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CASE REPORT

Paediatric clear cell meningioma with multiple distant recurrences after presumed intra-operative cell spread

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Introduction

Meningiomas are common neoplasms accounting for 24–30% of all primary intracranial tumours but are rarely seen during childhood [1]. If there are no signs of atypia, brain invasion or mitotic activity, most tumours are classified as WHO grade I tumours, depending on their histological subtype. However, there are histological variants with known aggressive course such as rhabdoid and papillary meningiomas (WHO grade III) and chordoid and clear cell variants (WHO grade II). Of these, clear cell meningiomas (CCMs) account for 0.2% of all meningiomas, thus being the rarest variant [2]. They tend to affect both children and young adults (mean age 29 years, range 2–82 years) [2, 3]. CCMs occur most frequently in the cerebellopontine angle and cauda equina [1], often show recurrences, occasionally cerebrospinal fluid (CSF) seeding and are generally associated with a more aggressive behaviour [2]. The risk to develop a higher grade tumour is twice as high for males than for females [4]. Tumours with a non-skull base location more likely have a WHO grade II or III than skull-based tumours [4].

Because of their rarity, large single institution series of CCMs are rare. Most of the clinical data regarding behaviour of these uncommon tumours is based on only two larger studies, one from India with nine cases and one American study with 13 cases, with two and eight recurrences, respectively [2, 5]. At our institution, the presented case is the second tumour since its introduction in the WHO classification in 2000.

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Case report

History A 10-year-old boy initially presented with left-sided deafness, atactic gait and paresis of the left hypoglossal nerve. A lesion of the left cerebellopontine angle (CPA) infiltrating the brainstem was surgically removed at an outside institution. Histology revealed a clear cell meningioma. Two years later, imaging showed a local tumour recurrence. The recurrence was treated with fractionated radiotherapy. Biannual MRI controls showed a constant size of the CPA lesion over the course of the following 3 years. At age 14, a juvenile myoclonic epilepsia (Janz' syndrome) with clonic seizures of the arms, mostly in the mornings, occurred and was treated successfully with valproic acid. At age 15, a mild aphasia in the sense of word retrieval problems was diagnosed. At age 16, control MRI showed a new tumour mass in the jugular foramen on the right side. The 12×8-mm

roundly shaped lesion in direct contact to cranial nerves IX, X and XI showed a homogenous contrast enhancement. A schwannoma was radiologically suspected. Furthermore, a second new lesion was seen in the right Meckel's cave, measuring 4×8 mm, also compatible with meningioma or schwannoma. Due to the suspected combination of meningioma and schwannoma, neurofibromatosis type 2 (NF2) was considered as underlying disease. However, the clinical examination showed no cutaneous signs of neurofibromatosis. Molecular genetic analysis of the merlin gene on chromosome 22q12.2 (NF2-gene) by sequencing of all exons 1–17 and the relative introns additionally with MLPA analysis remained non-informative. Since this approach normally detects only 90% of all mutations within the NF2-gene, subsequent direct molecular genetic analysis of the tumour material removed in 2002 was performed. Even then, an NF2 mutation or mosaicism could not be detected and the hypothesis of NF2 was rendered highly unlikely, but not impossible.

Half a year later, a follow-up MRI showed an expansion of both tumours, the jugular foramen tumour to 15×11 mm and the Meckel's cave lesion to 8×12 mm. Another new but very small manifestation attached to the left cerebellar tonsil was seen (Fig. 1). Thin-sliced CT showed no bony destructions at the level of the jugular foramen or Meckel's cave. At this stage, the boy was referred to our neurofibromatosis clinic for a second opinion, also regarding an indication for repeat surgery.

A microsurgical gross total resection of the right-sided jugular foramen tumour was performed in semi-sitting position using a retrosigmoid lateral–suboccipital approach. The tumour was located on top of the caudal cranial nerves below VII/VIII nerve. Strong adhesion but no infiltration of the lower cranial nerves was found (Fig. 2). The boy made an uneventful recovery without any additional cranial nerve deficits.

Follow-up imaging 3 months later showed complete tumour removal and stable disease regarding the tonsillar tumour manifestation. Eight months after the removal of the jugular foramen tumour, the right-sided Meckel's cave tumour was subjected to fractioned stereotactic radiation therapy using Linac 6 MV photons, due to slow but constant progression in size from initially 4×8 mm to 9×14×13 mm.

