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Case Report

Long-Term Survival of a Child with Atypical Teratoid-Rhabdoid Tumor and Acute Lymphoblastic Leukemia: A Case Report

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Abstract: Atypical teratoid-rhabdoid tumor (AT/RT) is a rare but one of the most aggressive embryonal tumors of the central nervous system (CNS), most often occurring in children under 3 years of age. AT/RT accounts for about 1–2% of all CNS neoplasms and has a very poor prognosis, high risk of secondary tumor development, recurrence and/or metastasis in patients in remission and limited therapeutic potential. The clinical manifestations are usually symptoms of increased intracranial pressure. The mainstay of tumor treatment is complex chemotherapy combined with radiation therapy. A clinical case of sequential occurrence of two cancers (AT/RT and leukemia) in a 3-year-old girl is presented.

Keywords: atypical teratoid-rhabdoid tumor; brain tumor; children; embryonic CNS tumor; acute lymphoblastic leukemia; brain tumor

Citation: Andreevna, K.M.; Vyacheslavovna, K.E.; Valeryevna, G.S.; Gunai Nariman, M.; Igorevich, L.M.; Yegorovich, C.G.; Nikolaevich, K.A.; Nikolaevich, U.V.; Encarnacion Ramirez, M.d.J.; Montemurro, N. Long-Term Survival of a Child with Atypical Teratoid-Rhabdoid Tumor and Acute Lymphoblastic Leukemia: A Case Report. *Surgeries* **2024**, *5*, 184–193. https://doi.org/10.3390/surgeries5020018

Academic Editors: Cornelis F. M. Sier and Mario Ganau

Received: 10 January 2024
Revised: 14 March 2024
Accepted: 30 March 2024
Published: 3 April 2024

1. Introduction

Atypical teratoid-rhabdoid tumor (AT/RT) is a malignant embryonic tumor of the central nervous system (CNS), consisting mainly of poorly differentiated elements, often with rhabdoid cells and inactivation of SMARCB1 (Rhabdoid predisposition syndrome 1, OMIM 609322) and INI 1–integrase-interceptor 1, respectively, or exceptionally rarely SMARCA4, as well as BAG1 [1–3]. Firstly, this type of tumor was described by Beckwith and Palmer [3] in 1978 as part of a different morphological characteristic of a rhabdoid tumor from a kidney tumor, which is the Wilms tumor (nephroblastoma).

The incidence of AT/RT depends on age: it reaches its maximum in children under one year of age and tends to zero in children aged 10 to 14 years [4,5]. Boys are slightly more likely to get sick than girls (1.5:1.3). In 2020, three molecular tumor groups were identified: ATRT-SHH, ATRT-TYR, and ATRT-MYC, which differ genetically, epigenetically, and clinically [6]. The ATRT-TYR group is genetically manifested by complete or partial loss of one copy of chromosome 22, accompanied by an inactivating mutation in the SMARCB1 gene. Clinically, patients with ATRT-TYR represent the youngest group with an average age at diagnosis of 12 months (range 0–108 months). This subgroup also had the highest proportion of patients under three years of age at diagnosis (90% in ATRT-TYR vs. 74.6% in ATRT-SHH vs. 52.3% in ATRT-MYC) [6].

The ATRT-SHH subgroup, also called Group 1 in Torchia et al.'s [7] classification, demonstrates overexpression of SHH genes (a family of and their corresponding proteins that control embryonic development of the nervous system). Genetically, ATRT-SHH cases differ from the other two subgroups in the type of SMARCB1 changes. Most ATRT-SHH cases exhibit complex heterozygous point mutations compared to other groups [6]. The ATRT-MYC subgroup was named based on increased expression of the MYC oncogene, in contrast to the MYCN oncogene, which is elevated in the ATRT-SHH group. The mean age of ATRT-MYC patients is significantly higher than in the other two subgroups (27 months). This is mainly due to many older patients [6]. Analysis of the results of MRI studies shows that ATRT-MYC tumors are characterized by severe peritumoral edema [8]. It should be noted that recent reports emphasize the similarity between extracranial malignant rhabdoid tumor (MRT) and ATRT-MYC in the level of DNA methylation [9,10]. Given the genetic similarity between ATRT-MYC and the subgroup of rhabdoid kidney tumors, there may be common molecular targets between extracranial rhabdoid tumors and subgroups [11].

