Case report

# A 71-year-old man with a rare rhabdoid brain tumour: using a multidisciplinary medical and rehabilitative model of care

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## SUMMARY

Atypical rhabdoid tumours (AT/RTs) of pineal origin are rare in adults with rapid progression and poor prognosis. We present the case of a 71-year-old man with confusion and memory loss who was diagnosed with a pineal AT/RT after genetic analysis. Due to his limited functional capacity and goal to return home with family, a multidisciplinary care approach was essential for coordination of medical management, radiation treatment and acute inpatient rehabilitation. After diagnosis and rehabilitation, his functional ability improved allowing him to tolerate cranial irradiation, initiate systemic chemotherapy and eventually returned home for a brief period with an improved quality of life. His progress was temporary due to rapid progression of the tumour. He required additional aggressive oncological treatment and was admitted for subsequent inpatient rehabilitation before opting for hospice care. This case underscores the importance of a multidisciplinary approach to cancer treatment in a patient with a rare and aggressive brain tumour, while respecting the individual goals of patients and their families.

## BACKGROUND

Malignant rhabdoid tumours (RTs) are described in the literature as a paediatric cancer of primitive renal tissue with poor prognosis. Extrarenal malignant RTs in children represent a rare subset, referred to as an atypical RT (AT/RT). AT/RTs predominantly occur in the posterior fossa of infants and young children less than 3 years of age. The clinical and pathological features of AT/RT were first defined in 1996, based on data from 52 infants and children. However, the overall prevalence of this tumour is quite low.[1] From 2007 to 2011, 16 044 children were registered with this diagnosis in the Central Brain Tumor Registry of the United States.[2] This malignancy constitutes 1 in 16 major embryonal tumour entities according to the 2016 WHO classification of central nervous system tumours.[3]

In adults, the first reported case of AT/RT was described in 1992. Since then, over 30 cases have been reported in adults. Dardis *et al* found that adult AT/RTs are diagnosed at a median age of 32, with 54% of cases discovered in women.[4] In contrast to paediatric cases which involve the cerebellum, ventricles or frontal lobe, most adult AT/RTs are located in the cerebral hemispheres and are rarely found in the pineal region.[4 5] At present, there are limited adult AT/RT cases of pineal origin described in the literature.[1] The increase in diagnosis of AT/RTs in adults is hypothesised to be due to increased sensitivity of diagnostic modalities, including array hybridisation and parallel sequencing, among others, which have allowed the identification of the tumour's unique genetic signatures.[1 4 5] These advances are projected to have a significant impact on the diagnosis and eventual clinical management of affected patients.

## CASE PRESENTATION

A retired 71-year-old man with a medical history of medication-controlled hypertension presented to a rural emergency department with acute confusion and memory loss. His wife reported that he became confused while driving around his hometown performing daily errands and could not find his way home. Preliminary physical examination was remarkable for decreased orientation status and lethargy without evidence of focal neurological deficits.

## INVESTIGATIONS

Workup was initiated at the referring hospital. Basic laboratory tests were within normal limits. Brain MRI revealed a 3.2×1.9×2.5 cm enhancing pineal mass extending into the quadrigeminal plate cistern resulting in hydrocephalus secondary to mass effect on the tectal plate.

The patient was admitted for endoscopic third ventriculostomy with biopsy of the mass. The immediate postoperative course was complicated by hyponatraemia, encephalopathy and functional decline secondary to new biventricular haemorrhage and hydrocephalus. He was medically stabilised and discharged to a local acute inpatient rehabilitation facility. However, he transferred back to the hospital after his mental status rapidly declined.

On re-evaluation, CT of the head revealed significant new hydrocephalus in the setting of rapid tumour growth, with the lesion now measuring 4.7×3.3×4.2 cm (figure 1). Emergent placement of an external ventricular drain (EVD) was required, followed by placement of a right-sided ventriculoperitoneal (VP) shunt. While the patient did not report further problems, his family noted behavioural changes, including paucity of speech and flat affect.



