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# THIRD VENTRICLE TERATOMA WITH MALIGNANT TRANSFORMATION

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Intracranial germ cell tumors (GCTs) are rare and heterogeneous group of primary brain tumors, mainly affecting pediatric population and young adults. The current understanding of the etiology of intracranial GCTs and their optimal management strategies remain controversial. Treatment plans differ depending on the subtype GCT and may vary among physicians and institutions. Central nervous system non-germinomatous germ cell tumor (NGGCT) usually requires surgical resection with histological verification, chemotherapy, and radiation. The extent of surgical resection is an important prognostic factor alongside the etiology and genetics of NGGCT.

This article presents a rare clinical case of a rapidly growing teratoma located in the posterior part of third ventricle of a 17-year-old male presenting with symptoms of intracranial hypertension. Surgical total resection was preceded by endoscopic third ventriculostomy. Immunohistochemistry revealed the presence of embryonal carcinoma and immature teratoma cells turning the tumor into mixed type NGGCT with unfavorable prognosis. Despite the complete resection of the tumor and the timely initiation of adjuvant therapy, a rapid progression of the disease with subsequent unfavorable outcome was observed 3.6 months after the surgical treatment.

**Keywords:** intracranial germ cell tumor, non-germinomatous germ-cell tumor, teratoma with malignant transformation, intraventricular tumor

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## BACKGROUND

Germ cell tumors (GCT) of the central nervous system (CNS) are a rare and histologically heterogenous group of tumors primarily seen in children, teenagers, and young adults [1]. In children and teenager population, they comprise between 3 and 5 % of primary brain tumors with a higher incidence in some regions of Asia [2–4].

Germ cell tumors of the CNS are divided into pure germinomas and non-germinomatous germ cell tumors (NGGCT). NGGCT include the following histological variants: mature teratoma, immature teratoma, teratoma with malignant transformation, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and mixed GCT (containing 2 or more malignant components) [5].

Patients with germinomas have a more favorable prognosis with overall survival above 90 % while survival for NGGCT varies between 40 and 70 %. Treatment of pure germinomas includes conservative methods such as radiotherapy and chemotherapy; biopsy is required only in cases of negative test results for tumor markers. NGGCT require more intense therapy with maximally possible tumor resection in combination with radiation and chemotherapy. An exception is mature teratomas which are considered benign and require only surgical tumor resection [1, 5, 6].

We present a clinical case of a patient with mixed CNS-NGGCT histologically verified as teratoma with malignant transformation. Immunohistochemical profile was identified as mixed NGGCT with elements of embryonal carcinoma and immature teratoma. Clinically, the patient had a fast-growing aggressive space-occupying tumor of the posterior third ventricle.

## CLINICAL CASE

***Patient,*** *17 years, was hospitalized with symptoms of hypertensive hydrocephalus: headache, vomiting, sleepiness.*

*Contrast-enhanced magnetic resonance imaging (MRI) of the brain showed a round tumor in the posterior third ventricle, size 20 × 17 × 19 mm, with signs of cerebrospinal fluid (CSF) pathway blockage (Fig. 1). Preliminary differential diagnosis was performed taking into account characteristic clinical and radiologic picture of tumors of the posterior third of the third ventricle and pineal area (Table 1).*

*At the 1st stage, endoscopic third ventriculocisternostomy with simultaneous tumor biopsy were performed to relieve hypertensive hydrocephalus. As per standard technique, at the Kocher»s point trephination hole was made, perforation of the third ventricle floor was performed. In the posterior part of the third ventricle, anterior surface of the pinkish tumor with dense highly vascularized capsule was visualized. Attempts of biological material sampling were accompanied by hard to stop hemorrhage, and it was decided not to perform biopsy.*