Further follow-up imaging at 16 and 22 months showed constant lesion sizes of all tumour manifestations especially

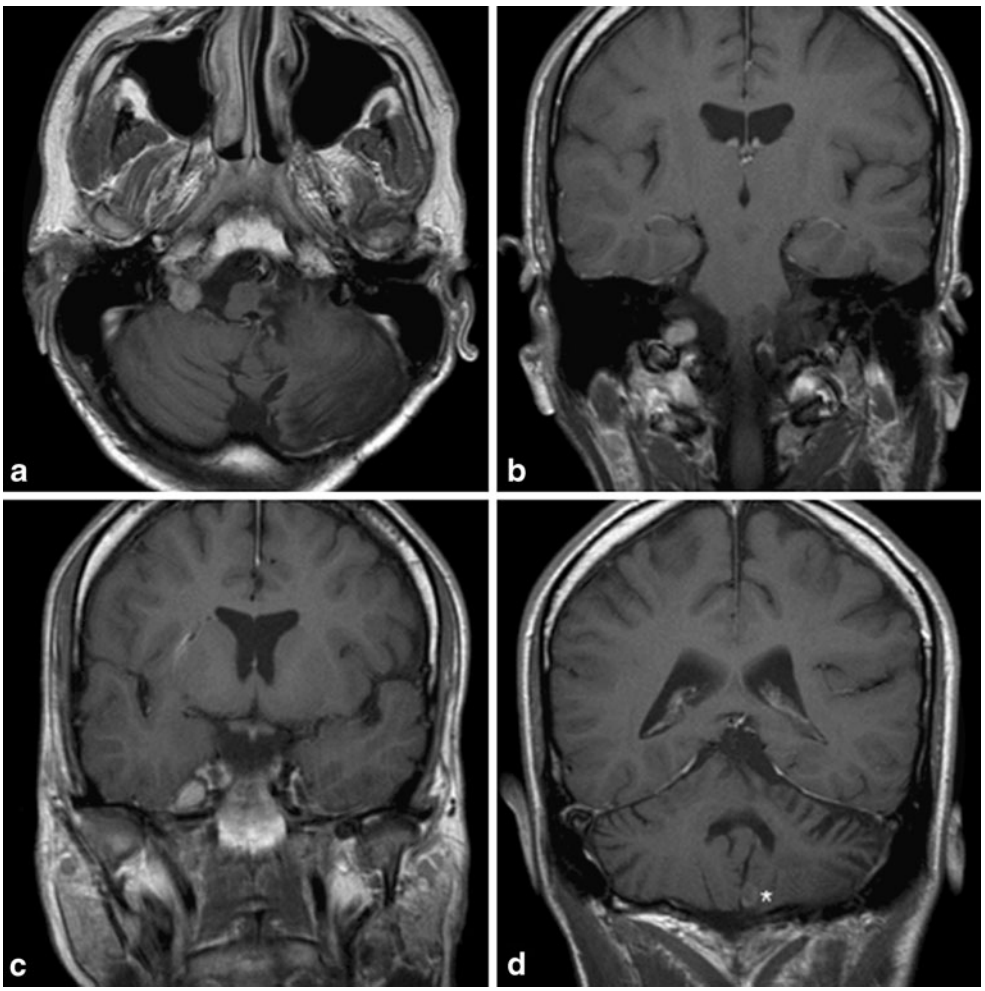

Fig. 1 Pre-operative MR imaging showing the CCM manifestation within the jugular foramen of the right side (**a**, **b**). **c** Meckel's cave manifestation and **d** the small tumour attached to the left cerebellar tonsil (*asterisk*)

