Clinical Case Study

Complex Treatment of A Rare Non-Germinomatous Germ Cell Optic-Chiasmal Brain Tumor In An Adolescent Child-A Clinical Case With Literature Review

Lena Marinova*, Vaska Vasileva, Nikolay Kahchiev, Katia Sergieva

Department of Radiation Oncology and Metabolic Brachytherapy, Medical Oncology Clinic, UMHAT “Queen Joanna” Sofia, Bulgaria.

*Corresponding Author
Lena Marinova, Department of Radiation Oncology and Metabolic Brachytherapy, Medical Oncology Clinic, UMHAT “Queen Joanna” Sofia, Bulgaria.

Submitted: 29 Mar 2024; Accepted: 08 Apr 2024; Published: 20 Apr 2024

Citation: Marinova L, Vasileva V, Kahchiev N, Sergieva K (2024) Complex Treatment of A Rare Non-Germinomatous Germ Cell Optic-Chiasmal Brain Tumor In An Adolescent Child-A Clinical Case With Literature Review. Medical & Clinical Research 9(4), 01-08.

Abstract
Non-germ cell tumours (NGCTs) are rare intracranial neoplasms occurring in adolescents and young adults. A multidisciplinary team including a neurosurgeon, oncologist, radiologist, pathohistologist, ophthalmologist, pediatric oncohematologist, neurologist and endocrinologist is required for diagnosis and treatment.

We present a rarely diagnosed optic-chiasmal non-germinomatous germ cell tumour (NGGCT) in a 16-year-old boy, accompanied by pituitary insufficiency (diabetes insipidus and central hypothyroidism) and severely impaired vision bilaterally. The immunohistochemistry (IHC) of the tumor biopsy, as well as the level of tumor markers (human chorionic gonadotropin and alpha-fetoprotein) in the serum and cerebrospinal fluid are significant factors for determining the diagnosis-germ cell or non-germ cell cranial tumor. Because the tumor was inoperable, we performed 3 courses of neoadjuvant chemotherapy followed by definitive radiotherapy to a total tumor dose of 55 Gy.

In such rare childhood brain tumors, complex treatment achieves long-term local tumor control, requiring long-term monitoring by an ophthalmologist and endocrinologist.

Keywords: Cranial Non-Germinomatous Germ Cell Tumors, Tumor Markers, Chemotherapy, Radiotherapy, Complex Treatment

Introduction
Intracranial germ cell tumors (IGCTs) are a group of rare pediatric brain tumors which include various subtypes [1]. In Western countries, IGCT accounts for approximately 3-5% of all primary brain tumors in children [2,3]. Non-germinomatous germ cell tumours (NGGCT) are rare intracranial tumours occurring in adolescents and young adults [4]. The immunohistochemistry of the tumor biopsy, as well as the level of tumor markers (human chorionic gonadotropin and alpha-fetoprotein) in the serum and cerebrospinal fluid (CSF) are significant factors for determining the diagnosis -germ cell or non-germ cell cranial tumor. The more common localization of the rare intracranial NGGCT predominantly seen in the pineal and suprasellar regions and account for 1% to 3% of cases [5,6]. An initial evaluation with neuroimaging, tumor markers, cytology from CSF, and biopsy is a must to distinguish further treatment and prognosis [7]. A multimodal approach was effective for treating NGGCTs [8]. We present a rarely diagnosed optico-chiasmal NGGCT in a 16-year-old boy with thrombosis of dural venous sinuses after one course of chemotherapy (Ch), accompanied by pituitary insufficiency (diabetes insipidus and central hypothyroidism) and severely impaired vision bilaterally.