*In the postoperative period, positive dynamics were observed. The patient was discharged with improvement without signs of hypertensive hydrocephalus; consultation of an oncologist at the place of residence, repeat planned hospitalization for open surgical intervention were recommended. However, 1 month after discharge the patient was urgently hospitalized due to significant deterioration of his condition (the recommended consultation with an oncologist was not performed). Contrast-enhanced MRI showed twofold growth of the tumor (48 × 40 × 36 mm) (Fig. 2). Neurological status evaluation showed moderate reduction of alertness at the level of stupor, Parinaud syndrome, short-term memory loss, moderate hypertension syndrome. Overall performance status per the Karnofsky scale was 60 %.*

*At the stage of surgical treatment selection, the deciding argument for open surgery was the presence of a highly vascularized capsule around the tumor. Anterior interhemispheric transcallosal interforniceal access on the right was performed. Whitish well vascularized tumor tissue with heterogenous solid and elastic structure was observed;*

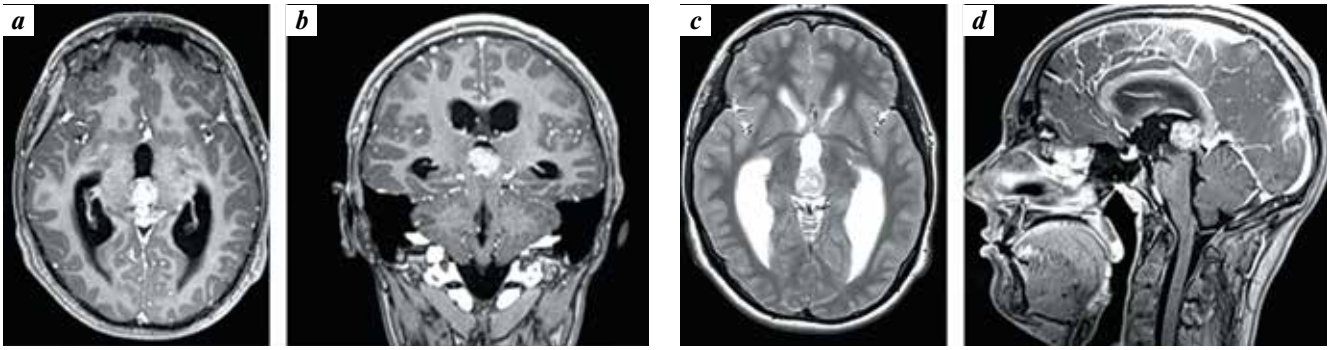


**Fig. 1.** *Brain magnetic resonance imaging with contrast-enhanced at admission. Well-defined irregular round shaped heterogeneous mass 20 × 17 × 19 mm in size with irregular enhancement post contrast administration is observed in posterior part of third ventricle. Signs of aqueduct compression resulting in obstructive hydrocephalus: a – axial T1-weighted imaging (WI): the tumor fills the posterior third ventricle; b – coronal T1-WI; c – axial T2-FLAIR: hydrocephalus signs (VCR-2 = 22 %), lateral ventricles occipital horns dilation and periventricular edema; d – sagittal T1-WI: cerebral aqueduct compressed by a tumor. Here and on Fig. 2–5: VCR-2 – ventriculocranial ratio-2*

