

Case Report

Coexistence of intracranial germ cell tumor and craniopharyngioma in an adolescent: case report and review of the literature

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Abstract: Purpose: We present the case of a patient treated for intracranial germ cell tumor in which elements of craniopharyngioma were found in the residual tumor mass. Findings: A 17 year old patient presented with a history of secondary amenorrhea. She deteriorated with headache and left eyelid drop, paresis of the abducent nerve and convergent strabismus (Parinaud syndrome). β -HCG was 722mIU/ml and pregnancy was excluded. AFP was 6322 ng/ml. Brain CT scan showed a large endosellar tumor to the hypersellar region. There was left papillary atrophy. MRI confirmed a tumor to dorsum sellae. Primary germ cell intracranial tumor was diagnosed. Severe clinically evident pituitary failure developed with signs of increased intracranial pressure and brain edema as well as diabetes insipidus, while AFP increased to 15786,3ng/ml. Urgent treatment with combination chemotherapy including cisplatin etoposide and bleomycin (PEB) was administered for 4 courses. As a result her clinical condition improved and tumor markers dropped but nevertheless did not become normal. In addition CT scans revealed a remaining endocranial mass and therefore the patient was subjected to high-dose chemotherapy followed by autologous stem-cell rescue which resulted in complete clinical and biochemical remission. Due to the persisting mass in the area, it was delivered radiotherapy. Conclusions: The above case is extremely rare in worldwide literature. Dysgerminoma may coexist with craniopharyngioma which in fact may be part of a germ cell tumor in the context of dysembryogenesis and benign "teratoma".

Keywords: Intracranial, germ cell tumor, craniopharyngioma, dysembryogenesis

Introduction

Intracranial germ cell tumors comprise a heterogeneous group of neoplasms. Their exact incidence is not known due to the morbidity of surgery in the pineal gland area. Another reason is the complex classification system which was used to identify these tumors. In western countries, intracranial germ cell tumors comprise 0,4 to 3,4% of the cases concerning primary tumors of the central nervous system, while this percentage is much higher in Asia. Germ cell tumors are usually located in the pineal gland area and in the area above the sella turcica. Between 5% and 10% of these tumors are diagnosed in both the suprasellar and the pineal gland area [1]. It is not yet ascertained whether this bifocal disease represents

spread of primary tumor or simultaneous two primaries growth in two locations. Germ cell intracranial tumors appear in other places of the brain as well, in particular in the midline of brain (fourth ventricle tumors, basic ganglia area tumors and thalamus tumors). Their occurrence is more frequent in men than in women especially during adolescence. The age distribution of afflicted patients is unimodal, centering with an abrupt surge in frequency in the early pubertal years. Seminomas are usually diagnosed between 10 and 21 years old, while non-seminomatous germ cell tumors are more frequent earlier during life [2].

The classification of germ cell tumors is diverse. Some claim that all germ cell tumors derive from a primordial germ cell which later evolves

Table 1. World Health Organization (WHO) classification of intracranial germ cell tumors. (Louis, DN, Ohgaki, H, Wies-terl, O, et al. WHO Classification of Tumours of the Central Nervous System, Third Edition. Albany, NY: WHO Publication Center, 2007: 197-204. Copyright ©2007 World Health Organization)

1. Germinomas
2. Nongerminomatous germ cell tumors
2.1 Embryonal carcinoma
2.2 Yolk sac tumor
2.3 Choriocarcinoma
2.4 Teratoma
a) <i>Benign teratomas</i>
Immature (may contain rare malignant germ cell elements)
Mature
b) <i>Teratoma with malignant transformation</i>
2.5 Mixed germ cell tumors

into seminomas or non-seminomatous tumors [3]. As far as embryonic carcinoma is concerned, its presence is considered to be a critical and indicative attribute of the non-seminomatous tumors, depending on the interaction of the stem cells with all types of nearby tissues. The tumor will then evolve into a choriocarcinoma, an endodermal sinus tumor or a teratoma. Other authors claim that only seminoma is developed by means of the primordial cell, while the other so called primordial cell tumors are dysembryogenesis which were randomly located in the side of the mesoderm, thus later growing in several areas of the brain. The most recent intracranial germ cell tumor classification according to the World Health Organization (WHO) is presented in **Table 1**. The classification is subjective and is greatly influenced by the tumor sample.

