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Teaching Case

Repeated Radiation Therapy of Recurrent Solitary Fibrous Tumors of the Brain: A Medical Case History Over 20 Years

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Introduction

Solitary fibrous tumors (SFTs) are a rare type of tumor with an incidence of 0.2/100.000 per year.[1] The most common sites are extrapleural: 10% to 15% in the trunk, 10% to 15% in the head and neck, 30% to 40% in the extremities, and 30% to 40% in deep soft tissues, pelvis, retroperitoneum, or in the abdominal cavity.[2] SFTs of the central nervous system (CNS) are mesenchymal, nonmeningothelial tumors, presenting intracranially or intraspinally, and are usually dural-based.[3] SFTs emerge from the diagnostic entity of hemangiopericytoma (HPC) and represented initially a distinct entity from both meningioma and SFT/hemangiopericytoma.[4] However, in 2016, the World Health Organization changed the classification to SFT/hemangiopericytoma and in 2021 eliminated the term "hemangiopericytoma" for simply "SFT."[3,5]

SFTs of the CNS mostly affect adults. The clinical presentation depends on the localization and the size of the tumor. Common chief complaints are headache, imbalance, weakness, visual complaints, cranial nerve dysfunction, nausea, and confusion.[6,7] The clinical course is usually benign, and recurrences arise in 10% to 30% of patients.[2,8] Incomplete surgical resection, atypical histologic characteristics, and cerebral infiltration are known risk factors for disease relapse. SFT is a sporadic disease and is not congenital.[9]

Diagnostic workup relies on magnetic resonance imaging (MRI). SFTs are usually well-defined and homogeneous lesions,[10] isointense in T1 and hyper- or hypointense in T2. The radiologic differential diagnoses include meningioma, HPC, and atypical presentation of schwannoma.[9-12] Histologic differentiation between SFT and HPC may be challenging. Mekni et al[13] describe that HPC shows more diffuse vascularity with more prominent staghorn vessels and tends to have round to oval nuclei, as opposed to the spindled nuclei of SFT. In addition, CD34 staining is more often focal and weak in HPC, whereas it is usually strong and diffuse in SFT. Other immunohistochemical differences include a higher positivity for bcl-2, CD99, and neuron-specific enolase in SFT.

According to the 2021 World Health Organization Classification of Tumors of the CNS, SFTs are genetically characterized by a *NAB2-STAT6* gene fusion leading to an accumulation of STAT6 protein in the nuclei.[3]

Standard treatment is complete resection.[14] As relapses may occur, long-term follow-up and restaging are necessary.[9] Radiation therapy (RT) with photons may be used

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in cases of incomplete resection, after relapse or in the presence of atypical histology.[15]

Here, we report our experience with a patient who underwent multiple retreatments in the brain for a relapsing, slowly growing disease evolving over many years to illustrate the clinical utility of multiple retreatment with highly conformal RT of brain and acceptable cumulative toxicity while maintaining an autonomous and self-determined life.

Patients and Methods

Medical records and ethics

All medical records and pathologic and radiologic examinations from 2004 to March 2022 were reviewed. From the MRIs, location and size of lesions were assessed. All medical events and all treatments were assessed. The patient understood and consented to anonymization for publication of his case. A letter of compliance was received by the ethic committee of the Ärztekammer Sachen-Anhalt, Halle (Saale), Germany.

Radiotherapy

All RT prescriptions were reviewed. A sum plan of all available plans since 2006 was calculated. The planning target volumes were in the range from 0.18 to 112.55 cm^3 (median of 1.93 cm^3). Irradiation series were normal or hypofractionated. For treatment planning, Eclipse, versions 8.6.15 to 11.0.47 with dose calculation algorithms PBC 8.6.15 and AAA 11.0.31 (Varian Medical Systems, Inc) were used. iPlan RT Dose, versions 4.5.3 to 4.5.6 with dose calculation algorithms CircularCone.X 1.1 and PencilBeam.X 2.1 (Brainlab AG) were employed as well. The energy doses were applied with the following irradiation techniques: 3-dimensional (3D) conformal, intensity modulated RT, HybridArcTM (Brainlab AG), dynamic conformal arcs, and static arcs with circular cones (Brainlab AG). A linear accelerator Clinac 2100C with a multileaf collimator 120TM or a Novalis powered by TrueBeamTM STx with a multileaf collimator HD 120TM (Varian Medical Systems, Inc) delivered the 6.0 MV photons and 5.6 MV flattening filter-free photons, respectively.