Clinical Case
It concerns a 16-year-old boy, born from a first normal pregnancy and delivery by operative route/elective section, due to breech presentation. Uncomplicated neonatal period with proper physical and neuropsychological development. The boy has no evidence of allergies to food or medication. The current complaints date back to 1 year, when the parents noticed that the boy increased the amount of fluids taken in and excreted many times, including at night, reaching 6-7 liters in total per day. In September 2022, on the occasion of progressive loss of vision, after consultation with a neuro-ophthalmologist, an MRI of the brain was performed, which established an infiltrative tumor in the diencephalon with involvement of the optic chiasm. Suprasellar MRI visualizes
a lumpy mass with predominant intermediate signal intensity, slightly inhomogeneous obliterating the intrasellar brain structures. Its cranio-caudal dimension is 2.5 cm along with its intrasellar contents/confluent with the pituitary gland (Figure 1). Cranially compresses the hypothalamus, involves the right optic tract to a greater extent than the left, forming a cystic area in the left optic tract. It generally extends from the anterior commissure to the mammary bodies without involving any of these structures, but the supra-optic recess is almost annihilated by the mass. In the diffuse analysis, it has signs of hypercellularity, and after contrast with an intravenous bolus, it moderately and slightly inhomogeneously shortens its T1 relaxation. No evidence of other changes in the brain structures and extra-axially below and above the tentorium, except for a small cystic lesion in the pineal gland - 6.7 mm, which did not affect the cerebrospinal fluid flow along the Sylvian aqueduct. Conclusion- Imaging data for optic-chiasmal glioma (Figure 2). A brain biopsy after right-sided parietal craniotomy was performed with the following histopathological examination: Small fragments of a tumor composed of large atypical cells with pale eosinophilic cytoplasm and round vesicular cells. Moderately expressed lymphoid infiltrates are also reported. The neoplastic cells are partially separated by fine fibrous septa.

Immunohistochemistry: Positive reaction for CD 117 and for placental alkaline phosphatase (PLAP), negative reaction for EMA, Chorionic gonadotropin- positive reaction in single syncytiotrophoblast cell elements, OCT ¾ - positive nuclear expression in tumor cells, Ki 67-25% proliferative activity.

Conclusion

Germ Cell Brain Tumor: A pediatric endocrinologist was consulted.

From the studies: LH<0.1 mIU/ml, FSH<0.11 mIU/ml, Prolactin 59.24 ng/ml (3.39-27.82), E2 67 pg/mlq Testosterone 7.7 ng/ml , TSH 3.569 micro IU/ml, Cortisol morning 0.4 µg/dl, afternoon 0.1 µg/dl. As a result of the above tests, diabetes insipidus and central hypothyroidism were diagnosed, requiring treatment with Minirin tablets and L-thyroxine tablets. In October 2022, a biopsy of the tumor was performed with the histological result of a germ cell tumor of the central nervous system, immunohistochemically positive for CD 117, PLAP, OCT ¾, as well as for chorionic gonadotropin in single syncytiotrophoblastic elements. The solid area is positive for OCT3/4 and CK117. These findings supported a diagnosis of mixed germ cell tumor with yolk sac carcinoma.