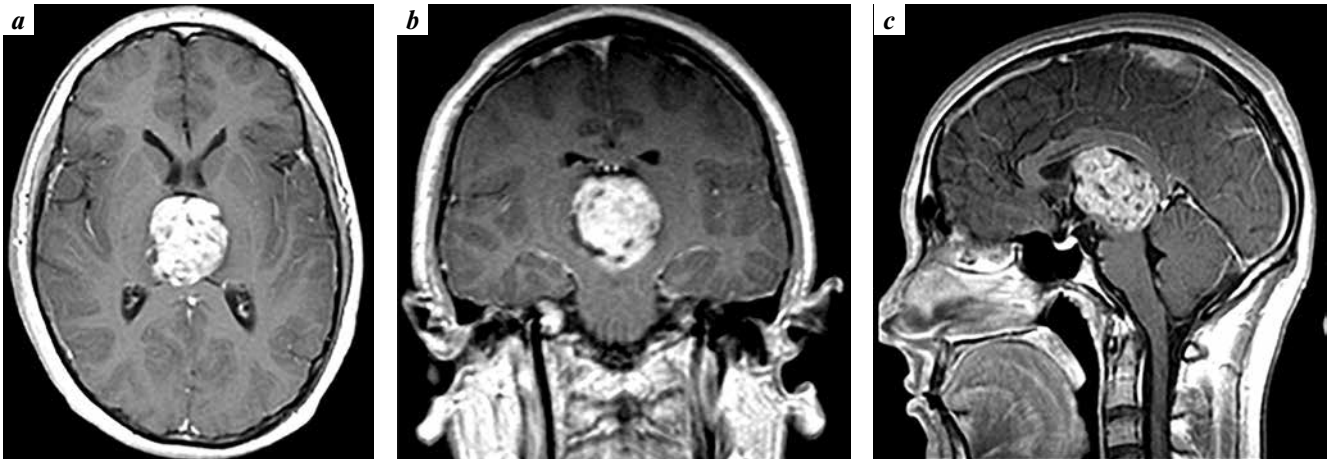


**Fig. 2.** *Brain magnetic resonance imaging with contrast enhancement 1 month post endoscopic third ventriculostomy following neurological deterioration (T1-weighted imaging): a – axial view; b – coronal view; c – sagittal view. Tumor size expansion. Rounded heterogeneous tumor of the third ventricle 48 × 40 × 36 mm in size, with irregular contrast enhancement. Tumor almost completely fills the entire third ventricle, pushes back and compresses the cerebral peduncles, thalamus and quadrigeminal plate. The lateral ventricles are not dilated (VKR-2 = 19 %)*

**Table 1.** *Tumors of the pineal region/posterior 3 rd ventricle*

| Tumor type | Radiological features | Male-female ratio | Patient's most common age | Growth/ progression rate | Most common tumors |
|---|---|---|---|---|---|
| Germinoma | CT: homogeneous hyperdense mass with uniform intense enhancement. MRI: isointense on T1-WI, hyperintense on T2-WI and FLAIR, restricted diffusion due to high cellularity. Dissemination along cerebrospinal fluid pathways and invasion into surrounding structures is common | 10:1 | Adolescence/ young | Slow | 50 % |
| Teratoma | A heterogeneous mass consisting of adipose tissue, soft tissue components, calcifications, and cystic elements. Hyperintense signal from the fatty components on T1-WI, the soft tissue component is iso-/hyperintense on T2-WI, with restricted diffusion observed in the soft tissue components | 2:1 | Early adulthood | Variable | Up to 20 % |
| NGGCT | The radiological characteristics may vary. CT: a heterogeneous mass with intense contrast enhancement, possibly containing cystic components and signs of hemorrhage. MRI: hypo-/isointense appearance on T1-WI, iso-/slightly hyperintense on T2-WI, with solid components showing hyperintensity on FLAIR and exhibiting restricted diffusion | 14:1 | Adulthood | Variable | Up to 10 % |
| Pineoblastoma | A highly aggressive, large-sized, heterogeneous mass with intense contrast enhancement. CT: a hyperintense mass with peripheral calcifications. MRI: a heterogeneous mass with necrosis/hemorrhage areas and cystic components. Significant mass effect. | 1:1 | Early childhood | Rapid | Up to 5–10 % |
| Primitive neuroectodermal tumor | A heterogeneous mass with heterogenous contrast enhancement. Minimal peritumoral edema. Diffusion restriction is common, along with signs of hemorrhage and necrosis. Calcifications are present in 50–70 % of cases. Invasion into surrounding structures and leptomeningeal dissemination are common (identified on post-contrast FLAIR images) | 1:1 | Childhood | Rapid | Up to 5–10 % |
| Papillary tumor of pineal origin | Cystic mass with enhancing solid component. CT: hyperdense mass, embedding pineal gland calcifications. MRI: heterogeneous iso-/hypointense mass with lobular architecture, characterized by intense contrast enhancement by solid component | 1:1 | Young adulthood | Variable | Up to 1–5 % |