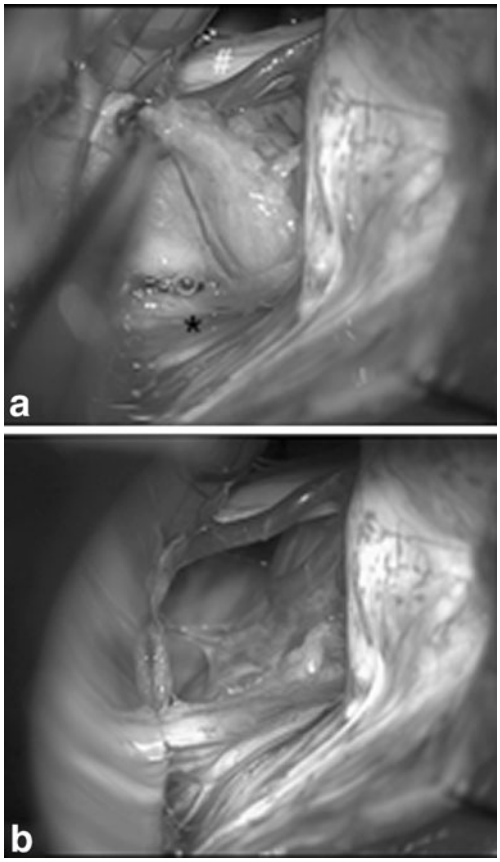

Fig. 2 Intra-operative view during resection of the jugular foramen manifestation of CCM. **a** The tumour is located between CN VII/VIII (*number sign*) and the anterior inferior cerebellar artery above and is lying on top of and being strongly adhesive to caudal cranial nerves (*asterisk*) within the jugular foramen. **b** After gross total resection and careful dissection, the uninjured lower cranial nerves can be seen as well as the full course of the anterior inferior cerebellar artery below CN VII/VIII

in the right Meckel's cave and no recurrence in the right jugular foramen (Fig. 3). Clinical examination did not reveal any additional neurological deficits after microsurgical tumour removal and radiation therapy.

Histology The excised specimen of the primary and recurrent tumour showed moderately pleomorphic tumour cells with ovoidal elongated nuclei in a mostly clear cell matrix, partly also filled with granular, PAS-positive intercellular deposits. Short collagenous bundles were inter-dispersed and whorl formations of the tumour cells were observed. Solid cell formations were centrally located with weak eosinophilic cytoplasm reminiscent of a typical pseudo-syncytial appearance of meningeothelial meningoma. Mitotic activity was very low and no necrosis was seen. Additional immunohistochemical studies showed an MIB-1 proliferation index of up to 3%, a membranous expression of EMA and lack of progesterone and oestrogen receptors (Fig. 4). The tumour also lacked S-100, pan-cytokeratin and synapthophysin expression. Therefore, a CCM was diagnosed and distant recurrence supposed.

Discussion

To date, more than 50 cases of clear cell meningioma have been reported [6]. Most of them are single case reports, complicating the evaluation regarding the significance of prognostic markers and immunohistochemical examinations. After extensive search, we retrieved 38 CCMs with one or more recurrences in the literature (Table 1). Twenty of 38 were female and 18 were male; 26 of 38 were located intracranially and 12 were intraspinal. In 12 cases, a second recurrence occurred after a mean interval of 39.1 months (range 1–80 months). In four cases, a third and in one case, a fourth recurrence was found.

We report an intracranial CCM with local and distant recurrences after 2 and 4 years, respectively, in an initially 10-year-old boy. The primary tumour was diagnosed and removed from the left cerebellopontine angle, where a local recurrence was treated with radiotherapy. Gross total removal of the distant recurrence in the right jugular foramen was possible, with no recurrence during 22 months of follow-up and stable disease regarding the two remaining tumour manifestations within the right Meckel's cave and the left cerebellar tonsil.

According to the very similar histopathological picture, both the primary and the distant recurrent tumour in the jugular foramen are classical CCMs with low proliferative activity (MIB-1 LI 3%). The location of the primary tumour in the cerebellopontine angle is typical for CCMs [1]. In contrast, the location of the recurrent CCM at the entrance of the contralateral jugular foramen with the appearance of a schwannoma initially raised the possibility of a neurofibromatosis type 2 or multiple inherited schwannomas, meningiomas and ependymomas syndrome. Because only 90% of the mutations within the NF2-gene are detected with conventional molecular methods, the clinical suspicion of NF2 persisted until the second surgery. The recurrence rate in CCMs is reported as 61% (n=8) in a series of 13 cases, including 15% (n=2) local discontinuous spread and 8% (n=1) widespread cranial to spinal metastasis [2]. The recurrence rates in spinal and intracranial CCMs are described as 80% and 46%, respectively, with an overall recurrence of 60.9% in a review of 23 CCMs including 14 recurrences [7].