Neuropsychological assessment

Neurologic and neuropsychological assessments were performed after the patient's neurologic performance status showed signs of changes. Two assessments were achieved: in October 2019 after 13 RT series and 663.8 Gy delivered to the brain and in March 2022 after 18 RT series and a total dose of 866.3 Gy. The neuropsychological tests used were: (1) a test for general intelligence. A vocabulary test (Wortschatztest WST)[16] was used to estimate the patient's premorbid general level of intelligence; (2) tests for memory functions. Episodic memory function for meaningful linguistic material was tested with the Verbal Learning and Memory Test.[17] With the Rey-Osterrieth Complex Figure Test,[18] spatial visual construction capability and visual memory performance were measured by drawing a meaningless figure composed of many geometric parts. This can also be used for observing executive functions (see the following sections). The Digit Span Test (subtest of the Wechsler Adult Intelligence Scale) was used to measure verbal short term and working memory[19-21]; (3) tests for attention performance. Two subtests of the Test battery of Attentional Performance were used: the Go/NoGo Test to analyze the ability to suppress reactions to irrelevant stimuli and to measure the reaction time under stimulus selection conditions and the divided attention test to capture the ability to focus attention on 2 different modalities at the same time.[22] These examinations were performed on a personal computer; and (4) tests for executive functions. Three distinct tests were carried out to evaluate executive functions. The Regensburger Word Fluency Test was used to assess divergent thinking as a problem solving strategy.[23] Cognitive processing speed and mental adaptability/cognitive flexibility were tested with the paper and pencil version of the Trail Making Test (part A and B).[24] In these tests, the patient must first connect only numbers in ascending order (part A), then numbers and letters in ascending order (part B) with a pencil line. The Rey-Osterrieth complex figure test was used here again to detect planning deficits by observing the patient when drawing the figure and logging the exact process of drawing.[18]

Case Presentation

Oncological summary

In 2004, a 44-year-old right-handed man welder presented with occasional hallucinations. After imaging studies (MRI), he was initially diagnosed with a meningioma in the left temporal lobe. It was surgically removed. A histologic diagnosis of meningioma was made. In 2005, follow-up imaging showed a recurrence in the same location, and the patient underwent a second radical resection. The diagnosis was changed to meningosarcoma and adjuvant RT was given using 7 noncoplanar fields, 4 with 15 MV and 3 with 6 MV, to deliver 60 Gy in 30 fractions.

The patient remained well until the end of 2011, when he complained about headaches, irritability, and episodes of apathy. MRI showed a relapse adjacent to the temporal

lobe. A third surgery was performed resulting in complete resection. The pathology was the same as in 2005. A second course of treatment of adjuvant RT using a tangential 3D-conformal RT applied with a coplanar beam geometry with 4 fields, 1 with 15 MV and 3 with 6 MV, was delivered with 63 Gy in 35 fractions.

Two years later, in 2013, a new lesion evolved in the right frontal lobe. Thus, the disease had begun to spread, suggesting systemic disease of the meninges. The patient underwent a fourth surgery in January 2014 resulting in complete removal. Postoperative RT was given targeting the new area using a 3D-conformal coplanar field geometry. Three series including 50.4 Gy in 28 fractions and 2 boosts of 10 Gy and 3.6 Gy in 7 fractions were delivered, for a total dose of 64 Gy in 35 fractions. Histologic reexamination revealed predominately spindle cells with elongated nuclei, summarized in Fig. 1. Proliferation activity (Ki67) was low (ca. 5%). Vimentin, CD34, Bcl-2, STAT-6, and CD99 were strongly expressed, but there was no epithelial membrane antigen expression. Strong, homogenous, and nuclear expression of STAT-6 allowed the final diagnosis of SFT. The change in the morphology as seen in Fig. 1A compared with Fig. 1B in the histologic analysis of the relapsing disease after prolonged time and repeated therapies is common, and time and therapies explain the change in appearance. Often, relapsing disease has a more aggressive morphology, which was indeed a case in our patient, and the diagnosis was confirmed with positive STAT-6 staining in 2019. Figure 2 illustrates the course of RT treatment courses over time, revealing acceleration.

Two years later, in 2015, follow-up MRI studies showed 3 new lesions: 1 was ventral to the pons, and the other 2 were on each side of the anterior cerebellum. Because of progressive disease and reluctance to keep using RT, chemotherapy with cisplatin 462 mg (20g/m^2), ifosfamide 258 mg (1200 mg/m^2), mesna, and etoposide 160 mg (75/m^2) were initiated. Disease progression was noticed after 3 cycles and chemotherapy was discontinued. Fractionated stereotactic radiosurgery (SRS) was used to deliver a total of 56 Gy divided into 3 series to the lesion ventral to the pons. The first series of 6 Gy was provided in 3 fractions, the second of 40 Gy in 16 fractions, and the third of 10 Gy in 5 fractions. Figure 3 shows the long-lasting control during follow-up. Figure 4 illustrates the volume reduction visualized on follow-up T2-MRI studies. The 2 lesions in the anterior cerebellum were treated with a total of 54.4 Gy each delivered in 2 series. The first series of 40 Gy was provided in 16 fractions and the second of 14.4 Gy in eighth fractions, resulting in a partial response without evidence of relapse during 7 years of follow-up.

One year later, the patient remained clinically stable until MRI follow-up studies in 2016 showed 3 new lesions: 1 in the left anterior cranial fossa and 2 in the left temporal area. The patient preferred nonsurgical therapies, so that in the years to follow SRS became the preferred treatment. The left frontal lesion was irradiated with a total dose of 50 Gy in 20 fractions, and the 2 temporal lesions were treated with 50 Gy in 10 fractions.