***Note.*** *NGCO – non-germinous germ-cell tumor; CT – computed tomography; MRI – magnetic resonance imaging; T1-WI – T1-weighted imaging; T2-WI – T2-weighted imaging.*

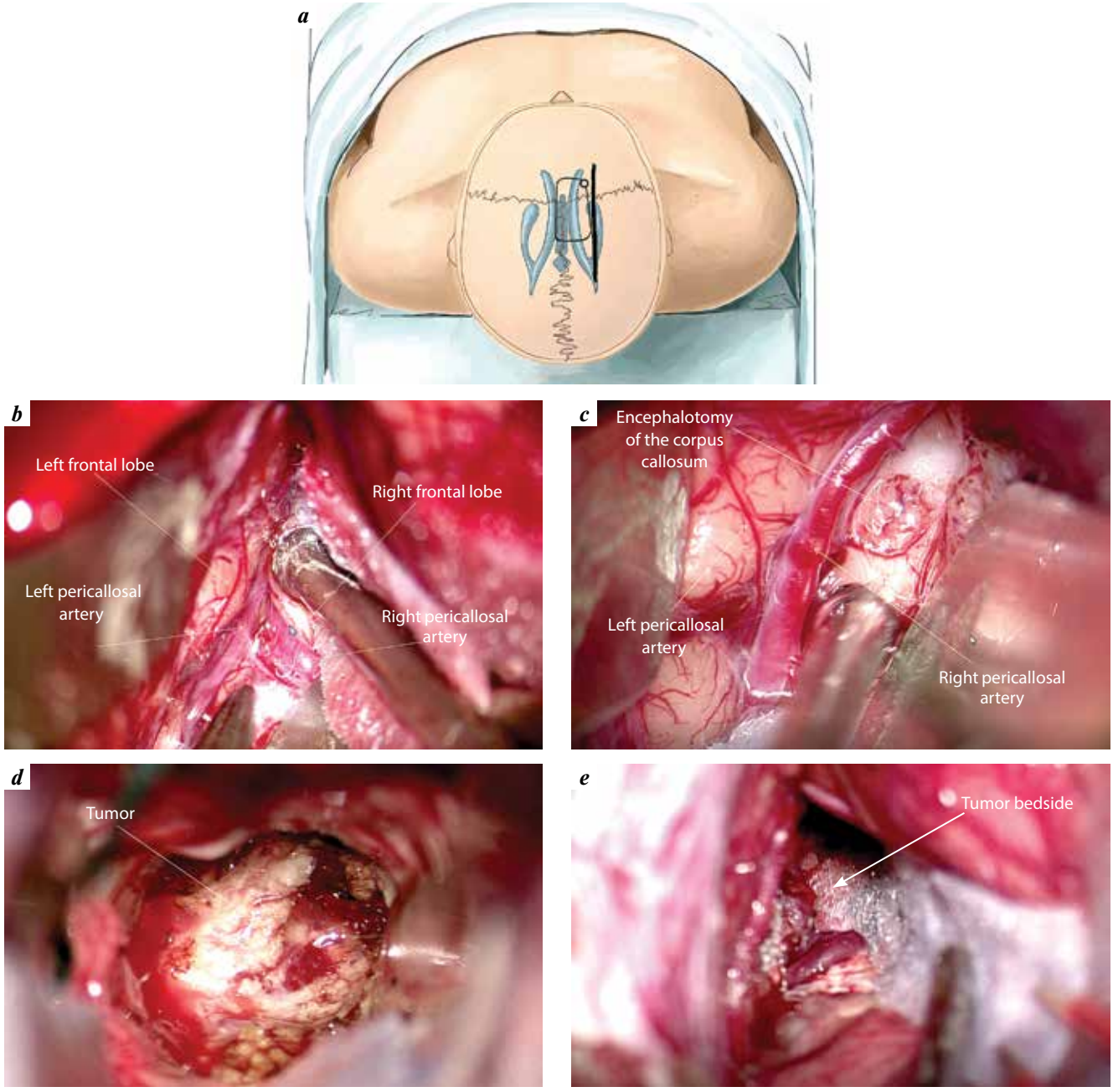


**Fig. 3.** *Schematic view of the surgical approach (a) and intraoperative images (b–e): a – skin incision and craniotomy; b, c – stages of surgical approach to the tumor; d – tumor in the cavity of the third ventricle; e – total resection of the tumor, residual tumor is not detected*

*marked adhesion to both thalami was noted (Fig. 3). The tumor was resected in fragments, totally. Final hemostasis was performed using SurgiFlo topical hemostatic matrix. For control of resection radicality and evaluation of third ventricle floor perforation, endoscopic revision was performed. Visually, no signs of residual tumor fragments were observed. Perforation of the third ventricle formed during previous surgery was functioning. In the third ventricle cavity, ventricular drain to the skin through a counterincision was installed. All operative stages were performed using frameless neuronavigation with neurophysiological monitoring.*

*According to the control spiral computed tomography of the brain performed on 1 day after surgery, the tumor was resected, no postoperative hemorrhagic/ischemic changes or CSF circulation abnormalities were observed (Fig. 4). The patient was transferred to the general ward on day 2 after surgical intervention, ventricular drain was removed on day 3, the patient was mobilized. During early postoperative rehabilitation unstable gait was observed which disappeared at the time of discharge.*

*The patient was discharged on day 14 after surgery in satisfactory condition with partial regression of diplopia,*