The most likely cause for the contralateral jugular foramen manifestation is a drop metastasis during initial left CPA surgery in park bench position with the right side down which enables loose tumour tissue to reach, driven by gravity, the contralateral jugular foramen. This also explains the position of the tumour on top of the caudal cranial nerves. Seeding of tumour cells through the CSF has been

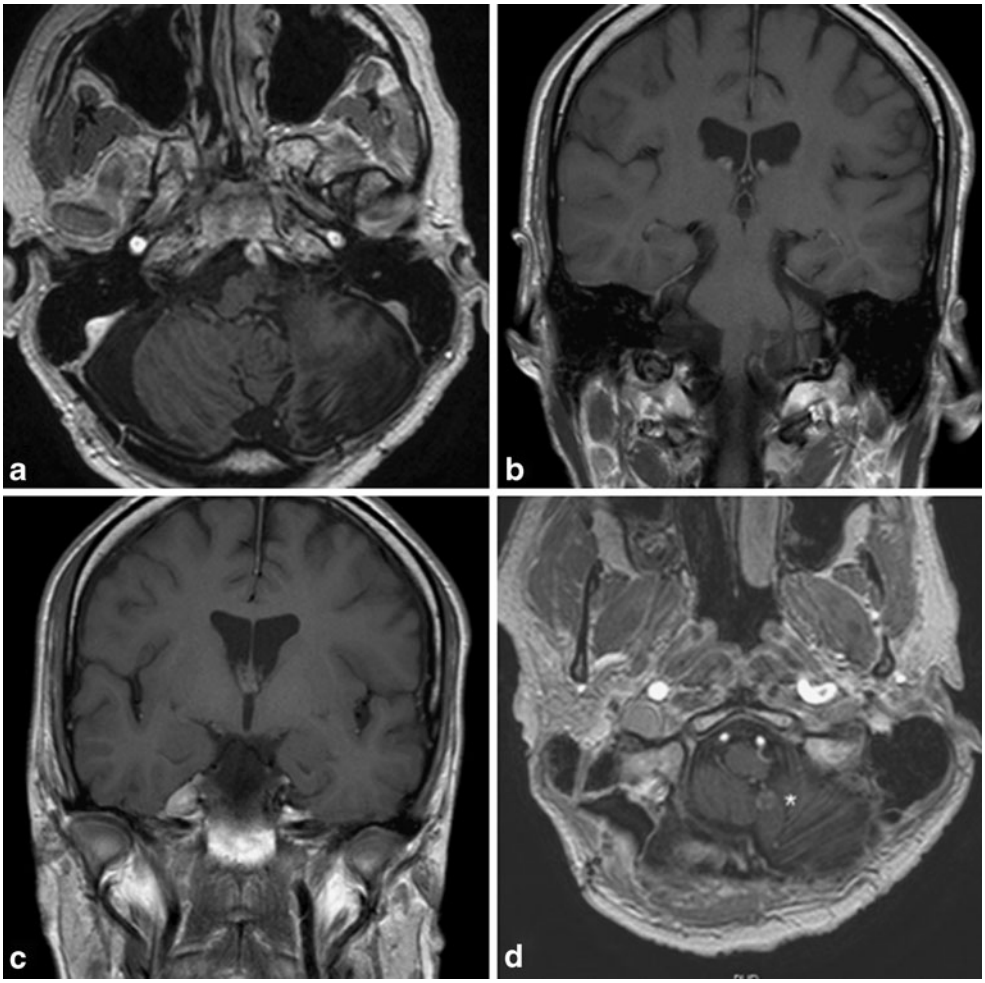

Fig. 3 Post-operative MR imaging showing the 3 months follow-up with no residual tumour at the jugular foramen of the right side (**a**, **b**). **c** Meckel's cave manifestation and **d** the small tumour attached to the left cerebellar tonsil (*asterisk*) unchanged in size

demonstrated in anaplastic meningiomas [8, 9] but has also been repeatedly reported in clear cell meningiomas after surgical intervention [2, 7]. Prognostic markers that might be associated with tumour recurrences remain to be identified. In one larger study, MIB-1 proliferation indices were considerably higher among recurring tumours [2]. However, another study reported generally high MIB-1 expression levels (mean, 9%) in CCMs, independent of tumour recurrence [5]. Nuclear progesterone receptor staining appears to be present in 77% of CCM, but oestrogen receptor staining is usually absent [2]. In our case, the MIB-1 labelling index was rather low with 2% of the primary tumour and 3% of the recurrent one. Both progesterone receptors and oestrogen receptors were absent in the current case. Rodriguez et al. demonstrated that clear cell meningiomas exhibit lower galectin-3 protein levels than other meningioma variants [10]. It is noteworthy that we were able to focally demonstrate immunoreactivity for c-KIT, which has only been observed in one anaplastic meningioma case [11]. This might become useful, as to date, there is no general therapeutical approach for distant tumour recurrences.