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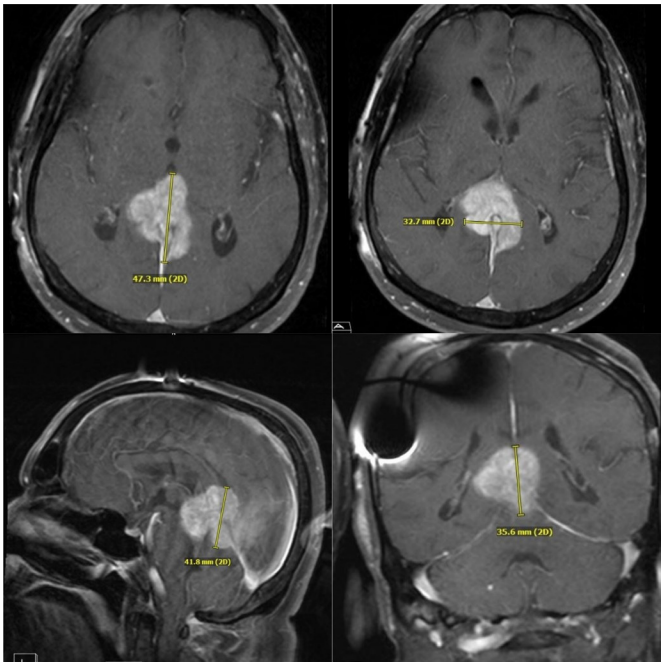


**Figure 1** Transverse (top left and top right), sagittal (bottom left) and coronal (bottom right) T2-weighted brain MRI images from referring hospital with measurements overlayed on the brain tumour. 2D, two dimensional.

Initial tumour pathology became available and revealed RT cells with large, eccentric nuclei, prominent nucleoli and ample eosinophilic cytoplasm. The cells tested positive for AE1/AE3, vimentin and focally positive for epithelial membrane antigen (EMA). Rare scattered tumour cells showed reactivity for smooth muscle actin (SMA). The cells were negative for CK 7, CK 20, synaptophysin, chromogranin, GFAP and pan-melanoma, TTF-1, PSA, S100, SALL4 and OCT3/4. Nuclear reactivity for INI-1 was lost in the tumour cells.

He was medically stabilised and his care was transferred to a tertiary, level I hospital system for further management due to the rare nature of his tumour. The patient's clinical course was progressive. Follow-up imaging demonstrated rapid growth of the tumour, now measuring 5.2×3.7×4.5 cm (figure 2). His course was further complicated by a subdural empyema that required evacuation, VP shunt revision and prolonged intravenous antibiotics. He required seizure prophylaxis and dexamethasone. Staging imaging was completed and demonstrated no evidence of metastatic disease. Recommendation was made to initiate cranial radiation treatment while he was admitted to an academic acute inpatient rehabilitation hospital. Systemic chemotherapy (a preferred combination of etoposide and carboplatin) was deferred due to concern for physical deconditioning and poor functional status.

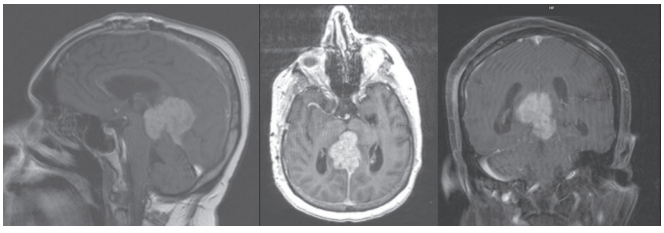

**Figure 2** T1-weighted sagittal (left), transverse three-dimensional T1-weighted with gradient-echo imaging (centre) and coronal T1-weighted with fat suppression (right) brain MRI images roughly 1 month after initial presentation from the referring medical facility.

During inpatient rehabilitation, the patient demonstrated impaired attention, poor initiation and significant impairments with safety, judgement, problem solving and comprehension. The functional independence measure (FIM) is the most widely accepted functional assessment measure in the rehabilitation community and is an 18-item ordinal scale for use with all rehabilitation diagnoses. FIM scores can be scored by therapists from total assist to complete independence depending on the functional status of each patient.[6] Physical therapy noted significant deconditioning. He required maximum assist with all transfers and was fully dependent to walk 10 feet with a wheeled walker. He needed total assistance for activities of daily living (ADLs) such as hygiene and dressing as well as instrumental ADLs.[6] His memory, both short and long term, was maximum assist. He was managed for disrupted sleep–wake cycle and intermittent agitation. His functional baseline prior to diagnosis was full independence with ADLs. His rehabilitation goal was to return home with family with appropriate assistive devices at a level of supervision to minimum assistance on a majority of functional tasks detailed above.