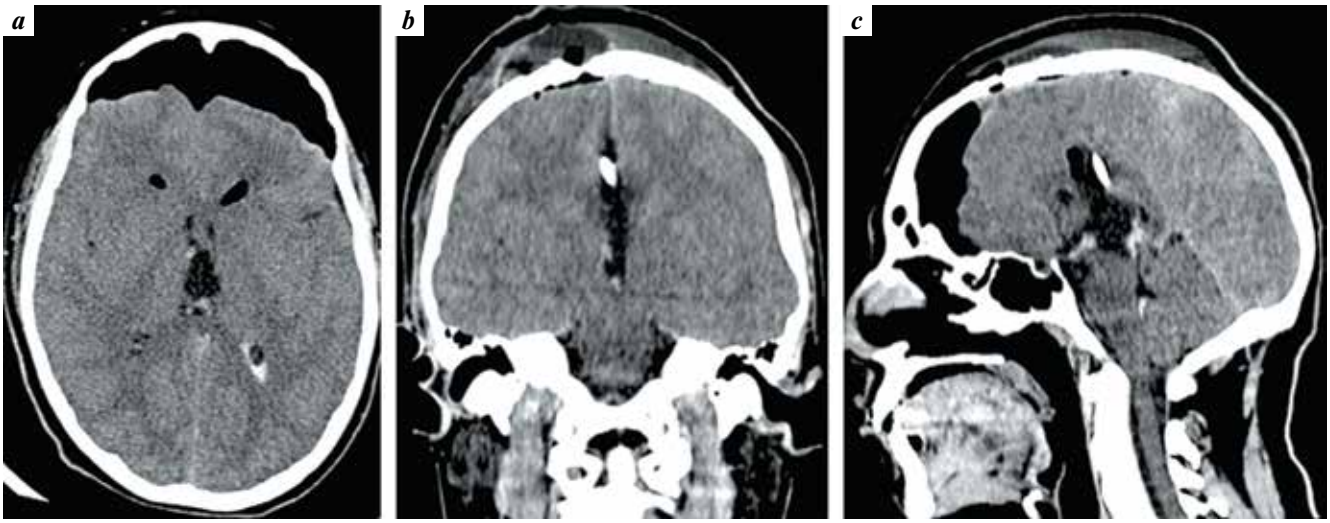


**Fig. 4.** *Brain multi-spiral computed tomography, post-operative day 1: a – axial view; b – coronal view; c – sagittal view. Total resection of the tumor. Post-operative no tension pneumocephalus. Ventricular drainage was inserted in the cavity of the third ventricle. There are no signs of hemorrhagic, ischemic complications. The lateral ventricles are not dilated, VKR-2 = 15 %*

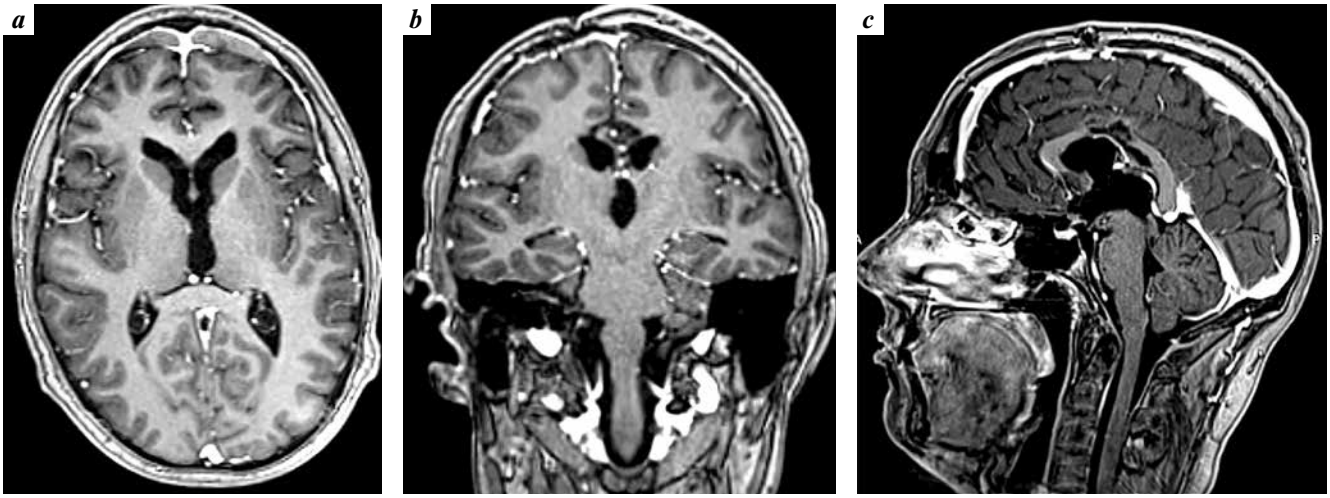


**Fig. 5.** *Brain magnetic resonance imaging with contrast enhancement 3 months post operative (T1-weighted imaging): a – axial view; b – coronal view; c – sagittal view. Total resection of the tumor. There are no signs of hydrocephalus, VKR-2 = 16 %*

*Parinaud syndrome. Karnofsky performance status improved and was evaluated as 80 %.*

*Histological examination showed teratoma with malignant transformation. Immunohistochemical examination of the histological material showed presence of embryonal carcinoma and immature teratoma cells. Tumor markers in blood tested 2 weeks after surgery were in the normal range (α-fetoprotein was 3.91 ng/mL, β subunit of human chorionic gonadotropin was 1.7 mIU/mL); contrast-enhanced computed tomography of the whole spine did not show any metastases. After consultation with an oncologist, 4 courses of 1st line chemotherapy per the SIOP CNS GCT II protocol were performed; radiotherapy was planned as the next stage.*

