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Clinical Case Study

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

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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-cranial GCT or cranial NGCT. 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 mlU/ml, FSH<0.11 mlU/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 mlU/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 is improved, while that of the right eye is limited to seeing light. Endocrine replacement therapy continues.

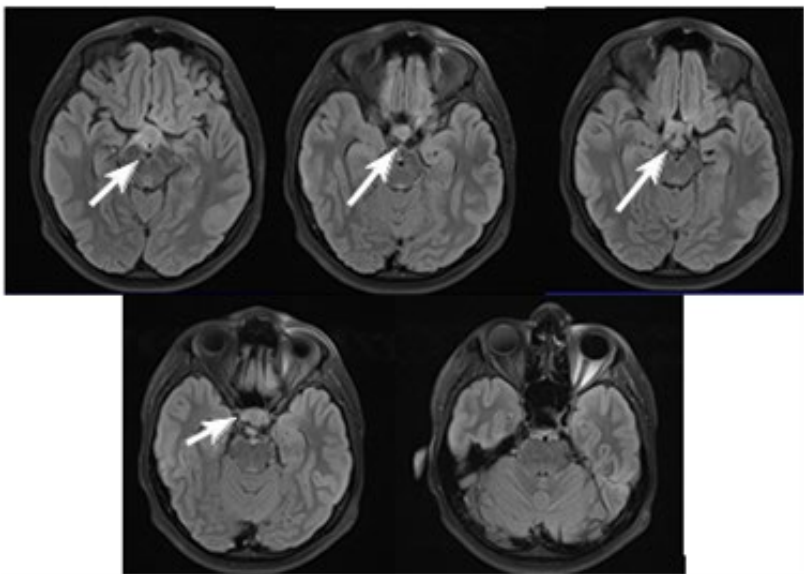

Figure 1: Suprasellar MRI visualizes a lumpy mass with predominant intermediate signal intensity, slightly inhomogeneous obliterating the intrasellar brain structures. Its cranio-caudal dimension is 2.5 cm along with its intrasellar contents/confluent with the pituitary gland.

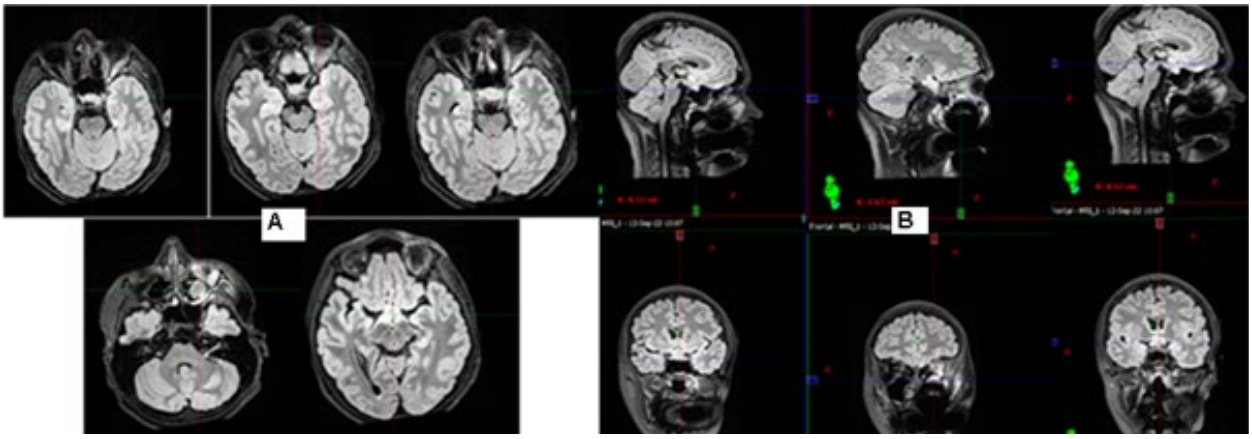

Figure 2: A) Axial MRI and B) Sagittal and frontal MRI-The lumpy mass cranially compresses the hypothalamus, involves the right optic tract to a greater extent than the left, forming a cystic area in the left optic tract. It generally extends from the anterior commissure to the mammary bodies without 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.