To aid in poor initiation and impaired attention, he was started on methylphenidate. After 1 month of acute rehabilitation, his function improved to moderate assist level with transfers and ambulation with a wheeled walker. He only required supervision for wheelchair propulsion. He attained minimal to moderate assist with bathing and toileting but was still maximum assist with lower extremity dressing. Although still moderate assist with comprehension, problem solving and memory, his attention and initiation were significantly improved. He was eventually able to return home with family support. His wife reported that the patient was able to return to running errands with her, read the newspaper daily and go out to dinner with friends and family. His cognition and comprehension still limited the depth of conversation, but he was easily able to interact with others.

The patient's functional status improved and allowed for initiation of maintenance chemotherapy with temozolomide. However, the patient became progressively encephalopathic in his first week of temozolomide treatment and he was admitted to the hospital. Initial workup was negative. He was returned to acute rehabilitation with the goal of once again improving his functional status to allow for reinitiation of chemotherapy. On initial examination, he was noted to have new cogwheel rigidity.

## DIFFERENTIAL DIAGNOSIS

Extensive laboratory and imaging tests were undertaken, as outlined. While the patient's recurrent enceophalopathy was evaluated at several stages of his course, the primary aetiology was thought to be related to tumour burden and resulting hydrocephalus. He was also found to have an intracerebral infection early in his hospital course, which likely contributed to his mental status change at that time. However, the cause of prolonged delirum was likely multifactorial and evolved throughout his course. Organic causes of delirum and decreased cognition were evaluated at different time points. At each time point, the differential diagnosis included hydrocephalus, hyponatraemia, systemic infection, polypharmacy, chemotherapy side effect, Parkinsonism and hospital-acquired delirium.

## TREATMENT

The treatment strategy established by oncology for his brain tumour included cranial irradiation (46 gray (Gy) in 23 fractions) scheduled over roughly 5 weeks. There was no recommendation for additional radiation, as the staging imaging, including spinal MRI, did not demonstrate extracranial disease. Due to his poor functional status and concern for myelosuppression, aggressive systemic chemotherapy (a preferred combination of etoposide and carboplatin) and other intervention were deferred. He was transferred to an academic acute inpatient rehabilitation hospital. The plan was to follow up with oncology a month after completion of radiation treatment to discuss possible single-agent chemotherapy protocols if his functional status improved. After completion of radiation therapy and discharge from acute inpatient rehabilitation to home, the patient was unable to tolerate repeat imaging to monitor for progression of disease and metastasis due to a panic attack. A T1-weighted brain MRI scan was partially completed and demonstrated decrease in tumour size (4.5×2.2×3.0 cm). Despite the high risk of recurrence, the family opted for a plan to attempt repeat imaging at 3-month follow-up. He was initiated on temozolomide maintenance therapy (150 mg/m$^2$) on days 1–5 of a 28-day cycle, but was discontinued after only a few doses as his condition worsened and he was readmitted to a local hospital.

To optimise his ability to participate in rehabilitation, the decision was made to start the patient on methylphenidate, extrapolating management strategies from the traumatic brain injury and oncology literature.[7 8] This improved his initial rehabilitation course, but proved unsuccessful in subsequent hospitalisations once his disease had progressed. After displaying cogwheel rigidity on examination, he was also trialled on carbidopa–levodopa (10–100 mg three times per day) with brief improvement in cognitive symptoms and participation with therapy.[9–12]

## OUTCOME AND FOLLOW-UP

At the last stage of his course, he developed sudden-onset neck pain along with left upper extremity weakness and flaccid paralysis of bilateral lower extremities. MRI imaging demonstrated an acute T2 compression fracture, epidural mass from C7–T4, cord compression from T1–T6 and enhancement of his primary lesion. The imaging was concerning for drop metastases extending from C7 inferiorly to T4 and leptomeningeal enhancement at the conus medullaris. Neurosurgery recommended no surgical intervention. Oncology recommended palliative spinal irradiation from C7–T4 (20 Gy in 5 fractions) and a dexamethasone taper. The family supported the patient as he completed palliative radiation therapy before returning home with hospice care 5 months after initial diagnosis. The patient passed away from his disease 8 months after initial presentation.