*During chemotherapy 3 months after discharge from the hospital, the patient's condition was considered stable. Serum tumor markers remained in the reference ranges. Contrast-enhanced control MRI of the brain did not show any signs of recurrence (Fig. 5). Contrast-enhanced computed tomography of the whole spine, thoracic organs, abdominal organs, pelvic organs also did show any signs of metastases.*

*In the 4th month after surgical intervention at examination before the start of radiotherapy, tumor marker elevation was observed: α-fetoprotein was 278 mg/mL, 1 month later it was 712 ng/mL. Positron emission tomography/computed tomography showed distant tumor seeding through the ventricular system with leptomeningeal lesions in the brain and cervical spine. MRI 6 months after surgery showed space-occupying lesion in the third ventricle near hypothalamus and pellucid septum. 2nd line chemotherapy was started during which tumor marker values decreased but did not reach reference values. Considering local and distant metastatic lesions in the CNS, chemotherapy, radiotherapy and surgical*

*treatment were not indicated. The patient was discharged from the oncology clinic with recommendations for symptomatic therapy. At discharge, Karnofsky performance status was 40 %, ECOG status was 3.*

## DISCUSSION

Currently, a universal standard for CNS-NGGCT treatment does not exist. Oncologists from various countries and regions (USA and Canada (Children's Oncology Group (COG)), Europe (International Society of Pediatric Oncology (SIOP)), Société Française d'Oncologie Pediatrique (SFOP) and Asia) use their own diagnostic criteria and treatment protocols.

However, the necessity of integrated approach to CNS-NGGCT is universally accepted. Data obtained through multicenter North American and European trials indicate that multimodal therapy including chemotherapy, maximally safe surgical resection and radiotherapy allow to achieve 5-year overall survival in patients with CNS-NGGCT between 82 and 92 % [6–8]. Similar results were obtained in Asian studies were 5-year event-free and overall survival values were 78.2 and 85.4 %, respectively [7].

It should be noted that 5-year survival of patients who received only full-dose craniospinal radiotherapy or only chemotherapy was significantly lower: 20–40 % [8–12]. It is important to emphasize that questions associated with radiotherapy volume and regimen remain a point of contention between European and North American protocols.

Integrated therapy does not always ensure successful treatment. In some patients with malignant intracranial CNS-NGGCT, response to therapy can be absent, progression during treatment or recurrence after completion of therapy are observed [13, 14]. Ineffectiveness of therapy is observed in 30–35 % patients with intracranial NGGCT [15–17]. Patients with CNS-NGGCT who do not respond to therapy comprise a significant percentage of cancer mortality rates in pediatric and especially adolescent age groups [18].

A study aimed at investigating the causes of unfavorable outcome in patients with CNS-NGGCT was performed by a group led by A. Fonseca. Clinical trials performed in Europe and North America in a timespan of 30 years were analyzed. In the cohort of patients included in prospective studies, treatment ineffectiveness was observed in 95 (23.5 %) of 404 cases. The authors identified 3 types of therapy ineffectiveness: disease progression, growing teratoma syndrome, and disease recurrence. Disease progression was defined as decline during therapy (in the first 6 months after diagnosis). Growing teratoma syndrome was characterized by radiological progression with simultaneous normalization of tumor marker levels and histologically conformed presence of primarily mature teratoma components. Disease recurrence was defined as an event which happens after completion of therapy [19].

Most frequently, therapy ineffectiveness was manifested as disease recurrence (70 % of cases) with median time between treatment completion and recurrence 14 (9–28) months; disease progression was significantly rarer (~20 % patients); and the rarest type was growing teratoma syndrome (~9 % patients) which usually was observed in younger children.