The occurrence of additional tumour manifestations attached to the cerebellar tonsil and within Meckel's cave is very unusual in our case. The entry opening of the trigeminal nerve into Meckel's cave would theoretically also allow floating tumour tissue to sediment at this location during primary resection, similar to the manifestation attached to the tonsil. In both cases, we suspect CCM as the underlying histology. Since the tumour attached to the cerebellar tonsil had not grown so far, removal was not attempted, whereas the Meckel's cave manifestation was subjected to radiation therapy.

Nevertheless, this case demonstrated that intra-operative spread and dissemination of a small amount of CCM tumour cells is a very likely reason for subsequent distant tumour recurrences. CCM cells seem to survive and efficiently regrow more easily during CSF spread compared to observations made after meningioma surgery in general, where this behaviour is largely unknown. Therefore, special care has to be taken during surgery of known or suspected clear cell meningioma to prevent intra-operative tumour cell dissemination at all means. Recent studies have shown that it is also likely that CCM tumour cells disseminate more easily without surgical intervention. Zorludemir et al. noted that two of their cases were already multifocal [2].

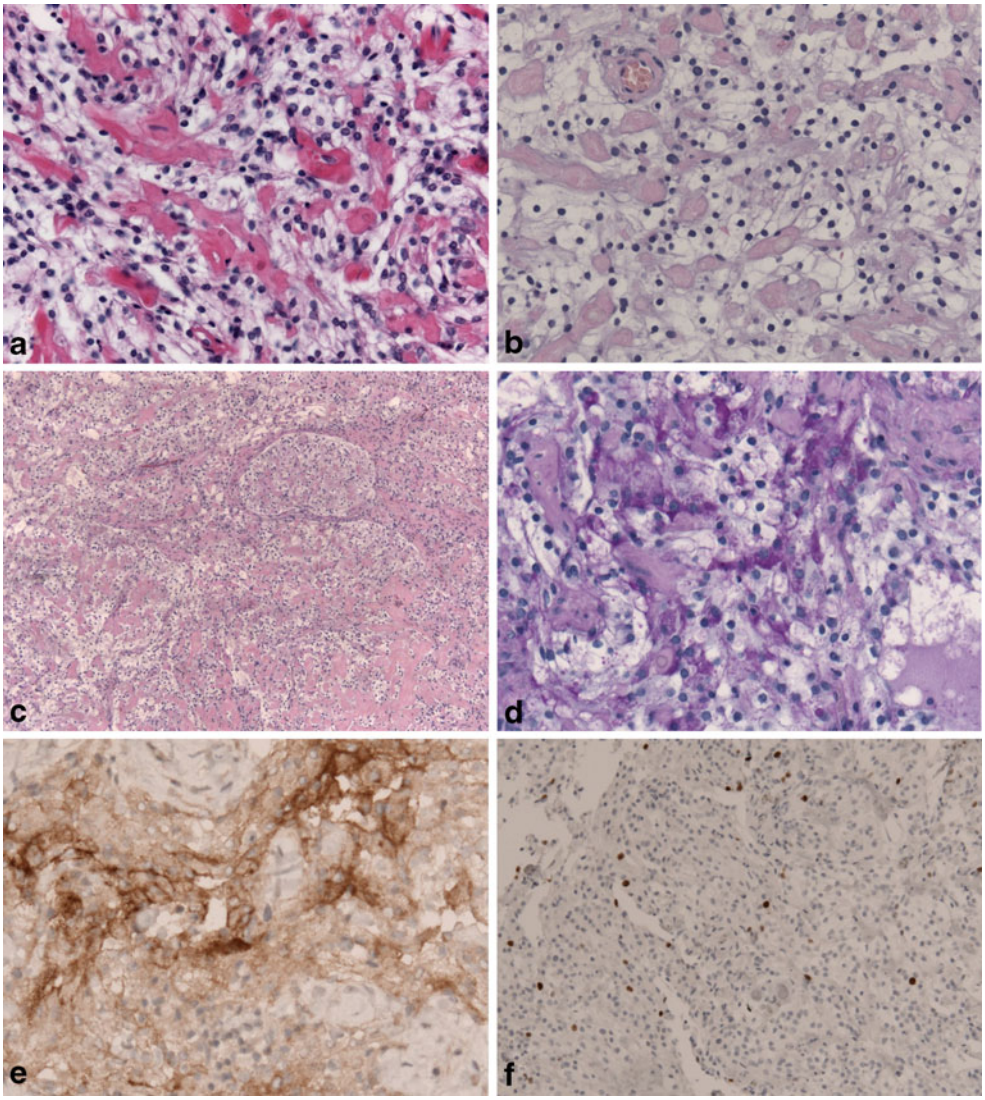

Fig. 4 Histology of (**a**) primary and (**b**) recurrent tumour with focal meningeothelial islands (**c**, HE stain) and (**d**) PAS-positive inclusions. The tumour exhibited focally immunoreactivity for epithelial membrane antigen (**e**) and a proliferative activity of 3% (**f**, MIB-1 immunohistochemistry)

Fractionated local radiotherapy after incomplete resection or local tumour recurrence at the primary lesion site is generally accepted [12]. Colen et al. reported a 2-year follow-up without tumour recurrence after gross complete resection followed by an adjuvant local radiotherapy [6]. A review of the literature (Table 1) shows a mean time of 32.2 months for tumour recurrence in clear cell meningiomas and a significant earlier tumour manifestation in women (women, mean 25.4, median 22.5, range 1.2–80; man, mean 35.9, median 36, range 1.8–76). However, recurrent tumours have been observed as late as 13 years after resection and