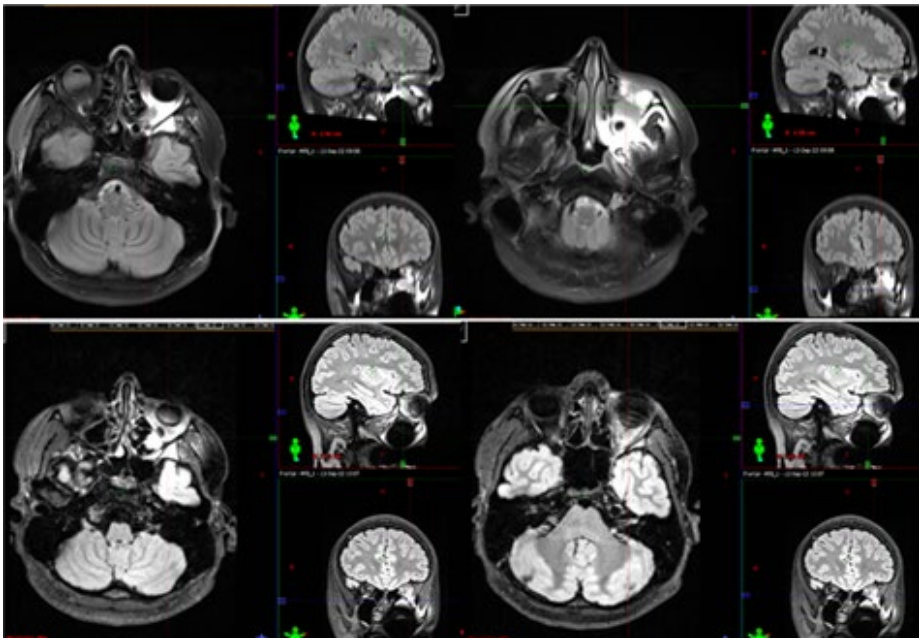

Figure 3: Axial MRI after completing 3 courses of chemotherapy/data on reverse development of thrombosis of dural venous sinuses with stasis of cortical veins on the convexity of the two large hemispheres. Data on reverse development of tracked parenchymal changes in the cortex and subcortical white matter of the left frontal lobe.

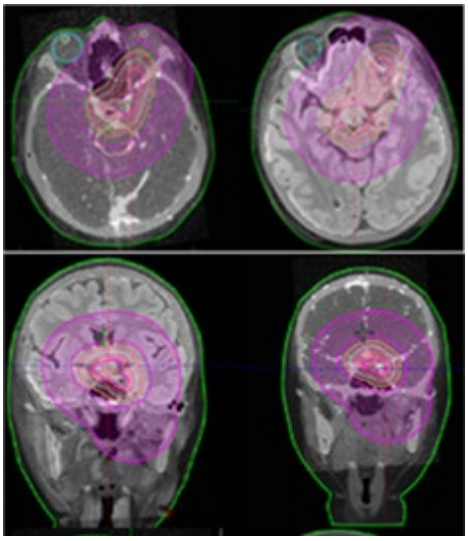

Figure 4: Contouring of the target volumes after fusion of the MR image and that of the planning CT. A) Axial; B) Coronal.