Prognostically, this classification does not change the outcome of the disease, but it may be the key to finding a specific, more personalized therapy in the future. AT/RT is a highly aggressive, malignant neoplasm of the central nervous system. In recent years the median survival of patients has increased from 6–10 months [12] to 43 months [13], and molecular groups and subgroups of the tumor have also been identified. The effectiveness of high-dose polychemotherapy supported by autologous peripheral stem cells (HD-CHT with auto PSC) is being investigated [14], especially in infants whose use of radiation therapy is fraught with an unfavorable prognosis for toxic effects on the central nervous system [15,16]. Attempts are being made to use targeted therapy in the form of such drugs as sirolimus (m-TOR inhibitor), tazemetostat (EZH2 inhibitor), and alisertib (kinase inhibitor) [17]. Despite this, AT/RT is still one of the darkest pages in modern neuro-oncology [3,5,11]. Currently, rare cases of AT/RT as a radiation-induced secondary tumor after cranial irradiation are described in patients with lymphoblastic leukemia [18]. The reported clinical case describes the sequential occurrence of ATRT and acute lymphoblastic leukemia in a 3-year-old girl.

2. Case Report

A 36-month-old girl (3 years old) with complaints of vomiting, with an increase in frequency and a single seizure, was referred to our Morozov Children's Clinical Hospital of the Moscow City Healthcare Department Hospital, Moscow (Morozov CCH). A brain magnetic resonance imaging (MRI) with contrast enhancement (CE) confirmed the presence of a left temporal tumor, spreading to the subcortical nuclei (46 × 38 × 27 mm) (Figure 1A,B). Surgery was performed with total removal of the tumor, confirmed by a postoperative brain MRI in the first 72 h (Figure 1C). Based on the results of histological and immunohistochemical studies, the diagnosis was established as AT/RT, WHO Grade IV, with negative INI1 expression. For AT/RT, a characteristic histological feature is medium-sized cells, from round to oval, with clear borders, an eccentric nucleus, and a usually pronounced nucleolus (Figure 1D–F) [19].

The tumor material was also studied at the "N.N. Burdenko National Medical Research Center of Neurosurgery" of the Ministry of Health of the Russian Federation, and the histological diagnosis was confirmed. Additionally, the tumor was identified using the DNA methylation technique based on CNS tumor profiles using the brain tumor classifier from Heidelberg, Germany (https://www.molecularneuropathology.org, accessed on 1 March 2024), which confirmed this tumor variant and its molecular subtype, which is the AT/RT subgroup SHH (Figure 2).