Another year later, in 2017, 4 new masses emerged on the MRI studies: 1 lesion in the right cerebellopontine angle, 1 between the crura cerebri and dorsal to the basilar artery, another on the left sphenoidal bone, and 1 in the left frontobasal cortex. This year, 2 lesions in the left brain

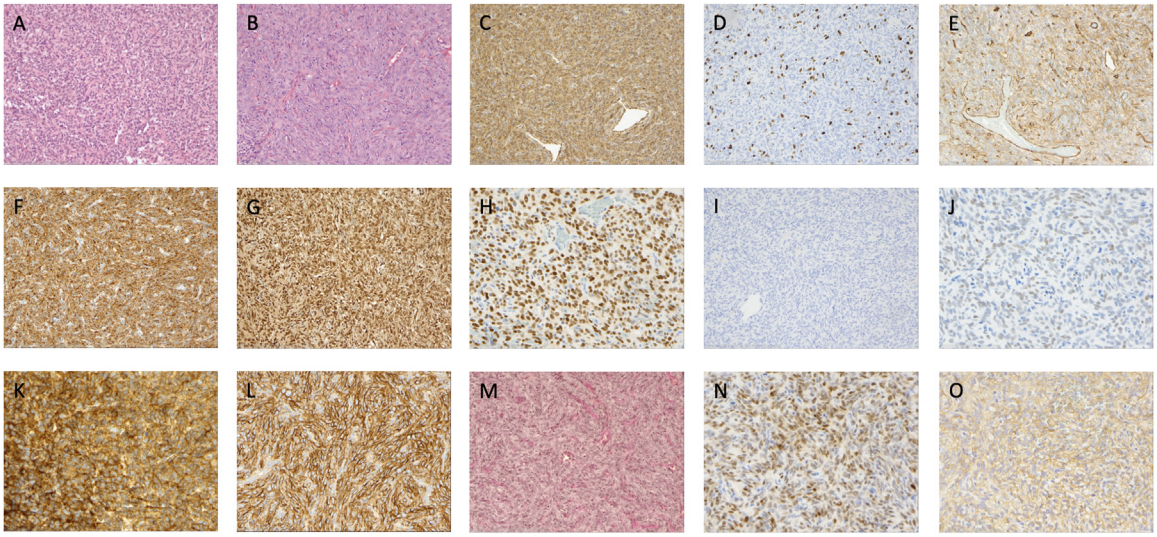

Figure 1 Histologic characteristics (magnification is f = 20 except for H, J, K, L, N, and O, f = 40; staining is from 2019 except for A and K, staining from 2014). (A) Hematoxylin eosin. (B) Hematoxylin eosin. (C) Vimentin. (D) Ki-67. (E) CD34. (F) Bcl-2. (G) STH. (H) STAT-6. (I) EMA. (J) CD117. (K) CD99. (L) CD99. (M) Van Gieson's stain (EvG). (N) CDK4. (O) Epidermal growth factor receptor.

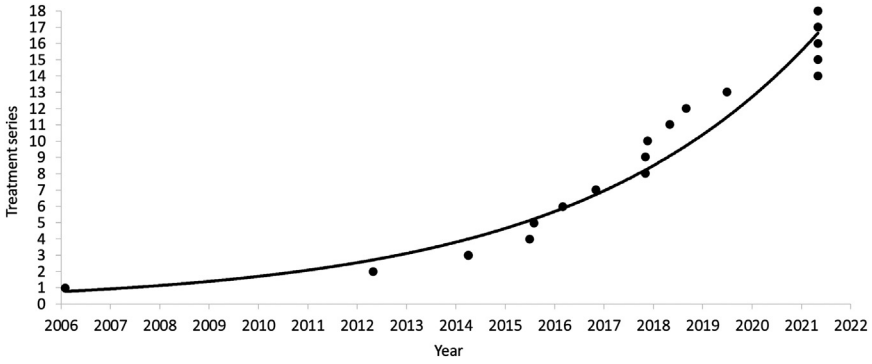

Figure 2 Timeline of radiation therapy series for 15 years. Hypofractionated radiation therapy was used beginning in February 2006. A total of 23 series were delivered. However, only 19 are visible: 3 series delivered ventral to the pons are resumed in 1 point, and 4 series given to the left and right anterior cerebellum in the same year are summarized in 2 points.