## DISCUSSION

AT/RT is a devastating and rare diagnosis characterised by very rapid progression and poor outcome. Younger age appears to be a significant prognostic factor with better survival rates, as compared with older individuals.[1 13–23] The origin of cancer cell lines in these tumours remains elusive as they display characteristics of rhabdoid cells, along with a variable combination of primitive neuroectodermal, mesenchymal and epithelial components. Traditionally, it is the varying combinations of ectodermal and mesodermal cell lines that have rendered AT/RTs difficult to diagnose as they display a wide range of positive staining with immunohistochemistry. Recently, advanced genetic techniques have enhanced our diagnostic ability: loss of INI-1 protein expression is now considered a defining feature of AT/RT.[24] Partial deletion of chromosome 22, where the chromatic remodelling complex gene SMARCB1 is located, has also been identified in the majority of cases.[25] When used in combination, these tests are considered to have a specificity of 100% for AT/RT.[4]

Adult patients present a unique diagnostic challenge, as the differential diagnosis for malignant tumour with rhabdoid features is broad. Prior to the widespread use of genetic testing, more common tumours such as rhabdoid glioblastoma, rhabdoid meningioma, metastatic melanoma and metastatic carcinomas with rhabdoid features may have been overdiagnosed.[1] In addition, adult AT/RTs of the pineal gland is uniquely difficult from a diagnostic standpoint (table 1). This is because this region is a common site for primary teratomas, which share some similar molecular features with AT/RT. Several adult cases of adult pineal AT/RT have been published and are summarised in table 1.

As with other rare tumours, there are no uniform treatment protocols for AT/RTs in adults and paradigms have been extracted from the paediatric literature. Regimens in the paediatric population vary, but commonly using vincristine with an alkylating and platinum agent. In the adult population, most centres recommend resection at diagnosis, with the eventual goal to continue treatment with adjuvant therapies. However, pineal tumours are less amenable to primary resection. In a review of 42 published cases of hemispheric adult AT/RT, Dardis *et al* summarised that radiotherapy was undertaken in 79%, systemic chemotherapy in 40% and craniospinal irradiation in 15% of patients. Mortality remained similar despite the differing treatment methods. Treatment strategies specific to adult pineal AT/RTs may be compared in table 1.

Parkinsonism has been closely related with brain tumours and include symptoms of akinesia, rigidity, resting tremor and impaired postural reflex.[10] Although there are no large studies to evaluate treatment options, there are small case series and case reports on the topic. Chuang *et al* reported chemotherapy-induced Parkinsonism as a rare neurological complication of cancer treatment.[9] There are multiple suggested pathways including de novo Parkinsonism or a worsening of pre-existing Parkinson's disease.[9] They reported three patients who responded well to levodopa, rapid even within the first few days after initiation.[9] The patient who improved, maintained it even after levodopa was discontinued.[9] Mehanna *et al* reported three cases of levodopa-resistant Parkinsonism after radiation therapy.[11] One patient was an elderly man who demonstrated progressive worsening gait, motor slowness and left-sided weakness that developed while undergoing 30 sessions of radiation therapy.[11] The patient was trialled on carbidopa–levodopa 10–100 mg three times per day with brief to no improvement in his symptoms.[11] Medication intervention to help with rehabilitation can be challenging balancing small series of case reports with inconsistent results.

