality of life of these patients.

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