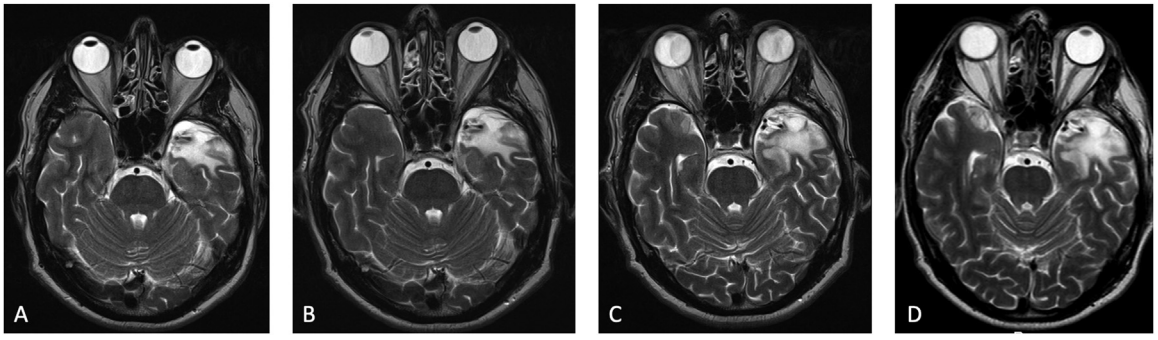

Figure 3 Evolution of left temporal brain structures shown on T2 magnetic resonance imaging studies: (A) 14.11.2011, (B) 06.11.2013, (C) 20.02.2016, (D) 15.02.2018.

were treated with RT: the retro-orbital and the frontal lesions were treated using SRS with 35 Gy in 5 fractions for each.

In 2018 a new lesion appeared, and the 2 so far untreated lesions were all treated. One with 45 Gy in 5 fractions located close to the sella turcica, 1 with 27 Gy in 3 fractions in the left posterior fossa, and 1 located in the temporoparietal brain on the left treated with 35 Gy in 5 fractions.

In 2018, a new mass appeared in the parasellar region, and 3 series of RT were applied: 1 of 45 Gy in 5 fractions targeting the new lesion close to the sella turcica, 1 of 27 Gy in 3 fractions aimed at the mass from 2017 in the left posterior fossa in the basal part of the cerebellum, and 35 Gy in 5 fractions targeting the temporoparietal lesion, another mass from 2017.

In 2019, a new lesion emerged in the left paramedian midbrain and was irradiated with 35 Gy in 5 fractions.

The last 5 RT treatment courses were given in 2021 because of disease progression. All lesions were treated with 40.5 Gy in 9 fractions. Targets were right paramedian and infratentorial, left temporobasal, frontal supraorbital, and parietal regions.

Figure 5 shows the pattern and sequence of recurrences of SFTs over the years, color-coded for the years of RT. The RTs in the first years were limited to the left middle fossa, then gradually moved to the anterior fossa, and finally to the posterior fossa.

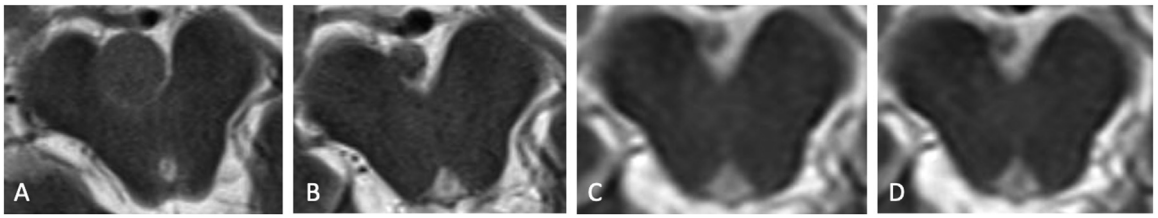

Figure 4 Evolution of the prepontine lesion shown on magnetic resonance imaging. T2-imaging studies: (A) 09.11.2015, (B) 13.03.2016, (C) 30.03.2017, (D) 15.02.2018.