The proliferative index Ki 67 is 25%. In November 2022, the boy is in a satisfactory general condition, with severely impaired vision bilaterally without other abnormalities in the somatic status. Lumbar puncture shows no tumor cells in the cerebrospinal fluid, but elevated tumor markers: total beta-HCG 1045 mIU/ml, alpha-Fetoprotein AFP 26.70 ng/ml. An MRI of the spine is scheduled. Because of the increased tumor markers in the cerebrospinal fluid, it was judged to be a non-germinoma germ cell brain tumor. According to the recommendations of the SIOP CNS GCT 2001 protocol, it was decided to conduct 3 courses of chemotherapy (Ch) according to the Cisplatin, Etoposide and Ifosfamide (PEI) scheme. After one course of Ch, due to headache, vomiting and drop in arterial pressure, MRI of the head with contrast reported evidence of thrombosis of dural venous sinuses with stasis of cortical veins on the convexity of both large hemispheres and in the cortex and subcortical white matter of the brain. Low molecular weight heparin therapy was started, which was subsequently switched to rivaroxaban. MRI after completing 3 courses of chemotherapy/ data on reverse development of thrombosis of dural venous sinuses with stasis of cortical veins on the convexity of the two large hemispheres. Data on reverse development of tracked parenchymal changes in the cortex and subcortical white matter of the left frontal lobe (Figure 3). The boy was referred for definitive radiation therapy to the area of the brain tumor. Intensity modulated radiotherapy (IMRT) using the VMAT method was performed. Target volumes are contoured after fusion of MRI and planning CT (Figure 4). IMRT by the VMAT method covers two target volumes, namely the tumor and the left optic pathway including the left optic nerve and the left retina up to a total dose (TD) 55 Gy with a daily dose (DD) 2.2 Gy and an insurance zone around the tumor of size 0,7 cm up to a TD 50 Gy with a DD 2 Gy, realized in 25 daily fractions, 5 times a week (Figure 5). Radiotherapy (RT) was performed against the background of endocrine replacement therapy. We did not observe any acute radiation reactions during the radiation treatment. After 1 year from completion of radiotherapy, the child is in good general condition, without neurological symptoms. The boy is being monitored by an endocrinologist and a neurosurgeon, but lives with his parents in Germany. According to the mother, the last MRI performed in February 2024 reported achieved local tumor control, without the presence of a vital tumor. After RT, the visual acuity of the left eye improved, while that of the right eye is limited to seeing light. Endocrine replacement therapy continues.
**Figure 1:** Suprasellar MRI visualizes a lumpy mass with predominant intermediate signal intensity, slightly inhomogeneous obliterating the intrasellar brain structures. Its cranio-caudal dimension is 2.5 cm along with its intrasellar contents/confluent with the pituitary gland.

**Figure 2:** A) Axial MRI and B) Sagittal and frontal MRI-The lumpy mass cranially compresses the hypothalamus, involves the right optic tract to a greater extent than the left, forming a cystic area in the left optic tract. It generally extends from the anterior commissure to the mammary bodies without involving any of these structures, but the supra-optic recess is almost annihilated by the mass. In the diffuse analysis, it has signs of hypercellularity, and after contrast with an intravenous bolus, it moderately and slightly inhomogeneously shortens its T1 relaxation.
Figure 3: Axial MRI after completing 3 courses of chemotherapy/data on reverse development of thrombosis of dural venous sinuses with stasis of cortical veins on the convexity of the two large hemispheres. Data on reverse development of tracked parenchymal changes in the cortex and subcortical white matter of the left frontal lobe.

Figure 4: Contouring of the target volumes after fusion of the MR image and that of the planning CT. A) Axial; B) Coronal.
**Discussion**

Germ cell tumors (GCTs) of the central nervous system (CNS) are classified according to the World Health Organization (WHO) into pure germinomas and non-germinomatous germ cell tumors (NGGCTs) on the basis of clinicopathological and laboratory features, including tumor markers [9-11]. In the United States, the overall GCT incidence is 0.6 per million per year while 1.0 per million per year in Europe and 2.7 per million per year in Japan [12]. The natural history of primary intracranial germ-cell tumors (GCT’s) is defined from 389 previously published cases, of which 65% were germinomas, 18% teratomas, 5% embryonal carcinomas, 7% endodermal sinus tumors, and 5% choriocarcinomas. Intracranial GCT’s display specificity in site of origin [13]. Alternatively Japanese classification of GCT subtypes is separated into good, intermediate, and poor prognosis groups [14]. Patient's clinical presentation varies by location and size including visual changes and signs of increased intracranial pressure. Parasellar germinomas commonly present with diabetes insipidus, visual field defects, and hypothalamic-pituitary failure [13]. Differentiating pure germinomas from NGGCTs is crucial because treatments and prognoses are quite different. Without a positive tumor marker result, a biopsy is required for a definitive diagnosis [12].