Comparing the case of our patient with patient data described in the A. Fonseca et al. study [19], we found similarities in multiple characteristics but also identified parameters not included in the general description. Male sex, adolescent age, and progressive increase in tumor marker levels correspond to the general characteristics of the subgroup. Additionally, in the disease progression group the majority of tumors (69.3 %) had mixed structure (2 or more malignant components). Mean time to progression was 5 months. The majority of patients with disease progression (87.5 %), like the patient in our case, did not get the chance to undergo radiotherapy (due to disease progression). Inconsistencies were observed in the following aspects. Our patient had atypical combination of local progression with local, leptomeningeal and spinal metastases which indicated more aggressive disease with unfavorable prognosis. Signs of metastasis at time of diagnosis in the A. Fonseca et al. study were observed in most cases (95.8 %) [19] which is different from our patient for whom imaging of the whole neuroaxis did not show signs of recurrence or metastasis for 3.5 months after surgical treatment.

In the context of disease recurrence, metastatic recurrences usually manifested sooner than local recurrences. Supposedly, this indicates the presence of a specific mechanism of therapy resistance and treatment ineffectiveness. Investigation of possible risk factors associated with metastatic recurrences did not identify any significant correlation with the following factors: age, sex, primary tumor location, tumor marker level at diagnosis, histological conclusion, radiotherapy volume, or therapeutic protocol used [19].

In the patient in our observation, disease progression was observed despite total tumor resection and 1st line chemotherapy shortly after. According to the immunohistochemical conclusion (embryonal carcinoma and immature teratoma according to the M. Matsutani et al. [4] classification), the patient was ascribed to the unfavorable prognosis group with high risk of tumor dissemination through subarachnoid spaces and spinal metastasis. Significant growth of tumor size in a short timespan also indicated high aggressiveness of tumor process.

According to the results of the A. Fonseca et al. study [19], disease progression of intracranial CNS-NGGCT can be caused by secreting tumor components responsible for resistance to therapy. In cases of mixed NGGCT, such as embryonal carcinoma and immature teratoma, as in the presented case, it is hard to identify which tumor component is the secreting one and responsible for resistance to therapy; this requires a more detailed

immunohistochemical examination with isolation of cell lines.

Personalized and targeted therapies based on unique molecular and genetic tumor characteristics are potential methods of overcoming resistance to treatment. Possibly, among the new approaches in modern oncological practice such as molecular targeted therapy, immune checkpoint inhibitors, angiogenesis inhibitors, epigenetic and hormone therapy, approaches capable of changing the current unfavorable statistics and give hope for patients with CNS-NGGCT will be found. An example is the study by J.K. Woods et al. [20] in which after successful treatment of mixed CNS-NGGCT with dominant choriocarcinoma component, archival data on patients with CNS-NGGCT were re-evaluated. Re-evaluation confirmed expression of PD-1 and PD-L1 (programmed cell death protein 1 and its ligand, respectively) in CNS-NGGCT cells indicating their immune activity. This allows to explain the effectiveness of immunotherapy with PD-1/PD-L1 inhibitors – immune checkpoint inhibitors. The number of such studies is currently small but further analysis and large trials could help implement new methods with proved effectiveness in cases of unsuccessful treatment using current therapeutic protocols.

## CONCLUSION

Non-germinomatous germ cell tumors of the CNS are rare in clinical practice. Despite improved treatment results due to modern multimodal protocols, 17–35 % of patients do not respond to integrated therapy, as in the case described here, which leads to a severely unfavorable prognosis even with total tumor resection, chemotherapy and radiotherapy.

Further studies aimed at understanding the mechanisms of resistance and biomolecular characteristics of CNS-NGGCT could significantly improve treatment results and prognosis in patients with disease progression even with standard therapy. Implementation of new therapeutic treatment approaches such as immunotherapy could become a promising way to overcome ineffectiveness of standard treatment methods.

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V.A. Gorozhanin: data collection for analysis, analysis of publications on the topic of the article, patient monitoring;
T.A. Shatokhin, V.A. Lukyanchikov: data analysis, scientific consulting, scientific editing.

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