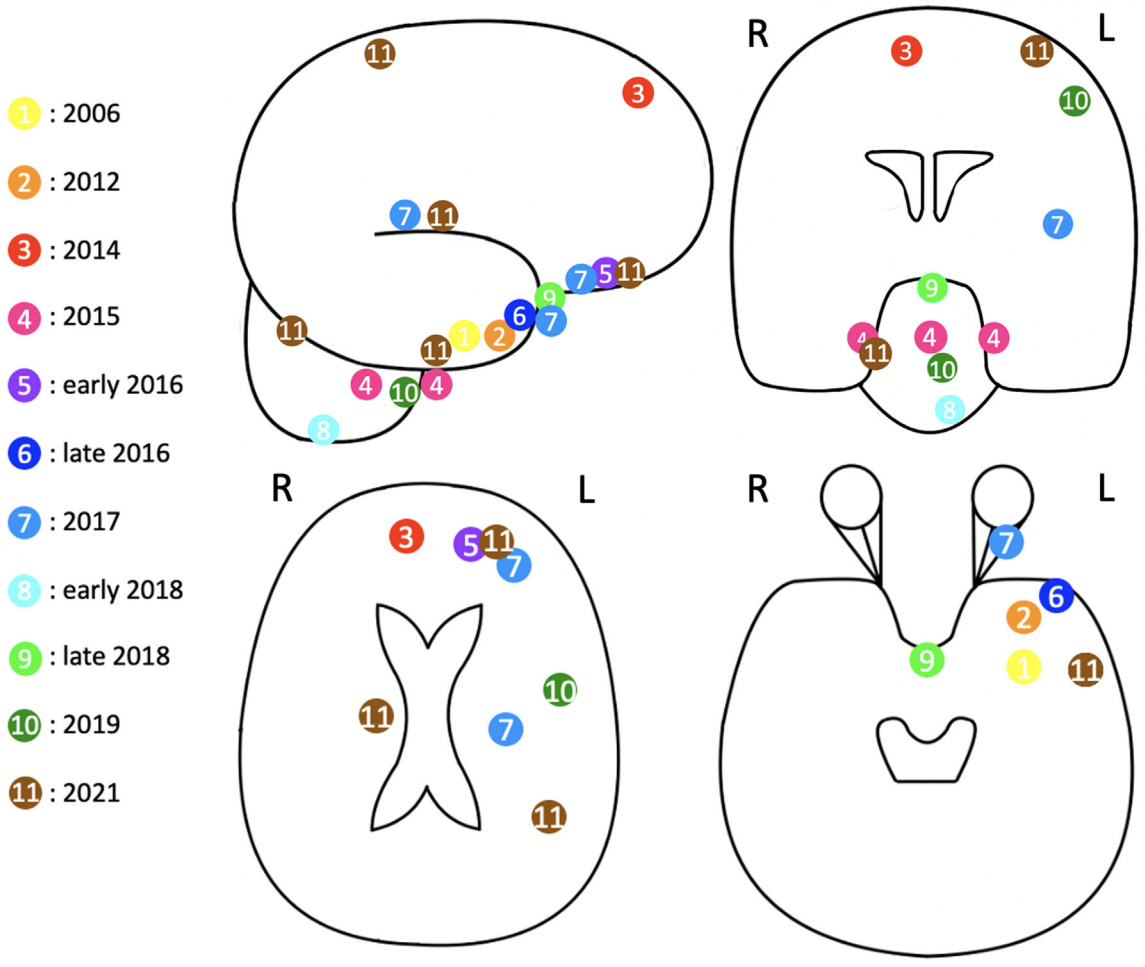

Figure 5 Irradiated lesions (all recurrences treated with radiation therapy are represented in the sagittal plane and in at least 1 other plane). (A) Sagittal, (B) coronal, (C) axial superior, and (D) axial inferior. The division by colors is done by periods. The 3 series delivered in mid-2015 are shown with the same color, as are the 2 from 2017, the 2 from late 2018, and the 5 from 2021 (see Fig. 3).

The frequency of RT and thus of relapse rate seemed to accelerate over the years. Figure 3 illustrates the RT series over time. In fact, for more than 6 years, from 2006 to 2012, the patient had no RT treatment. Then the frequency of relapses gradually increased.

In summary, from 2006 to 2021, the patient underwent 26 series of RT with a total prescribed dose of 866.3 Gy. $D_{2\%}$ was 114.78 Gy, and D_{max} was 153.15 Gy; 283.3 mL of a total of 1568.7 mL brain tissue was treated with more than 66 Gy; 485.9 mL was treated with a dose exceeding 50 Gy and 660.3 mL with a dose exceeding 40 Gy. Figure 4 shows the sum plan in 3 views. Although the prescribed dose exceeded any known dose levels used in clinical radiation oncology, the patient did not suffer from tissue necrosis, high intracranial pressure, or any other symptoms treatable with corticosteroids. Figure 6 shows the sum plan of the photon treatments revealing the highest doses achieved in the temporal lobe left and frontal left. The cumulative treatment in that left temporo-anterior lobe resulted from 3 relapses in that area from 2004 until 2021 and 3 RT courses in 2006, 2016, and 2021 treated with 60 Gy in 30 fractions, 50 Gy in 5 fractions, and 40.5 Gy in 5 fractions, resulting in a corresponding equivalent dose in 2 Gy fractions of 205.12 Gy assuming an α:β ratio of the brain of 2.6.

Figure 7 shows the dose-volume-histogram of the cumulative RT dose delivered over a 16-year period to selected structures. We restrain from normalization to 2 Gy equivalent dose because of lack of comparative data and clinical relevance. Interestingly, despite the cumulative dose given to the left hippocampal region exceeding the dose given to the right hippocampus, the right-handed patient (left dominant hemisphere) showed no deficit.