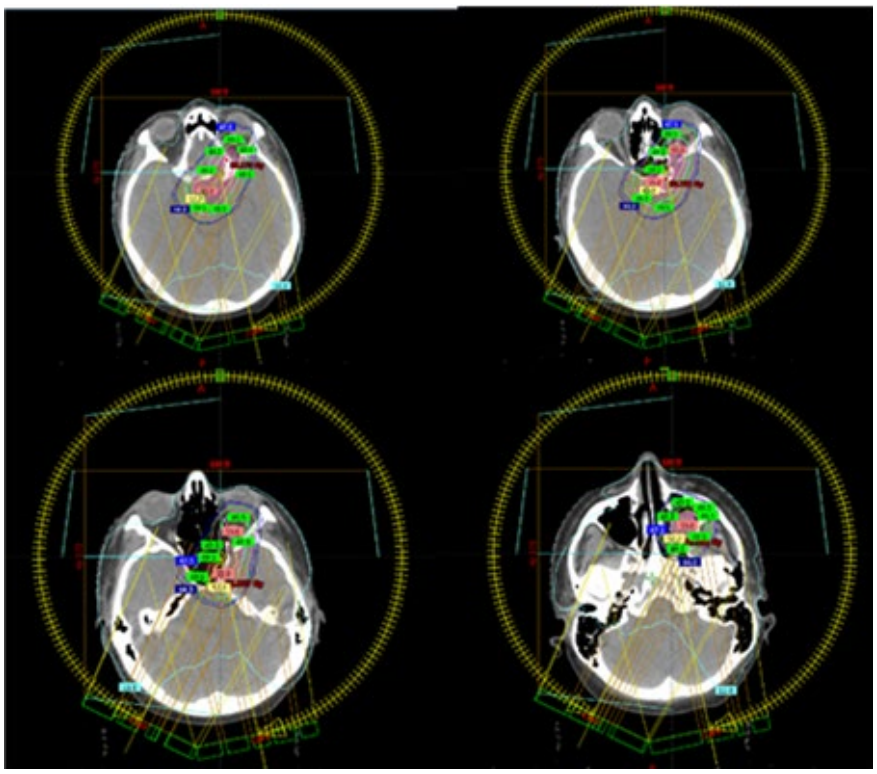

Figure 5: IMRT by the VMAT method covers two target volumes, namely the tumor and the left optic pathway including the left optic nerve and the left retina up to a total dose (TD) 55 Gy with a daily dose (DD) 2.2 Gy and an insurance zone around the tumor of size 0,7 cm up to a TD 50 Gy with a DD 2 Gy, realized in 25 daily fractions, 5 times a week.

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

of pediatric oncology (SIOP) and children's oncology group (COG), NGGCTs can be defined clinically by the elevation of AFP level (AFP>10 mg/L) in serum or CSF, which includes yolk sac tumors, immature teratoma, and embryonic carcinoma [17]. The automated immunochemical method is fit for quantification of hCG and AFP in cerebrospinal fluid (CSF), allowing selective and specific diagnosis of secreting germ cell tumors [18]. AFP is detected in endodermal sinus tumors such as yolk sac tumors, and β-HCG is a marker of choriocarcinomas [19]. In our clinical case lumbar puncture shows no tumor cells in the cerebrospinal fluid, but elevated tumor markers: total beta-HCG 1045 mlU/ml, alpha-fetoprotein (AFP) 26.70 ng/ml. Immunohistochemistry of tumor cells and elevated tumor markers for total beta-HCG and alpha-Fetoprotein AFP prove non-germinal cell brain tumor. AFP levels greater than 1000 ng/mL are considered high risk and may require intensified chemotherapy and radiation [20].

Complex treatment: The treatment of patients with intracranial non-germinomatous malignant germ cell tumors should be based on tumor histology. For patients in the intermediate prognosis group, multimodal treatment, including surgical resection, radiotherapy, and chemotherapy, was effective [21]. An alternative therapeutic classification in Japan distinguishes three groups on the basis of their prognosis: good prognosis (e.g., germinoma), intermediate prognosis (e.g., immature teratoma with malignant transformation), and poor prognosis (e.g., yolk sac tumor, choriocarcinoma, embryonal carcinoma, and mixed tumors of those entities) [11]. Specific recommendations regarding the necessity of histological diagnosis and staging of the extent of disease are made in light of modern chemotherapeutic advances [13]. For all defined as the “intermediate and poor prognosis” group, two or three courses of Ch and high-dose Ch were administered with peripheral blood stem cell transplantation and radiotherapy (24–30 Gy) applied to the whole ventricle or a larger field with or without local boost irradiation (20 Gy), which was applied as needed [22]. While germinomas can be treated only with radiotherapy, NGGCTs often require a combined approach for a better survival outcome [23]. In the SIOP CNS GCT-96 trial, localized disease was treated with four cycles of induction Ch followed by focal RT to 54 Gy, leading to a 5-year PFS and OS of 72% ± 4% and 82% ± 4%, respectively [22]. Patients who received Ch had a 3-year survival rate of 56% compared to 8% for those patients who did not receive chemotherapy (p= 0.0001) [24]. For NGGCTs, the combined use of more intensive neoadjuvant Ch followed by either localized or craniospinal irradiation (CSI) has resulted in improved survival rates in the last decade [25-27]. The use of Ch before RT has increased survival rates. However, the specific Ch regimen, length of therapy, and the optimal radiation field, timing, and dose remain under investigation [14,28,29]. Studies had shown that neoadjuvant therapy before initiation of RT resulted in long-term survival (60-70% of cases) [30]. Twenty-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 whole-brain RT (WBRT) (20-36 Gy) or focal RT (50.4-54 Gy) [8]. The SIOP-CNS-GCT-96 (NCT00293358) trial employed involved RT fields only for these patients with no radiographic evidence of residual or disseminated disease [31]. Aoyama et al presented promising excellent results in a second Japanese series including 16 germinomas treated with surgery, followed by chemotherapy and low-dose involved-field radiotherapy [32]. In a study with 48 patients that were confirmed by histology to have a primary CNS germ cell tumor, it was revealed that treatment with radiation with doses higher than 40 Gy to the primary tumor was associated with better control [33]. After one course of Ch including cisplatin, our patient recovered 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 (Figure 3).Thromboembolic events such as pulmonary embolism, arterial or deep venous thrombosis and cerebral ischemic stroke are rare but known complications during chemotherapy for germ cell cancer [34] An extensive retrospective analysis found that patients undergoing cisplatin-based Ch are at higher risk for thromboembolic events if they suffer from germ cell cancer rather than other tumors [35].