Recently, the histological diagnosis has become easier with the measuring of tumor markers. The presence of special proteins-the tumor markers-that are produced and secreted from the specific neoplastic cells has been very helpful in the diagnosis of intracranial germ cell tumors [4]. In high levels, these tumor markers may be measured in the serum as well as in the cerebrospinal fluid [5]. They act as a sensitive and reliable indicator for the presence of a tumor. In many cases, marker measurements in serum or in the cerebrospinal fluid have replaced the need for a biopsy and negated the consequent elevated danger of infection during the neurosurgical operation.

Approximately 60% of the intracranial germ cell tumors are pure germinomas (seminomas) while 40% are teratomas and non-seminomatous germ cell tumors. Mixed tumors, germinomas with non germinomatous elements, such as the yolk sack tumors, choriocarcinoma or embryonic carcinoma are rare. In cases of patients with pure germinomas the α -fetoprotein levels are generally within the normal limits, while for a certain amount of patients human chorion gonadotrophin (β -HCG) levels might be slightly elevated and below 50mIU/ml. On the contrary, in the cases of intracranial non germinomatous germ cell tumors, human chorion gonadotrophins (β -HCG) levels as well as

α -fetoprotein in the serum or the cerebrospinal fluid are frequently elevated. As far as therapy is concerned, treatment for patients with intracranial germ cell tumors is commenced according to the characteristic radiological image and the high α -fetoprotein or/and human chorion gonadotrophin (β -HCG) levels in the serum or the cerebrospinal fluid. If the tumor markers are normal or if β -HCG is below 50mIU/ml, then stereotactic biopsy is required prior to the treatment. If the biopsy doesn't provide a diagnosis, or if the histology reveals a mature teratoma then surgical operation is recommended.

Craniopharyngioma is rare, usually appears as a solid or a mixed solid and cystic suprasellar tumor. This tumor derives from the remnants of Rathke's pouch along the line from the nasopharynx to the diencephalon [6]. Its frequency fluctuates between 1-3% of intracranial tumors which means 0.5 to 2 cases per million of population, annually. The tumors' size varies between small solid well circumscribed masses and large multilobular cysts which cover the sella turcica and displace the adjacent brain structures. The largest part of a craniopharyngioma is comprised by a big single cyst or many cysts which contain cholesterol crystals. They usually have calcifications in the suprasellar area, in 80% of the cases, and at least one cyst in 75% of the cases. Despite the characteristic findings the discrimination between craniopharyngioma and other intracranial tumors is difficult clinically and radiologically [7]. Although it is histologically benign, craniopharyngioma

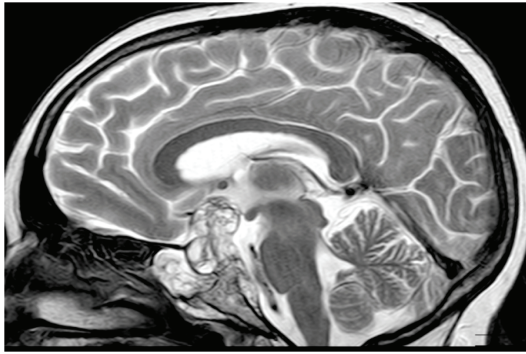


Figure 1. Suprasellar mass extending to the sphenoid sinus with both solid and cystic compounds. Inhomogeneous enhancement after Gd administration (Sagittal T2 WI.).