The clinical course until 2017 was remarkably quiet and only persistent alopecia of the left skull was documented. However, the patient experienced activity-induced headaches since the end of 2015, followed by occasional dizziness and complains of light-headedness. Apart from that, he did not mention any physical issue

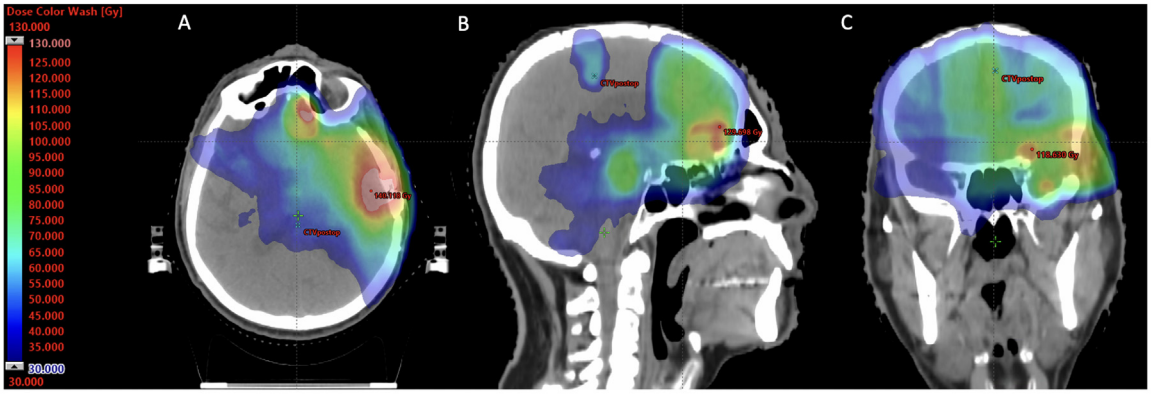

Figure 6 Sum plan of treatments with photons and dose distribution from 2006 until 2021. Magnetic resonance imaging planes. (A) Axial, (B) sagittal, (C) coronal. Rainbow color-coded dose distribution indicates highest doses in the left temporal and left frontal areas. Large areas of the brain were spared from significant radiation dose.

and there were no obvious psychopathologic abnormalities. He retired from work in 2015 at the age of 55 years.

The neurologic status changed after the treatments in 2019. The quality of the communication with the patient during medical visitations had changed. Over the years, the patient became more deliberate and content, whereas for many years before he had difficulties coping with the relapsing disease and retreatments, as well as with the impact on his ability to speak and express himself fluently after the retreatments of the temporal left lobe. Slight dysarthria, amnesic aphasia, and sluggishness were noticed. Motor and sensory functions remained normal. A neuropsychological examination was performed in October 2019 after 13 RT series and 653.8 Gy delivered to the brain and then repeated in March 2022 after 26 RT series and 866.3 Gy of total dose given to the encephalon.

Neuropsychological assessments

In 2019, a standard premorbid level of intelligence (IQ) of 92 was measured using a vocabulary test (WST) to assess the baseline for subsequent neuropsychological tests (normal range of IQ is between 85 and 115). The follow-up test results are given in percentage ranks (PR), T-values, and age value points. The normal range of PR is 16 to 84, 40 to 60 for T-values and ranges from 7 to 13 for age value points.

Memory function

The verbal learning and memory functions assessed with the Verbal Learning and Memory Test are presented by means of PR. The patient's short-term memory was in the average range and stable with a PR = 70 to 85 in 2019 and 2022. Learning performance decreased from PR = 70 in 2019 to PR = 30 to 35 in 2022. Both measurements remained within normal range. The retrieval effectiveness was stable with a PR of 50 to 60 in 2019 and 2022, as well as the word-recognition performance with a PR > 80 in 2019 and 80 to 95 in 2022.

Visual memory performance was verified by the Rey-Osterrieth Complex Figure Test. In the immediate and delayed free retrieval of the Rey complex figure our

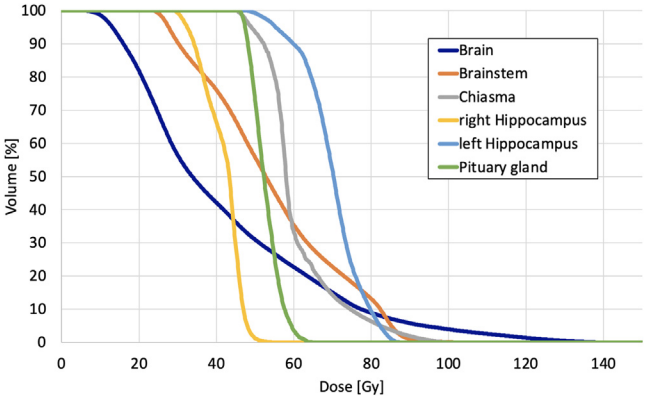

Figure 7 Dose-volume histogram of the cumulative dose delivered over a period of 16 years to selected structures at risk in the central nervous system.

patient achieved a result within the average range at both times of investigation (2019: PR = 82 | 2022: PR = 58).

Attention performance

Attention performance assessed with the Test battery of Attentional Performance measures was stable from 2019 to 2022. In the Go/NoGo Test, time for decision making was average (2019: T-value = 56 | 2022: T-value = 53), as was the ability to control reactions measured by the number of errors (2019: T-value > 48 | 2022: T-value > 48). Regarding the multitasking ability in the Divided Attention Test, the number of omission errors was stable from 2019 (T-value = 42) to 2022 (T-value = 59), indicating a very good ability to handle more than 1 metal task at the same time. In 2019 (T-value = 61) and 2022 (T-value = 63), no false reactions were observed, showing a performance above the average.