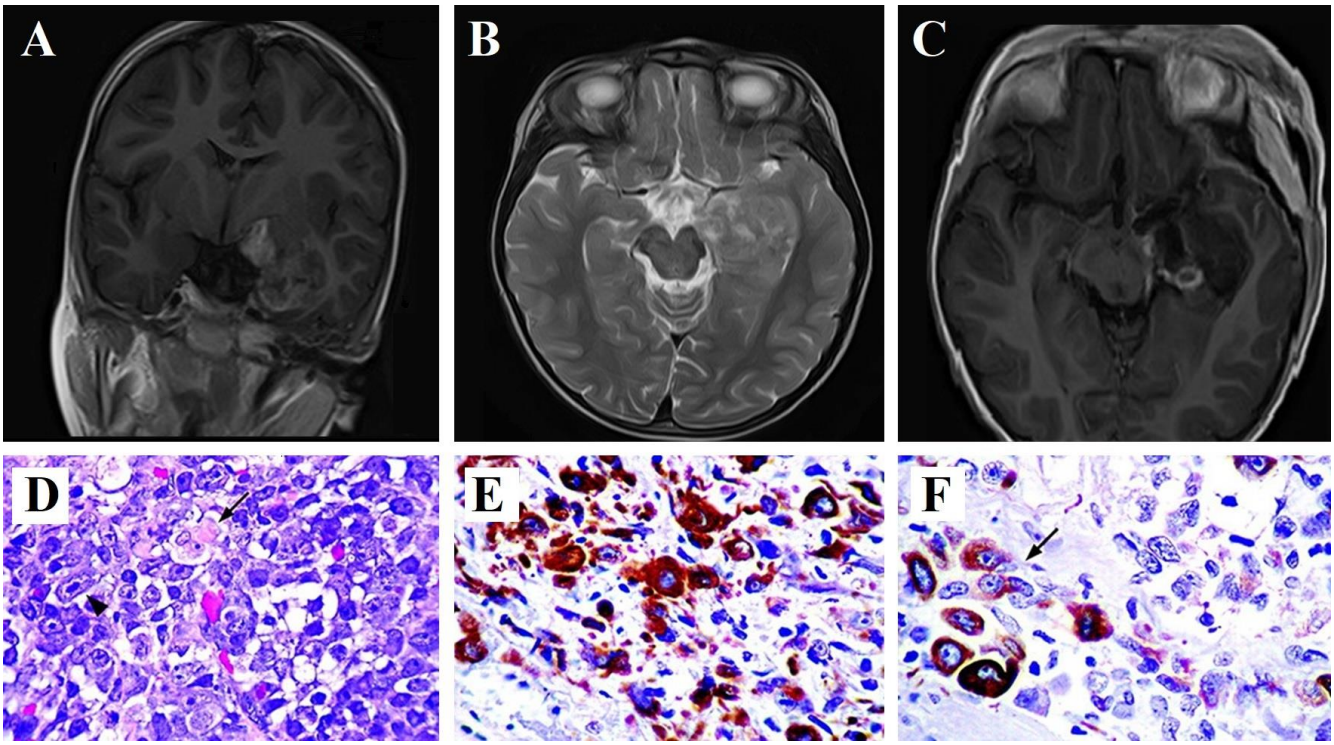

Figure 1. A dynamic contrast enhanced (CE) T1-weighted (**A**) and T2-weighted (**B**) MRI scan before surgery show a left temporal tumor. Axial MRI scan (**C**) with CE in T1 after operation shows an area of EF accumulation (6 × 14 mm in size). Histological features of AT/RT: cells have large nuclei with pronounced nucleoli (black arrow), and some cells have abundant eosinophilic cytoplasm (black arrow) (**D**). The reactivity of vimentin (**E**) is universal, and positive staining of the epithelial membrane antigen (**F**) is characteristic of cell groups (arrow). Staining with hematoxylin-eosin, vimentin, and epithelial membrane antigen; magnification 400× [18]. The tumor immunophenotype is broad, as large rod-shaped cells show a range of immunoreactivity with clusters of cells almost always positive for epithelial membrane antigen and reacting to vimentin. Reactivity to glial fibrillar acidic protein and cytokeratin is also common, and less often reactivity to smooth muscle actin and neurofilament protein. Rhabdoid cells are negative for desmin and any of the markers of germinogenic tumors [20,21].

Only 70% of patients with AT/RT are known to have SMARCB1 (INI1). If it is not possible to perform the DNA methylation technique in such cases, a panel of biomarkers can be proposed that are useful for differentiating small cell supratentorial CNS tumors in children [21]. Senger sequencing and fluorescent in situ hybridization (FISH) will allow us to identify embryonic CNS tumors that occur supratentorially in children and develop the most appropriate strategy for management of such patients.

The patient was transferred to the Department of Clinical Oncology of the "Morozov CCH" for further examination and chemoradiotherapy. Screening examination of the patient revealed the R0M0 stage of disease. Further therapy was performed according to the chemo/radiation therapy for CNS AR/RT protocol. The protocol was introduced for the first time in Russia in the "Morozov CCH" and was later distributed to other hospital of the Russian Federation specializing in the treatment of CNS tumors in children. For more than 10 years, it has been the standard approach for comprehensive treatment of children with AT/RT in the Russian Federation [22–24]. From the 10th to the 17th week of the protocol, local radiation therapy (RT) was performed of 55 Gy, and in parallel, Vincristine 1.5 mg/m^2/day was administered weekly. At the time of the RT launch, the girl was 2.7 years old (less than 3 years old). Considering the patient's age of less than 3 years and the R0M0 stage of the tumor process in accordance with the chemo/radiation therapy for CNS AR/RT protocol, the patient received only local radiation therapy on the tumor bed

area without craniospinal radiation. Then polychemotherapy was continued in accordance with the protocol. The planned amount of treatment was completed in full. According to MRI data, at the end of therapy, a complete response was preserved without signs of local and metastatic tumor spread (Figure 3A).