Radiotherapy: Intensity modulated radiotherapy (IMRT) covers two target volumes, namely the tumor and optic pathway on the left 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 1 cm up to a TD 50 Gy with a 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

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

1. Huang X, Zhang R, Mao Y, Zhou LF, Zhang C (2016) Recent advances in molecular biology and treatment strategies for intracranial germ cell tumors. World J Pediatr 12(3):275-282.
2. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS (2021) CBTRUS Statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol 23:iii1–iii105.
3. McCarthy BJ, Shibui S, Kayama T, Miyaoka E, Narita Y, et al. (2012) Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries. Neuro Oncol 14:1194-1200.
4. Vipin K, Saikat D, Arnav T, Manish G (2022) A Case of Non-Germinomatous Germ Cell Tumors of the Frontal Lobe Arising From the Lateral Ventricle With a Synchronous Pineal Lesion. Cureus 14(10):e29895.
5. Frappaz D, Dhall G, Murray MJ, Goldman S, Faure Conter C, et al. (2022) EANO, SNO and Euracan consensus review on the current management and future development of intracranial germ cell tumors in adolescents and young adults. Neuro Oncol 24:516-527.
6. Thakkar JP, Chew L, Villano JL (2013) Primary CNS germ cell tumors: Current epidemiology and update on treatment. Med Oncol 30:496.
7. Nandi M, Anil R, Hamaty E Jr, Adams W, Stidd D, et al. (2020) A Rare Case of Intracranial Nongerminomatous Germ Cell Tumor in a 21-Year-Old Romanian Male. Case Rep Oncol Med 2020:3787250.
8. Kim JW, Kim WC, Cho JH, Kim DS, Shim KW, et al. (2012) A multimodal approach including craniospinal irradiation improves the treatment outcome of high-risk intracranial nongerminomatous germ cell tumors. Int J Radiat Oncol Biol Phys 84(3):625-631.
9. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, et al. (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97-109.
10. WHO Classification of Tumours Editorial Board, ed. (2021) WHO Classification of Tumours: Central Nervous System Tumours. Vol. 6. 5th ed. IARC.
11. Louis DN, Ohgaki H, Wiestler OD (2016) WHO Classification of Tumours of the Central Nervous System. 4th rev.ed. IARC.
12. Murray MJ, Bartels U, Nishikawa R, Fangusaro J, Matsutani M, et al. (2015) Consensus on the management of intracranial germ-cell tumours. The Lancet. Oncology 16(9):e470-e477
13. Jennings MT, Gelman R, Hochberg F (1985) Intracranial germ-cell tumors: natural history and pathogenesis. J Neurosurg 63 (2):155-167.
14. Matsutani M (2001) Combined chemotherapy and radiation therapy for CNS germ cell tumors--the Japanese experience. Journal of neuro-oncology 54(3):311-316.
15. Morana G, Alves CA, Tortora D, Finlay JL, Severino M, et al. (2018) T2*-based MR imaging (gradient echo or susceptibility-weighted imaging) in midline and off-midline intracranial germ cell tumors: a pilot study. Neuroradiology 60:89-99.
16. Packer RJ, Cohen BH, Cooney K (2000) Intracranial germ cell tumors. Oncologist 5:312-320.
17. Bowzyk Al-Naeeb A, Murray M, Horan G, Harris F, Kortmann RD, et al. (2018) Current management of intracranial germ cell tumours. Clin Oncol (R Coll Radiol):30(4):204-214.
18. D'Alessandro A, Ciavardelli D, Pastore A, Giannone G, Del Baldo G, Carai A, et al. (2021) Cerebrospinal Fluid Levels of AFP and hCG: Validation of the Analytical Method and Application in the Diagnosis of Central Nervous System Germ Cell Tumors. Diagnostics (Basel) 11(11):1980.
19. Haase J, Borgaard-Pedersen B (1979) Alpha-feto-protein (AFP) and human chorionic gonadotropin (HCG) as biochemical markers of intracranial germ-cell tumours. Acta Neurochir 50:67-69.
20. 20. Dufour C, Guerrini-Rousseau L, Grill J (2014) Central nervous system germ cell tumors: An update. Curr. Opin. Oncol 26:622-626.
21. Ogawa K, Toita T, Nakamura K, Uno T, Onishi H, Itami J, et al. (2003) Treatment and prognosis of patients with intracranial nongerminomatous malignant germ cell tumors: a multiinstitutional retrospective analysis of 41 patients. Cancer 98(2):369-376.
22. Takada A, Ii N, Hirayama M, Toyoda H, Matsubara T, et al. (2018) Long-term follow-up of intensive chemotherapy followed by reduced-dose and reduced-field irradiation for intracranial germ cell tumor. Neurosurg Pediatric 23(3):317-324.
23. Calaminus G, Frappaz D, Kortmann RD, Krefeld B, Saran F, et al. (2017) Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial. Neuro Oncol 19:1661-1672.
24. Schild SE, Haddock MG, Scheithauer BW, Marks LB, Norman MG, et al. (1996) Nongerminomatous germ cell tumors of the brain. Int J Radiat Oncol Biol Phys 36(3):557-563.
25. Khatua S, Dhall G, O'Neil S, Jubran R, Villablanca JG, et al. (2010) Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. Pediatr Blood Cancer 55(1):42-46.
26. O'Neil S, Ji L, Buranahirun C, Azoff J, Dhall G, et al. (2011) Neurocognitive outcomes in pediatric and adolescent patients with central nervous system germinoma treated with a strategy of chemotherapy followed by reduced-dose and volume irradiation. Pediatr Blood Cancer 57(4):669-673.
27. Lee DS, Lim DH, Kim IH, Kim JY, Han JW, et al. (2019) Upfront chemotherapy followed by response adaptive radiotherapy for intracranial germinoma: Prospective multicenter cohort study. Radiother Oncol 138:180-186.
28. Robertson PL, DaRosso RC, Allen JC (1997) Improved prognosis of intracranial non-germinoma germ cell tumors with multimodality therapy. J Neurooncol 32 (1):71-80.
29. Calaminus G, Bamberg M, Jürgens H, Kortmann RD,