The third test was a subtest of the Wechsler Adult Intelligence Scale: The Digit Span Test, used to measure attention span and working memory. Assessment in 2019 revealed 6 age value points, equivalent to 20 raw value points. In 2022, the patient had a total of 21 raw value points, which corresponded to 7 age-corrected value points. With a difference of 1 raw value point between 2019 and 2022, performance remained stable at a low average level.

Executive functions

In most of the paradigms of the Regensburger Word Fluency Test, the patient yielded normal results (semantic-categorical word fluency: PR = 63 in 2019 ["animals"] and PR = 42 in 2022 ["food"] | semantic category change: PR = 17 in 2019 ["sports-fruits"] and PR = 29 in 2022 ["garments-flowers"] | formal lexical word fluency: PR = 19 in 2019 ["S-words"] and PR = 23 in 2022 ["P-words"]). For the subtest assessing the formal lexical category change, 2022 showed a significant deterioration in performance to a far below-average level in comparison to 2019 (PR = 26 in 2019 ["switch G-R-words"] and PR < 1 in 2022 ["switch H-T-words"]).

The Trail Making Test revealed an average processing speed (part A) but a below-average performance (PR = 5-10) in part B, indicating reduced cognitive flexibility remaining unchanged from 2019 to 2022.

The last test in the section of executive functions to discover possible planning deficits was the qualitative evaluation when drawing the complex Rey figure. The patient showed no evidence of planning deficits in either 2019 or 2022 (2019: 32 out of 32 possible points achieved | 2022: 31 out of 32).

In 2022, the patient's cognitive performance deteriorated only in the category of partial performance of the executive functions (formal lexical category) compared with 2019. In the other sections of the test study, the results were comparable to normal, and therefore, the global cognitive functions were estimated to have retained as stable overall.

In summary, with normal everyday competence but abnormalities in a few subtests of the neuropsychological examination, the diagnosis of a mild cognitive disorder was retained. The patient's performance and life in daily routine remained stable, being self-sufficient and with an independent lifestyle.

Because of new lesions in the right anterior and parietal parts of the meninges, a treatment with sunitinib was started in July 2022 and changed to pazopanib 3 months later because of minor progression shown on MRI studies.[25] In early 2023, without any clinical changes, subtle progression of the frontal lesion on the right was confirmed and surgical resection was discussed with the patient, who was reluctant to undergo further invasive therapy, and elective resection was planned for summer 2023. Unfortunately, the patient suffered from a first and single episode of a massive right hemi-cranial cerebral hemorrhage and died on July 4, 2023. An autopsy could not be performed.

Discussion

SFTs are rare fibroblastic tumors with the feature of having a NAB2-STAT2 gene rearrangement,[3] leading to an atypical accumulation of STAT6 protein in the nuclei of tumor cells.[26] Martin-Broto et al[27] proposed a classification to estimate the risk of relapses based on age, size, mitotic count, tumor necrosis, and tumor localization. In general, SFTs are considered to be benign and indolent tumors. The prognosis is favorable for most patients after complete resection. However, the term "solitary" may be misleading because relapses do occur, as seen in the present case. In the first reported cases of SFTs in 1996, this type of tumor was described without recurrences.[28] Atypical histology and incomplete resection are unfavorable prognostic features.[9] However, the prognostic factors have not been elucidated conclusively,[2] and only short-term follow-ups have been published with just a few relapses.[9] Only in more recent literature with a longer follow-up was it revealed that recurrences may occur.[2]

Local control is achieved with radical surgery and pre- or postoperative RT, especially if only subtotal resection can be achieved, as in the case of broad-based tumor attachment to the dura.[15,29-32] RT is used in cases of incomplete resection, after relapse, or in the presence of atypical histology. Intensity modulated RT might be preferable to postoperative stereotactic radiosurgery, especially if it is important to achieve a good coverage dose.[33] Haas et al[34] reported the outcome of 89 patients with SFTs and observed a better local tumor control with adjuvant RT after surgery compared with surgery alone. Because of the lack of randomized controlled trials, the role of postoperative or adjuvant RT remains unproven.

An example of the efficacy of RT without any surgery in the present case is illustrated in Fig. 4. A prepontine lesion treated with RT alone decreased in size from 2015 to 2018 after 60 Gy using daily doses of 2 Gy. Hence, macroscopic disease can be reliably controlled with highly conformal RT. Therefore, we think it is reasonable to await relapses after initial surgery and use RT for salvage therapy, especially if multiple recurrences are observed and gross total resection can be repeated safely.