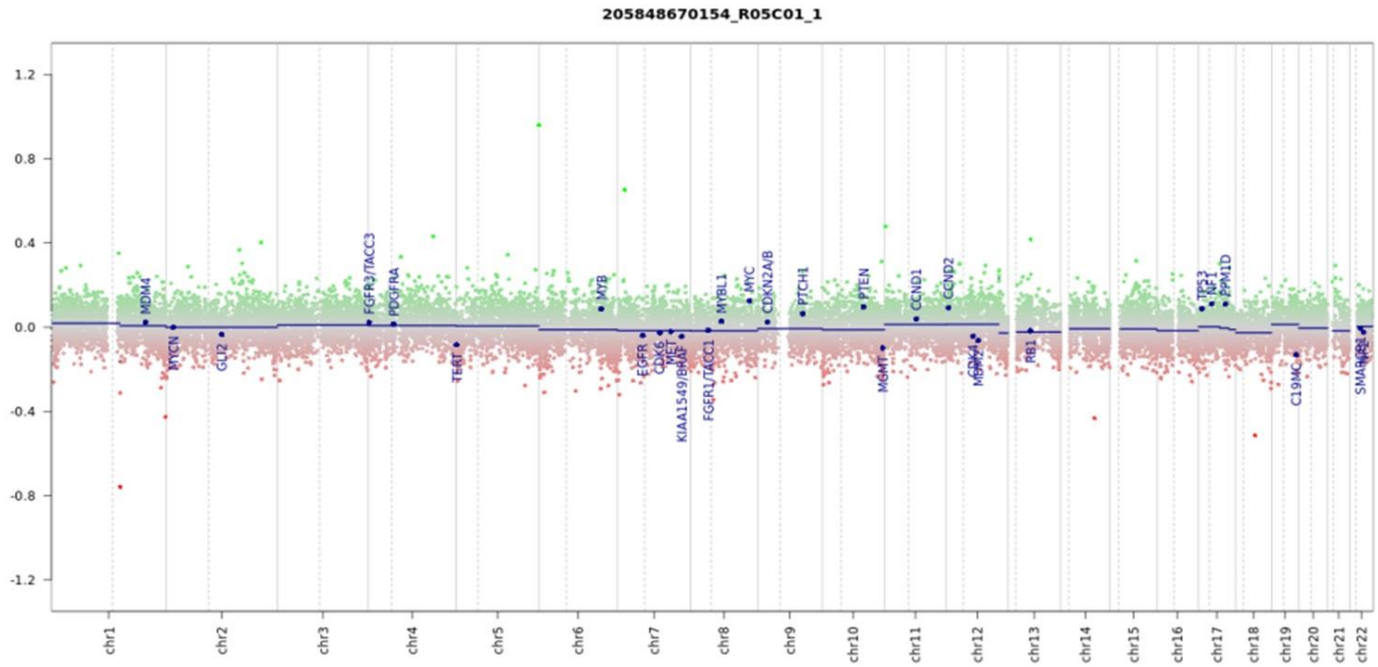

Figure 2. The result of DNA methylation of the tumor material, which determined the molecular subgroup of the tumor to SHH. Tumor entity and molecular types were identified using the brain tumor classifier which is a platform for DNA methylation-based classification of CNS tumors. Depiction of chromosome 1 to 22 (and X/Y if automatic prediction was successful). Gains/amplifications represent positive and losses negative deviations from the baseline. A total of 29 brain tumor-relevant gene regions are highlighted for easier assessment. Molecularly, virtually all cases show loss of INI1 (SMARCB1) protein, and this subtype shows SHH pathway activation.