Notwithstanding the nature of the treatment regimen, studies suggest that patients who participate in cancer rehabilitation may experience better functional outcomes and quality of life.[26] This occurs after the time of cancer diagnosis but before systemic treatment, and includes both physical and neuropsychological assessments to establish a baseline functional level. This allows for targeted intervention to help improve status and by extension allow for an increased ability to tolerate toxic therapies. The patient in our case underwent rehabilitation in several phases, which was coordinated with the oncological and surgical teams to maximise both treatment and functional goals. While he ultimately did decline and opted for palliative management, he experienced significant short-term improvement in his

**Table 1** Summary of patient characteristics and treatment strategies for current reported cases of pineal atypical rhabdoid tumour in adults

| Author | Year | Patient demographics | Brief overview of treatment | Outcome |
|---|---|---|---|---|
| Sugita *et al*[13] | 1999 | 27 yo M | Surgery, radiochemotherapy | Died 2 years after diagnosis |
| Ingold *et al*[14] | 2006 | 45 yo F | Surgery x2, radiochemotherapy, ventriculoperitoneal shunt | Died approximately 8 months after diagnosis |
| Takei *et al*[1] | 2010 | 33 yo F | Surgery, radiochemotherapy, ventriculoperitoneal shunt | Alive at 13 months after diagnosis |
| Shonka *et al*[15] | 2011 | 33 yo F | Chemotherapy with ifosphamide, etoposide and carboplatin then changed to vincristine and temozolomide. | Alive and stable at 18 months after diagnosis |
| Kuge *et al*[16] | 2012 | 20 yo F | Endoscopic biopsy and third ventriculostomy, gamma knife radiosurgery | Died 27 months after initial treatment |
| Las Heras *et al*[17] | 2010 | 46 yo F | Not discussed | Not discussed |
| Moretti *et al*[18] | 2013 | 60 yo F | Resection x2, stereotactic radiotherapy, doxorubicin and vinorelbine x 9 cycles, stereotactic radiotherapy, carboplatin every 21 days | Died 30 months after initiation of treatment |
| Shitara and Akiyama[19] | 2014 | 44 yo F | Three drug chemotherapies were performed at 3-week intervals for a total of five cycles. Each cycle consisted of ifosfamide, cisplatin and etoposide administered on days 1–5. Radiotherapy was given. | Died 17 months after diagnosis |
| Schneiderhan *et al*[20] | 2011 | 61 yo F<br>57 yo F | Resection × 2<br>Resection, radiotherapy and chemotherapy with three cycles of doxorubicin and cisplatin | Died within 4–5 months<br>Alive after 6 months |
| Raisanen *et al*[21] | 2005 | 20 yo F<br>45 yo M<br>31 yo F | Resection<br>Resection, high-dose chemotherapy, cranial radiation<br>Resection | Alive at 28 months<br>Alive at 15 months<br>Died at 9 months |
| Lev *et al*[22] | 2015 | 36 yo F | Multiple surgical resections, radiation and chemotherapy (cytoxan, adriamycin and vincristine and with cisplatin and VP16) | Died 2.5 years after initial presentation |
| Liebigt *et al*[23] | 2016 | 19 yo M | Stereotactic biopsy, VP shunt, combined radiotherapy and chemotherapy | Alive and stable at 18 months after diagnosis |

VP, ventriculoperitoneal; yo, years old.

functional status after acute rehabilitation, which enabled him to be a candidate for a course of systemic chemotherapy. Future studies should seek to investigate the impact of cancer rehabilitation on overall life expectancy.

It is clear that a multidisciplinary approach to care with frequent communication between providers was necessary to maximise positive outcomes in this patient. It is also important to note that rehabilitation has a role in patients who opt for palliative treatment, as it may allow patients and their families to maximise quality of life.

AT/RTs are a rare cancer in adults with rapid progression and poor prognosis. Adult patients are surviving longer, with several reported longer term survivors. Rare pineal variants can be identified quickly due to modern genetic testing, leading to prompt and accurate diagnosis. Multidisciplinary care, including acute rehabilitation, is necessary in order to optimise patients' functional status for medical and surgical care. It also may allow for improved quality of life.

## Learning points

- Atypical rhabdoid tumours are a very rare form of cancer in adults that have a rapid progression and poor prognosis.
- With the advancement of modern genetic testing, prompt and accurate diagnoses for atypical rhabdoid tumours may be accurately diagnosed with increasing frequency.
- A multidisciplinary care team plays a valuable role to help understand the goals of care and improve quality of life for patients and family.

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