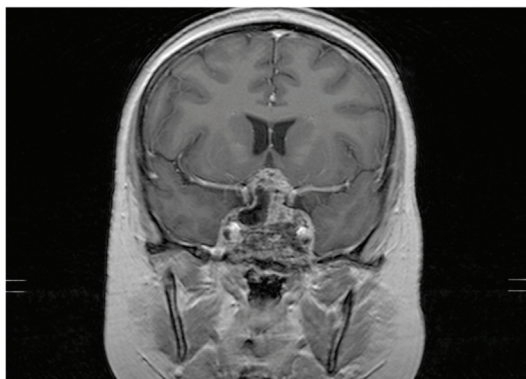


Figure 2. Suprasellar mass extending to the sphenoid sinus with both solid and cystic compounds. Inhomogeneous enhancement after Gd administration (Coronal T1WI / FFE + Gd).

decreases survival chances and should be considered as an indolent malignancy. Treatment of craniopharyngioma includes surgery, radiotherapy or even combination of both. Nevertheless, the initial enthusiasm about extended surgical operation has receded for a variety of reasons thus being replaced by more conservative surgical operations along with radiotherapy. Moreover, in some cases deterioration continues despite extensive treatment approaches [8].

We present a female patient with intracranial germ cell tumor in whom, after treatment, craniopharyngioma elements were found in the remaining mass. Relevant literature will be analyzed. We have also obtained the informed consent of the patient.

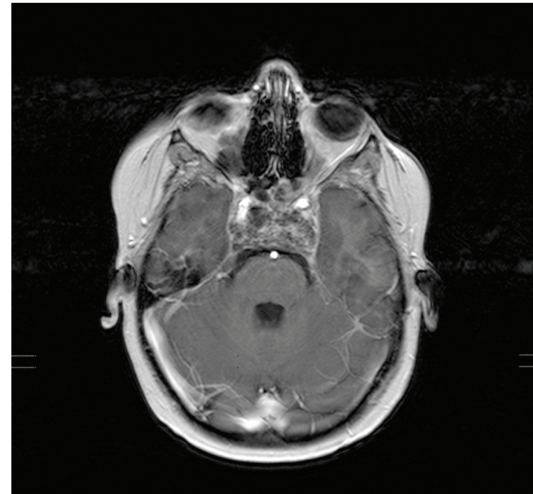


Figure 3. Suprasellar mass extending to the sphenoid sinus with both solid and cystic compounds. Inhomogeneous enhancement after Gd administration (Axial T1 WI / FFE + Gd).

Case presentation

A 17 year old girl whose menstruation had stopped two years ago (since July 2001), begun to suffer from gradually deteriorating occipital and frontal headaches followed by bilious vomiting. Within a short period there was an abrupt fall of the left cilium and paresis of the abducent nerve resulting in convergent strabismus. She was transferred to the emergency department of a general hospital where a test for human chorionic gonadotrophin (β -HCG) was conducted which showed 722mIU/ml and the ultrasound excluded pregnancy. Ten days later, she visited a neurologist who recommended a brain CT scan, which was conducted and showed large endo- and suprasellar tumor mass. She was then admitted in the neurosurgical department of a central hospital in Athens, where decolorization of the left papilla was found and the patient started treatment with 6 mg of dexamethasone per day for her brain edema. The MRI of the brain and the pituitary showed tumor mass in the dorsum sellae area expanding to the interior of the sphenoidal sinus in the endo- and suprasellar area causing erosions of the dorsum sella area and the clinoid process (**Figures 1-3**). In addition its expansion infiltrated the cavernous sinus, and pressed the optic chiasm up to the third ventricle. At that time the α -fetoprotein level was