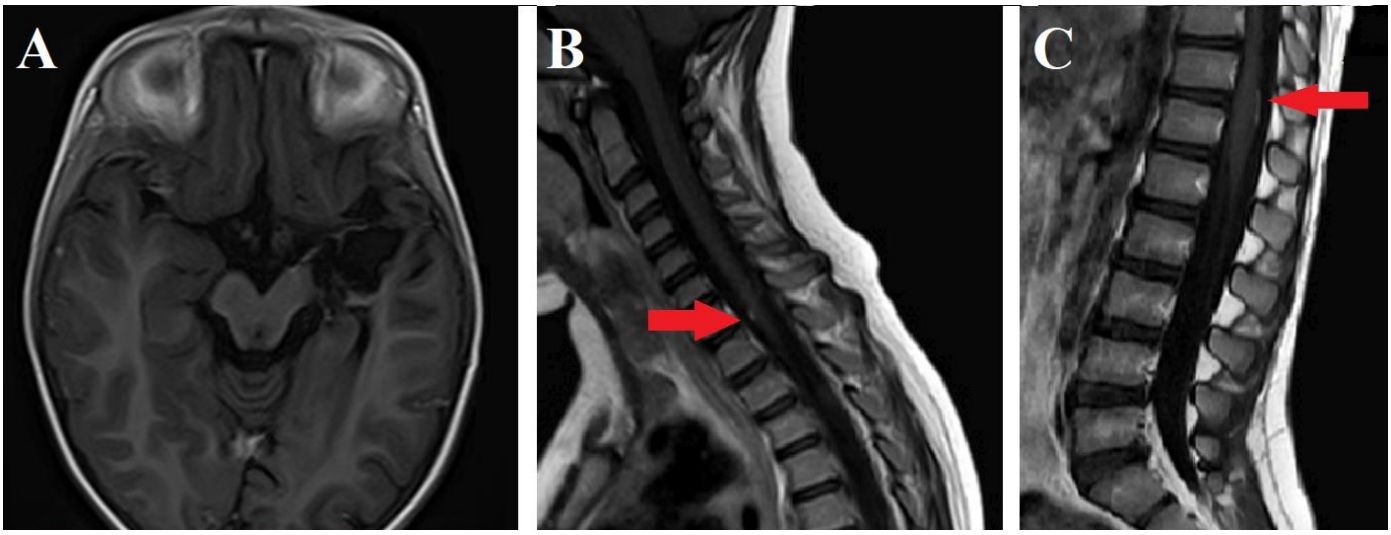

Figure 3. A CE T1-weighted brain MRI (**A**) at the end of the chemoradiotherapy protocol shows a complete response. A spinal cord T1-weighted MRI (**B**,**C**) shows an age-related enhancement (red arrows) 3 years after the end of therapy. Linear sections of CE accumulation are marked.

At a follow-up MRI of the central nervous system after the end of therapy (at 35 months), two small areas of contrast agent accumulation were detected in the cervical spinal cord at the C6–C7 level (Figure 3B), as well as linear CE-accumulation at the Th11–Th12 level (Figure 3C). Thus, a metastatic relapse of AT/RT was suspected. Due to the small size of the detected foci and the absence of neurological deficits in the patient, it was decided to continue with observation.

Thirty-eight months (3 years 2 months) after the therapy for AT/RT, the patient was diagnosed with acute lymphoblastic leukemia (ALL). The disease debuted with thrombocytopenia up to 40.000/μL in a control study of a general blood test after tonsillitis. The child was hospitalized at the Department of Oncology and Hematology of the "Morozov CCH". Polychemotherapy was initiated according to the ALL BFM IC2002 protocol with intrathecal administration of CHT (cytorabine + dexamethasone). The patient received a full course of ALL treatment in the planned volume; remission was achieved.

During maintenance chemotherapy for ALL, dynamic MRI of the central nervous system was performed (60 months after completion of treatment for AT/RT) showing an increase in the size of the previously described foci in the spinal cord, whereas locally in the left temporal lobe and left thalamus a complete response was maintained. When studying the dynamics of the spinal cord in the cervical region at the level of C6–C7 and in the thoracic region at the level of Th11–Th12, two small areas of accumulation of CE along the anterior and posterior surfaces of the spinal cord, of the same size, were preserved. The "N. N. Burdenko National Medical Research Center of Neurosurgery" of the Ministry of Health of the Russian Federation performed a biopsy of spinal cord foci at T11–T12 levels. Histological examination of the tumor material confirmed the presence of ATRT metastasis in the spinal cord.

MRI of the central nervous system with contrast after the second surgery (biopsy) revealed previously absent small foci of accumulation of CE in the area of the left cerebellum and along the anterior surface of the medulla oblongata (2–4 mm in size). The primary tumor shows no signs of local recurrence. At thoracic and cervical regions, nodular formations persisted, unevenly accumulating CE (Figure 4A). In connection with the continued growth of proven multiple metastases of AT/RT, proton radiation therapy was performed in the amount of cranio-spinal radiation up to 36 Gy and boost to metastatic nodes in the brain up to 54 Gy, in the spinal cord up to 50.4 Gy. A control MRI study, after completing a second course of radiation therapy (after 3 months), showed a partial response in the form of a decrease in the size of metastatic nodes in the spinal cord (Figure 4B,C). During a control MRI, 12 months after the repeated course of radiation therapy, the previously described pathological areas of CE accumulation in the spinal cord were not detected. The postoperative area of the brain is shown—without dynamics in comparison with previous studies (Figure 4D–F).