Sörensen N, et al. (2004) Impact of surgery, chemotherapy and irradiation on long term outcome of intracranial malignant non-germinomatous germ cell tumors: results of the German Cooperative Trial MAKEI 89. Klin Padiatr 216(3):141-149.
30. Calaminus G, Bamberg M, Harms D, Jürgens H, Kortmann RD, et al. (2005) AFP/beta-HCG secreting CNS germ cell tumors: long-term outcome with respect to initial symptoms and primary tumor resection. Results of the cooperative trial MAKEI 89. Neuropediatrics 36(2):71-77.
31. O'Neil S, Ji L, Buranahirun C, Azoff J, Dhall G, et al. (2011) Neurocognitive outcomes in pediatric and adolescent patients with central nervous system germinoma treated with a strategy of chemotherapy followed by reduced-dose and volume irradiation. Pediatr Blood Cancer 57(4):669-673.
32. Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, et al. (2002) Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol 20:857-865.
33. Bamberg M, Kortmann RD, Calaminus G, Becker G, Meisner C, et al. (1999) Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. Journal of Clinical Oncology 17(8):2585-2592.
34. Weijl NI, Rutten MF, Zwinderman AH, Keizer HJ, Nooy MA, et al. (2000) Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. J Clin Oncol 18:2169-2178.
35. Piketty AC, Fléchon A, Laplanche A, Nouyrigat E, Droz JP, et al. (2005) The risk of thrombo-embolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. Br J Cancer 93:909-914.
36. Rosenblum MK, Matsutani M, Van Meir EG (2000) CNS germ cell tumours. In: Kleihues P, Cavenee WK, eds.: Pathology and Genetics of Tumours of the Nervous System. International Agency for Research on Cancer 208-214.
37. Hoffman HJ, Otsubo H, Hendrick EB, et al. (1991): Intracranial germ-cell tumors in children. J Neurosurg 74 (4):545-551.