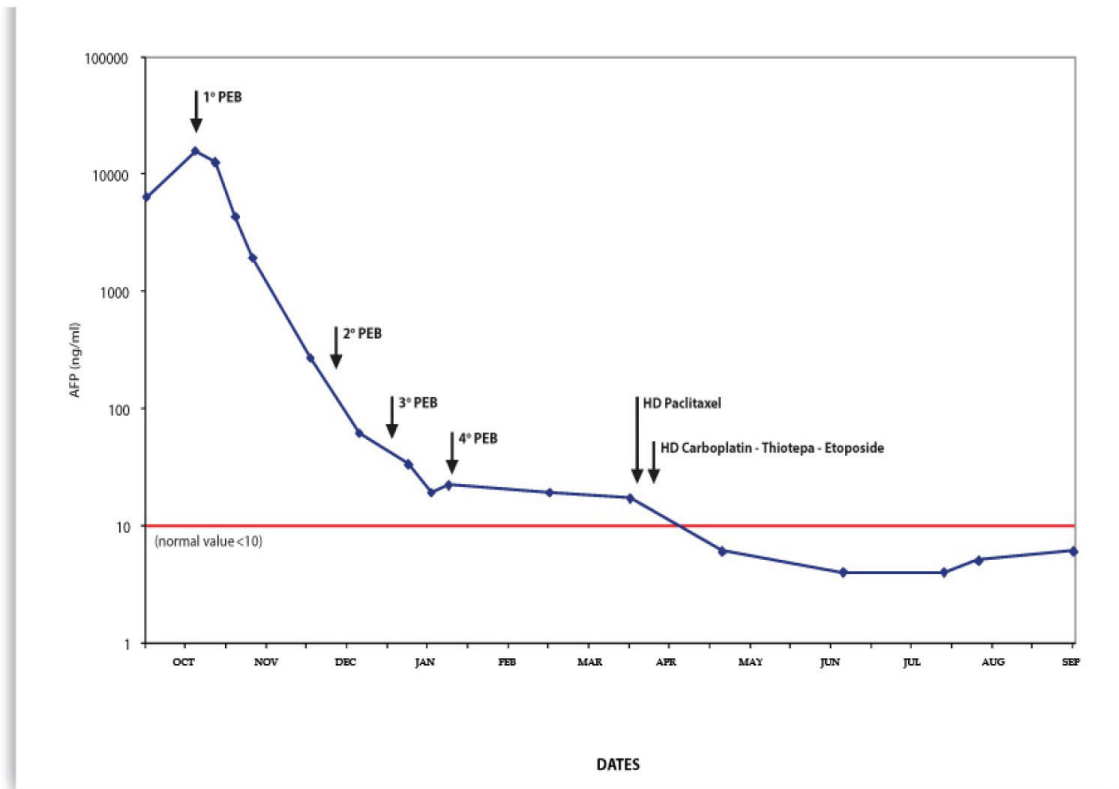


Figure 4. Linear graph that illustrate the fluctuations of a-fetoprotein.

6322ng/ml. After that the patient was diagnosed with primary germ cell intracranial tumor.

The patient was transferred to the endocrinology department of the same hospital in order to test the efficiency of the pituitary hormones. The clinical examination was indicative of a fit person with hypothyroidism (impaired speaking, dry skin, delayed tendon reflexes). Left abducent nerve paresis was found, accompanied by convergent strabism. During her hospitalization patient showed symptoms of diabetes insipidus with polyuria, low urine specific weight and disability of urine concentration during the water deprivation test. The efficiency test of the pituitary's frontal lobe showed somatotrophin deficiency with GH 0,1ng/ml and low levels of IGF-1 35ng/ml, non countable gonadotrophine levels, amenorrhea, thyroid hormones deficiency with low levels of T3, FT4 and inappropriately normal levels of TSH. The patient was treated with thyrohormone while there was gradual reduction of cortisone resulting into a substitution dosage of 20mg of hydrocortisone in the morning and 10mg in the night.

After the relevant treatment of the patient's problems she was transferred to an anticancer hospital for further treatment with the diagnosis of large suprasellar germ cell tumor, pituitary frontal lobe deficiency and transient diabetes insipidus. At presentation patient showed reduced psychomotor evolution, delayed growth and impaired communication. She suffered also from convergent strabismus of the left eye. The level of human chorionic gonadotrophin (β -HCG) was 576,6mIU/ml and a-fetoprotein was 15786,3ng/ml. Due to the seriousness of the patient's condition, she was subjected to combined chemotherapy with 4 cycles of BEP with impressive improvement of her clinical condition and a rapid fall of the markers which nevertheless did not become normal.