At the time of the clinical case description, the girl was under the dynamic supervision of specialists from the Outpatient Cancer Care Center of the "Morozov CCH"; remission of AT/RT and ALL is confirmed by control studies of a general blood test and MRI. The progression-free survival rate after metastatic recurrence of AT/RT is 38 months. The maximum follow-up period from the moment of diagnosis of AT/RT is 101 months (8.5 years). In 2022, an analysis for genomic profiling of tumor tissue was performed, and a mutation of the SMARCB 1 gene was detected.

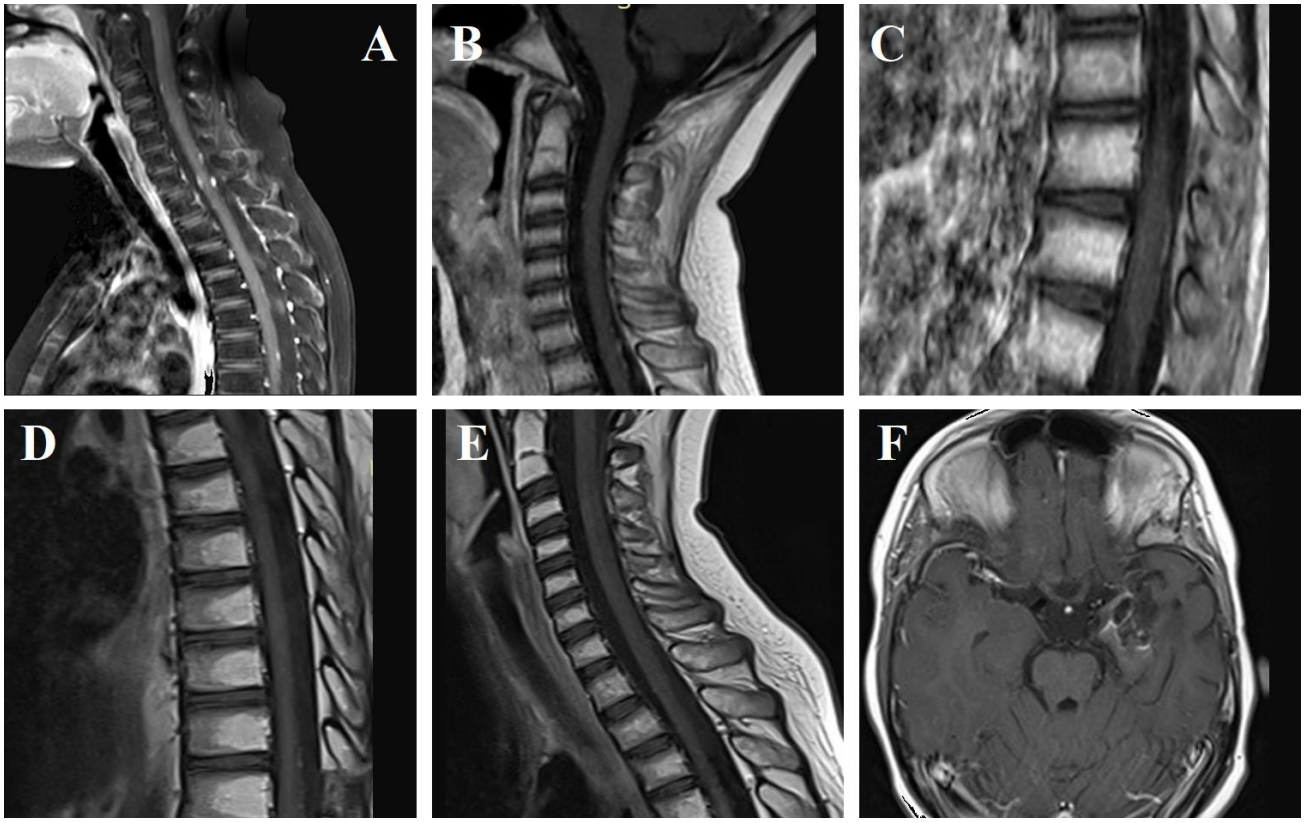

Figure 4. A CE T1 MRI scan (**A**) shows the appearance of new pathological areas of the spinal cord in the cervical and thoracic regions, as well as along the ventral surface of the medulla oblongata. The MRI scans (**B**,**C**) after a cycle of RT in T1 mode with CE—there is a partial regression of the previously described foci. A control T1-weighted MRI (**D**–**F**) with CE shows the situation at 12 months after the second course of radiation therapy: metastatic nodes in the spinal cord with positive dynamics; the area of localization of the primary tumor in the brain—without signs of relapse.