Chemotherapy is rarely used for SFTs. There is a lack of controlled studies of standard cytotoxic drugs on this type of tumor.[27] Few cases treated with dacarbazine or temozolomide have been reported with positive results.[35] Antiangiogenic drugs have been proposed for the treatment of SFTs. Pazopanib, sunitinib, and sorafenib are multitargeted kinase inhibitors that inhibit vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and block angiogenesis, as does bevacizumab. In the present case, pazopanib was initiated in October 2022 after new lesions emerged in 2022. Unfortunately, excellent tolerance of the medical treatment and reluctance by patient and doctor to proceed once more with another invasive therapy without any new symptoms led to prolonged treatment with pazopanib over a period of 9 months. We can only speculate that immediate local therapy in spring 2023 could have prevented lethal cerebral hemorrhage in early summer 2023. Indeed, treatment with antiangiogenic tyrosin-kinase inhibitors has been associated with intracerebral bleeding.[36]

Radiation techniques and practice evolved from 2006 to 2021. The first RT series delivered to our patient was with 3D conformal RT, while SRS and stereotactic body RT were used in the series beginning in 2015. We use a linear accelerator based radiosurgery system and a technique with multiple noncoplanar partial arcs and modulated fields to ascertain the delivery of at least 90% of the prescribed dose to the margin of the tumors and to limit overdosage within the target, as described previously.[37] Clearly, damaging healthy brain tissue has been a major concern and highly conformal dose delivery a major issue in repeated RT. RT impacts cognitive functions leading to memory disorders, focal neurologic deficits, and progressive dementia. Risk factors that lead to more serious cognitive dysfunctions are advanced age, smoking, high radiation dose, and simultaneous chemotherapy. The injury caused by radiation is the result of dynamic interactions between astrocytes, microglia, oligodendrocytes, endothelial cells, and neurons that initiate an inflammatory cascade causing neurologic damage. Factors contributing to this cascade are damage to the blood-brain barrier, neural progenitor cell death, astrocyte senescence, and loss of hippocampal neurogenesis.[38] Jalali et al[39] compared conventional RT and SRS in 200 patients with benign or low-grade brain tumors. They concluded that after 5 years, patients treated with radiosurgery had better neurocognitive functional results than those treated with conventional RT.

Figure 7 shows the dose volume histogram of the cumulative RT cumulative nominal dose to structures at risk for radiation-induced damage. The neuronal stem cell compartment of the hippocampus is of major concern. If exposed to ionizing radiation, it may be damaged and result in neurologic deficits.[38] Noteworthy, the left hippocampus was irradiated with a cumulative high dose over many years in this right-handed patient. Therefore, dose delivery extended over many years, clearly increasing the tolerability of critical neural structures. The sequelae of repeated RT on the left temporal brain structures between 2011 and 2017 are illustrated in Fig. 3, revealing gliosis (especially in the left temporal lobe), dilatation of the ventricles, and atrophy of the ventral part of the corpus callosum. It is well established that RT causes accelerated loss of brain tissue compared with the physiological atrophy during aging.[40,41] Reirradiation, however, does not seem to accelerate the loss of healthy brain tissue.[42] More recently, McGovern et al[43] reported the feasibility of retreatment with dose constraints up to max D1 cc [brain − planning target volume] of 105 Gy, with only 1 of 20 patients suffering from radionecrosis of the brain. In the present case, D2% was only 114 Gy and the Dmax only 153 Gy, although conversion of the applied doses from hypofractionated treatments to equivalent dose in 2 Gy fractions resulted in an estimated cumulative dose exceeding 200 Gy. Reirradiation with highly conformal dose-delivery targeting techniques is a valid treatment option for intracranial control for relapsing SFTs. Dose distributions as used in stereotactic body RT and SRS might be especially useful.

Our patient tolerated a total prescribed dose of 866.3 Gy to a limited volume of the brain, delivered over a period of 16 years. A good quality of life despite recurrences, characterized by independence and autonomy, was maintained. The highest dose of radiation so far prescribed and reported in the literature for a patient with SFT of the brain is a series of 60 Gy of adjuvant RT after primary resection. However, the patient died 22 months later from fulminant radionecrosis. In the present case, the patient received a prescribed total dose much higher than generally accepted for RT of the brain, but over many years. During that time, there was no need for medication with corticosteroids in the context of RT, antiepileptics, or hormonal substitution therapy.

Neurologic alterations after RT of the brain evolve over time and are gradual. Especially in children, it has been well documented that neurotoxic therapy of the brain can reduce brain substance, leading to impaired intelligence and attention.[44] In the present case, we were repeatedly challenged to withhold RT and had to weigh the risk of repeated surgery against reirradiation of any new lesions because of the additional damage and the preceding treatments. Neuropsychological assessment was performed

only late during the disease, and the noticed changes suggested a serious impact of repeated RT. Executive functions were impaired and seemed to be more affected than intelligence or attention capacities, in contrast to observations in children, who seem less prone to impairment of executive functions after RT to the brain.[45] Rigorous reassessments of the clinical status and of the perceived benefits of reirradiation define an important interdisciplinary setting for radiation oncologists, neurologists, neurosurgeons, and neuropsychologists.

Conclusion

Highly conformal RT and SRS can achieve long-term control of SFTs. This is especially true in a situation with multiple recurrences. The present case reports the highest dose of ionizing radiation ever prescribed to a human brain. Highly conformal dose delivery is critical to minimize long-term toxicity and preserve neurologic and cognitive functions.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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