Due to persistence of markers and a remaining intracranial mass she was subjected to high-dose chemotherapy followed by autologous stem-cell rescue. Her progress was satisfactory, the hematological toxicity minimum and the patient finally achieved full biological improve-

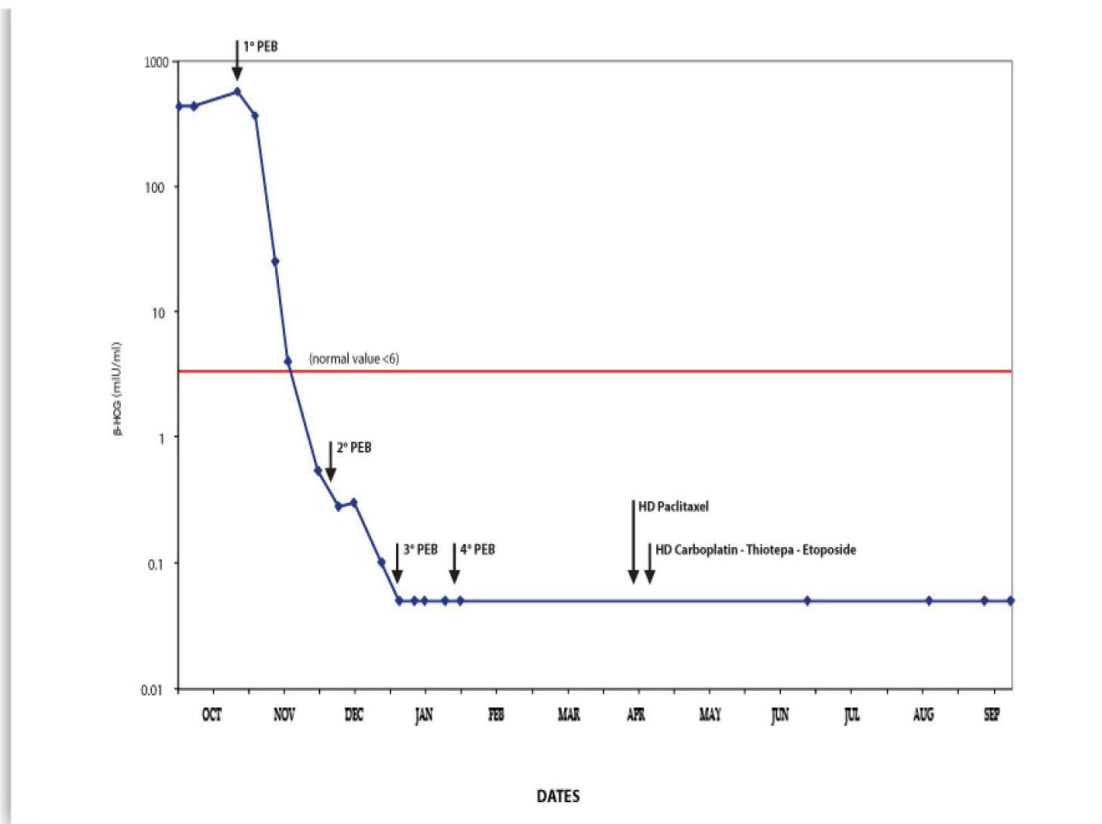


Figure 5. Linear graphs that illustrate the fluctuations of β -HCG.

ment as the α -fetoprotein and β -HCG levels were normalized. In **Figures 4 and 5** there are two linear graphs that illustrate the fluctuations of these tumor markers (α -fetoprotein and β -HCG respectively). Following this, and due to the persisting mass in the area, it was delivered radiotherapy. Two months later the patient was again admitted to hospital with signs of thrombocytopenia while she was in the process of steroid reduction. During her hospitalization she developed acute respiratory distress that necessitated her transfer to the intensive care unit of another hospital where she deceased 20 days later. During autopsy, a 2cm lesion was noted on the sellar region. Pathology showed residual neoplasm with morphological characteristics resembling craniopharyngioma (**Figures 6-8**). Foci of necrosis were also described, in the context of previous response to chemotherapy.