3. Discussion

In the 21st century, AT/RT remains the most aggressive and resistant to CNS tumor therapy. In a 1978 study by Beckwith and Palmer [3], the tumor was identified as an independent morphological unit that differs in its characteristics from the Wilms tumor. Later, AT/RT was recognized as an analog of rhabdoid tumors in the kidneys and soft tissues of the central nervous system, which dictates the need for further search for optimal therapy [21]. The 2016 World Health Organization Central Nervous System tumor classification evolved from the 2007 edition with the integration of molecular and genetic profiling into the diagnosis, the addition of new entities, and the removal of others [25,26]. The division of AT/RT into three molecular groups revived the interest of researchers in this seemingly unpromising problem [27]. ATRT-SHH represents the most common molecular group [28], and overexpression signaling pathway of the SHH signaling pathway and Notch transmission pathways (a type of transmembrane protein) are a characteristic feature of the above subgroup. The issue of predictive application of this classification remains debatable. The results of clinical trials and registries are contradictory: in the EU-RHAB registry (European Registry of AT/RT), the survival rate in children with a verified molecular group of ATRT-SHH and ATRT-MYC was worse than in ATRT-TYR [28], while in the ACNS0333 study, a longer disease-free period and longer survival rate in children with the ATRT-SHH molecular subgroup were reported [29,30]. In 2022, the ATRT-SHH molecular group was divided into three subgroups: SHH-1a, SHH-1b, and SHH-2, which differ in the age of the patient's tumor and its localization [31]. A comparative description of the above subgroup is shown in Figure 5.

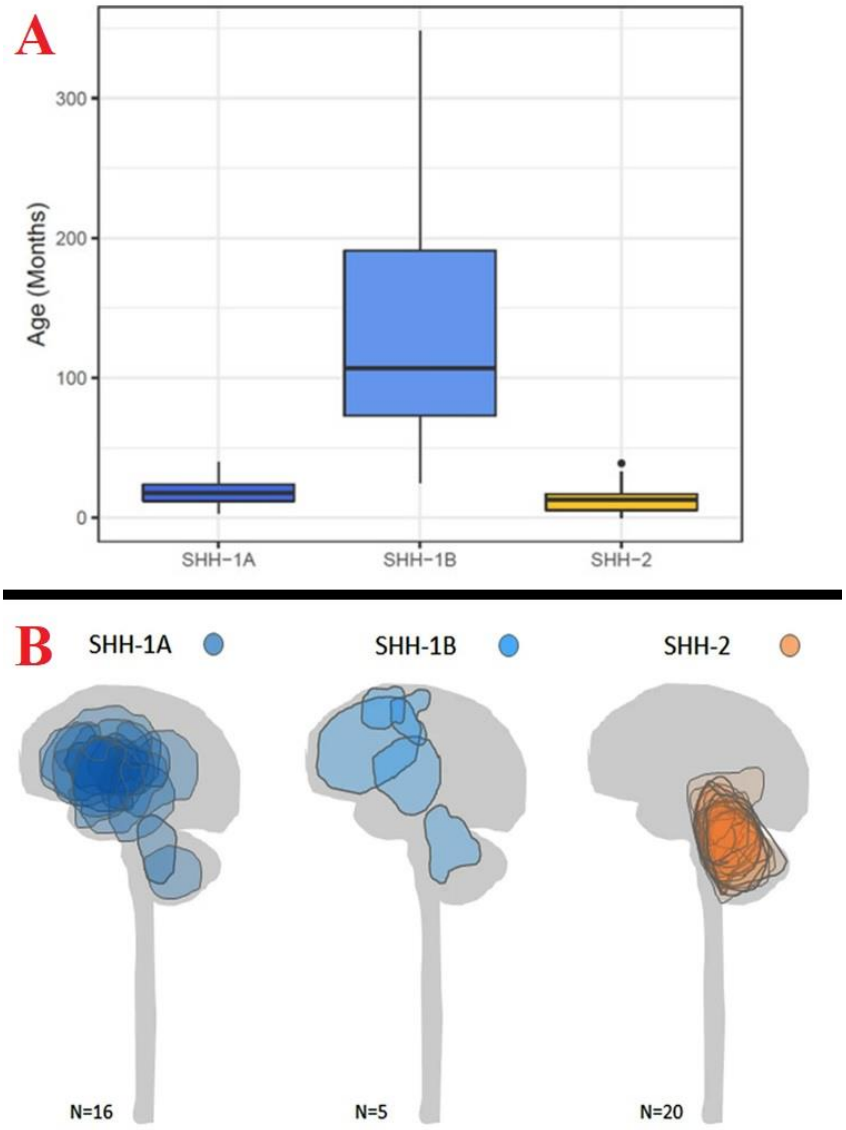

Figure 5. Age (**A**) and localization (**B**) distribution of the tumor in the ATRT-SHH subgroups. For visualization, the maximum size of the tumor was determined in the sagittal plane and projected into the schematic drawing of the central nervous system [27,31].