**Imaging diagnostics:** On MRI, NGGCTs usually appear isointense to hyperintense, with localised hypointensity and heterogeneous enhancement [15]. The following MRI data are reported for the child we are presenting: Suprasellar MRI visualizes a lumpy mass with predominant intermediate signal intensity, slightly inhomogeneous obliterating the intrasellar brain structures. Its cranio-caudal dimension is 2.5 cm along with its intrasellar contents/ confluent with the pituitary gland (Figure 1). It has signs of hypercellularity, and after contrast with an intravenous bolus, it moderately and slightly inhomogeneously shortens its T1 relaxation (Figure 2).

**Immunohistochemical analysis:** In the presented rare intracranial tumor, we must first discuss the differential diagnosis between a germinoma and a non-germinoma tumor. If a biopsy is possible, an immunohistochemical examination of the tumor cells for CD 117, PLAP, OCT ¾, as well as for chorionic gonadotropin and the proliferative index Ki 67 is required. In our clinical case, the immunohistochemical analysis of the biopsy material showed that the solid area is positive for OCT3/4 and CK117. These findings supported a diagnosis of mixed germ cell tumor with yolk sac carcinoma. AFP and beta-hCG from CSF are more sensitive than serum, and both should be obtained in the absence of clinical contraindication [7].

**Tumor markers:** The relative increase in hCG and AFP values at the serum and/or CSF level is also of fundamental importance not only for diagnosis, but also for monitoring the response to treatments and follow-up, even in the absence of histological data [16]. According to the standards of the international society...
The SIOP-CNS-GCT-96 (NCT00293358) trial employed involved whole-brain RT (WBRT) (20-36 Gy) or focal RT (50.4-54 Gy) [8]. Seven patients received CSI with a median of 36 Gy (range, 20-41 Gy) plus focal boost of 18-30.6 Gy, and 5 patients received IMRT covering the tumor volume and the zone around the tumor of size 1 cm up to a TD 55 Gy with a DD 2.2 Gy and an insurance dose (TD) 55 Gy with a daily dose (DD) 2 Gy, realized in 25 daily fractions, 5 times a week (Figure 4 and Figure 5). Due to tumor infiltration of the right optic tract and optic chiasm, the vision of the right eye was completely restricted, and hemianopsia was reported in the left eye. This led us to include the left optic nerve in the tumor volume, where we could achieve a high total dose of 55 Gy with a coverage area of 0.7 cm up to 50 Gy. The boy tolerated radiation therapy well without acute radiation reactions on the part of the CNS. One year after radiation therapy, improved vision in the left eye was noted, with no improvement in the right vision, limited to light perception only. On endocrine replacement therapy, MRI showed local tumor control. A significant proportion of children with central nervous system (CNS) germ cell tumors (GCTs) present with endocrinopathies, including diabetes insipidus and panhypopituitarism. In most cases, these endocrinopathies are permanent despite tumor control, and patients will need continuous hormone replacement therapy [36,37].

Conclusion

We present an extremely rare NGGCT in a 16-year-old boy. The diagnosis of these tumors is extremely important to determine the necessary complex treatment strategy. A biopsy followed by immunohistochemistry of the tumor cells, as well as determination of the level of the tumor markers alpha-fetoprotein and beta-human chorionic gonadotropin in the serum and cerebrospinal fluid is required. A multidisciplinary team including a neurosurgeon, oncologist, radiologist, pathohistologist, ophthalmologist, pediatric oncohematologist, neurologist and endocrinologist is required for diagnosis and treatment. The treatment includes 2-3 courses of chemotherapy according to the PEI scheme (Cisplatin, Etoposide, Ifosfamide, and Bleomycin) [31,32].
and Ifosfamide), followed by local radiotherapy with doses higher than 50 Gy. Long-term follow-up by an ophthalmologist and hormone replacement therapy under the guidance of an endocrinologist are required.

References
10. WHO Classification of Tumours Editorial Board, ed. (2021) WHO Classification of Tumours: Central Nervous System Tumours. Vol. 6. 5th ed. IARC.
29. Calaminus G, Bamberg M, Jürgens H, Kortmann RD,