Discussion

The clinical condition of a young patient with an intracranial tumor found in the midline of the

brain, combined with increased levels of tumor markers, α -fetoprotein and human chorion gonadotrophin (β -HCG) either in blood or in the cerebrospinal fluid or in both, renders any other diagnosis quite improbable. As far as treatment is concerned, due to the great sensitivity (chemo-radiosensitivity) of intracranial germ cell tumors there is no indication for radical surgical operation. In addition, the administration of chemotherapy enables the reduction of the dosage and the field of radiation in order to prevent the serious side effects of radiation on the neuroaxis [9]. The clinical condition of the patient and the tumor markers are able to provide for a diagnosis without biopsy, thus obviating the need for stereotactic biopsy or any other kind of biopsy or surgical operation. Their prognosis is very good when chemotherapy is combined with radiotherapy [10].

This view has many supporters among researchers who, based on the existence of tumor markers in the serum and in the cerebrospinal fluid, supported the diagnosis as well as the follow up of the response to treatment while trying to

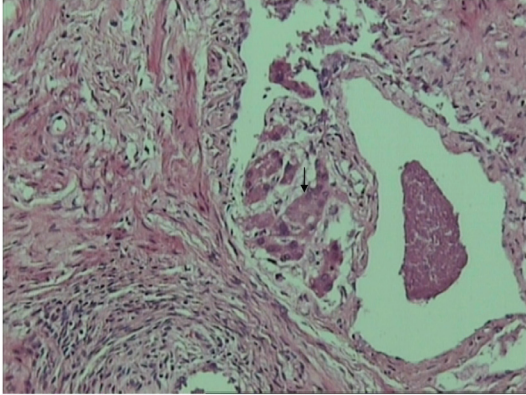


Figure 6. Pathological specimen of the residual lesion (black arrow) of craniopharyngioma (HE x100).

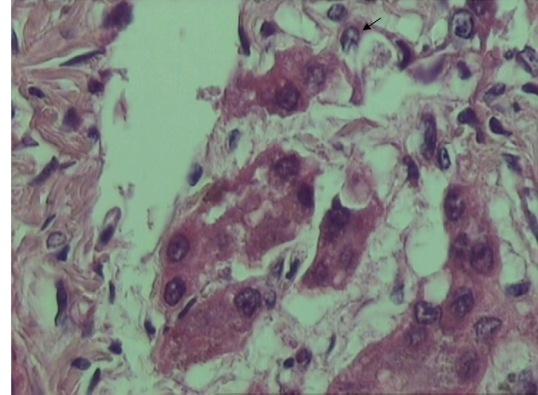


Figure 8. Pathological specimen of the residual lesion (Black Arrow) of craniopharyngioma (HE x400).

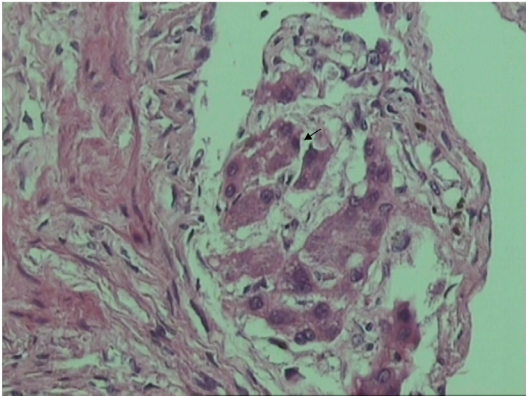


Figure 7. Pathological specimen of the residual lesion (black arrow) of craniopharyngioma (HE x200).