In our clinical case, the tumor belonged to the ATRT-SHH group; a more detailed molecular analysis that would determine the subgroup had not yet been performed. The greatest interest in our observation is the long-term life of a patient (more than 8 years) with one of the most aggressive embryonic tumors of the central nervous system with the subsequent occurrence of ALL. There are multiple reports of the development of ALL after radiation therapy; leukemia is the most radiation-sensitive malignancy, which often appears earlier after radiation exposure than any other radio-induced tumor [32–34]. According to available data, in most cases, the onset of ALL in children occurs in the first 10 years after radiation therapy [35]. According to our data, there are no reports in the literature about the sequential course of these two oncological processes, only the occurrence of ATRT as a radiation-induced tumor after radiation therapy for ALL. Such cases require testing the patient for tumor-associated hereditary TP53 syndrome (Li-Fraumeni syndrome) and RTPS (rhabdoid predisposition syndrome) mutations in the SMARCB1 and SMARCA4 genes, which in the future may help in choosing the optimal therapeutic strategy. In our case, the patient was not examined for standard tumor-associated syndromes that determine the prognosis and management strategy of the disease. A relapsed patient was monitored as

oncological events occurred and considering the previously used methods and treatment volumes. The development of a confirmed metastatic relapse of AT/RT in a patient with only local radiotherapy for the primary tumor focus (performed in accordance with the requirements of the chemo/radiation therapy for CNS AR/RT protocol protocol) would probably have been prevented (given the continued local remission in the brain) if the patient had been initially irradiated craniospinally with a boost on the tumor bed, as it should have been irradiated like all embryonic CNS tumors. However, the patient's age, the volume of resection of the primary tumor (R0), and the absence of metastases at the start of therapy (M0-stage) dictated the need to refrain from CSI. Currently, there is no evidence that leukemia drugs are effective against AT/RT, which could explain the prolonged survival in our case. It is important to note that chemotherapy preparations for the treatment of AT/RT have no overlap with the chemotherapy preparation in the guideline for ALL therapy in our case [5,36].

4. Conclusions

AT/RT is still an oncological disease with an extremely unfavorable prognosis. However, further molecular studies and the identification of separate molecular subgroups of AT/RT with different prognoses, including more favorable ones, can potentially help stratify patients in groups requiring less aggressive treatment in future clinical trials and be a key factor in finding the optimal therapy. Considering the localization of the primary focus and later onset, including in relapse of the disease, as well as in combination with other oncological diseases, the ATRT-SHH subgroup may be the most promising prognostically. Adequate dynamic monitoring and timely diagnosis, as well as the applied treatment methods, made it possible to achieve a long-term positive effect in a child with a secondary tumor—ALL and AT/RT metastasis to the central nervous system. We did not find in the literature any cases of combination of these two (ALL and AT/RT) oncological diseases in a single patient. A more detailed examination of the patient for tumor-associated syndromes and identification of targeted mutations will help to find the optimal treatment of rare patients.

Author Contributions: Conceptualization, K.M.A., K.E.V., G.S.V., M.G.N., M.d.J.E.R. and N.M.; validation, K.M.A., M.G.N., M.d.J.E.R. and N.M.; formal analysis, L.M.I., C.G.Y., K.A.N. and U.V.N.; investigation, L.M.I., C.G.Y., K.A.N. and U.V.N.; resources, K.M.A., M.G.N., M.d.J.E.R. and N.M.; data curation, K.M.A., M.G.N., M.d.J.E.R. and N.M.; writing—original draft preparation, K.M.A. and M.G.N.; writing—review and editing, M.d.J.E.R. and N.M.; visualization, K.M.A., M.d.J.E.R. and N.M.; supervision, K.M.A. and N.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the Morozovskaya Children's City Clinical Hospital, Moscow, Russia (April 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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