reduce radiotherapy due to the problems it creates [11]. German researchers announced the results of the MAKEI cooperative study [12]. This research analyzed the contribution of surgical operation, chemotherapy, and radiotherapy in the long term progress of malignant non-germinomatous germ cell intracranial tumors. The results showed that a surgical operation (full or incomplete) did not contribute much in overall survival, $p = 0,12$, while radiotherapy of the axis (brain and spinal cord) contributed significantly to survival $p = 0,035$ but at the cost of side effects. It was also proved that radiotherapy lacked prognostic capacity compared to the total dosage of cisplatin administered during chemotherapy. Specifically, cisplatin administration in doses larger or equal to $400\text{mg}/\text{m}^2$ of body surface was the main prognostic factor $p = 0,002$ for survival. In a publication of the same research group showed that despite the normalization of the tumor markers, tumor size

was not affected [13]. Treatment of intracranial germinomatous germ cell tumors relies mainly on radiotherapy, while the combination of chemotherapy and radiotherapy, is valid towards the direction of reducing the side effects of radiotherapy. On the contrary, chemotherapy is the main treatment of non-germinomatous intracranial germ cell tumors.

Even though the disease is sensitive to chemotherapy it remains with a low survival rate. Hence, there is a need for a more effective treatment and a possible role for high-dose chemotherapy followed by autologous stem-cell rescue. There are researches where the administration of high dosage of chemotherapy with cisplatin, etoposide and BCNU along with autologous stem-cell rescue and it has been proved by the Tada research team, while this treatment program is able to improve the long term survival rate of patients suffering from non-germinomatous germ cell brain tumors. Similar trials were conducted by the German cooperative research for testicular cancer, where high dose chemotherapy with carboplatin, etoposide and ifosfamide followed by autologous stem-cell rescue on patients with germ cell tumors that relapsed or were refractory showed that 24 out of 45 (53.3%) patients who suffered from a disease sensitive to chemotherapy had a survival rate of 50% in two years [15]. This study included also patients refractory to the treatment with bad prognosis, only one out of 23 survived without problems for 7 months. Consequently, high-dose chemotherapy followed by autologous stem-cell rescue may be used in cases of refractory or relapsed germ cell tumors with acceptable toxicity and it com-

prises an effective and potentially healing treatment. Margolin and his team came to the same conclusions [16].

It has been observed that in the area of sella turcica lie adjacent tumors of different histological origin. Thus, Oxford researchers published the case of a patient where two tumors coexisted, one being a gonadotrophic adenoma with craniopharyngioma and the other being a corticotrope adenoma with a cyst from the Rathke pouch [17]. Nada and his team announced the case of a patient in whom the first surgical tissue samples of a brain tumor were explained as craniopharyngioma [18]. Nevertheless, the clinical deterioration and the increasing tumor size led to a second operation where the histological examination of the new specimen showed areas of embryonic carcinoma and yolk sack tumors adjacent to squamous epithelium cysts, thus proving the diagnosis of mixed malignant germ cell tumors. It has to be stressed that the α -fetoprotein levels in the serum and the cerebrospinal fluid were very high. This shows that it is possible that craniopharyngioma may co-exist with other germ cell tumors or according to the view of disembryogenesis, craniopharyngioma may be one more element of this mass. Researchers at the Mayo clinic found remnant tumor on the epiphysis, after treatment for germ cell intracranial tumor, comprised of elements of mature teratoma [19]. Also Yagi and his team presented the case of a 16 year old girl with non germinomatous tumor of the neurohypophysis which was in the form of immature teratoma and received chemotherapy with the combination of ifosfamide, etoposide and cisplatin [20]. While the tumor markers were significantly reduced the tumor size increased after the chemotherapy. The histological examination of the tissue sample after the second surgical operation showed that it was a mature teratoma. Writers refer to the occurrence of the increasing teratoma syndrome, which is a very rare case of non-germinomatous germ cell intracranial tumor.

The above case is extremely rare in worldwide literature. The diagnosis of mixed malignant germ cell tumor with high serum α -fetoprotein proves the coexistence of craniopharyngioma with germ cell tumors and it has been proposed that craniopharyngioma may be part of a germ cell tumor in the context of dysembryogenesis and benign "teratoma".

Conflict of interest statement

The authors declare that they have no conflict of interest.

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