adjuvant radiotherapy [2], so that longer follow-up studies are needed. In a further review of 49 CCM cases, 46 were treated with surgery alone; 24 of these suffered a recurrence, and among these, five were distant ones. Twelve of the recurrent tumours were treated with resection only and five recurred again. Seven were treated by resection and radiotherapy, with two further recurrences. Thus, the rate of recurrence after resection alone is higher (41.7%) than that after surgery and radiotherapy (28.6%) [3]. For the distant tumour recurrence, an 18-month tumour-free follow-up after reoperation alone has been reported [3], while others have recommended postoperative adjuvant therapy [13].

Conclusion

CCM is a rare tumour with high recurrence rates. Due to its rarity, CCMs are mainly mentioned in case reports and not in larger series. Thus, prognostic markers are usually non-informative and there is no general therapeutical approach for distant tumour recurrences. Surgical gross total tumour resection remains the most important therapeutic goal, however, special attendance should be paid to measures minimising tumour cell spread during surgery. It appears that small amounts of CCM cells are more likely to survive after dissemination than normal meningioma cells and are able to

Table 1 Overview of cases with recurrent clear cell meningioma

Study	Sex	Age at first tumor (years)	Location of first tumor	MIB-1 (%)	Month till first recurrence	Location of first recurrence	Month till second recurrence	Location of second recurrence	Month till third day of recurrence	Location of third recurrence	Location/month of fourth recurrence
Zorludemir et al. [2]	F	32	IC	n.a.	36	IC	60	n.a.			
	M	11	IC	n.a.	13	IC					
	M	34	Spinal	n.a.	12	Spinal	16	Spinal	28		
	F	9	Spinal	n.a.	6	Spinal					
	M	16	IC	n.a.	6	IC	13	Spinal			
	M	34	IC	n.a.	24	IC	36	IC			
	M	47	Spinal	n.a.	36	Spinal	48	Spinal	60	IC	
	F	21	IC	n.a.	156	IC	168				
Prinz et al. [14]	M	38	Spinal	5	Few months	n.a.	n.a.	n.a.	n.a.	n.a.	n.a
Cances et al. [15]	F	9	Spinal	n.a.	5	Spinal					
Dubois et al. [16]	F	10	Spinal	n.a.	6	Spinal					
Imlay et al. [17]	F	21	IC	n.a.	84	Spinal					
Pimentel et al. [18]	F	24	IC	3	16	n.a.					
	M	19	IC	1.1	1.5	n.a.					
Lee at al. [7]	M	17	IC	n.a.	7	IC					
Park et al. [19]	F	12	Spinal	3	8	Spinal					
Jallo et al. [20]	F	18	Spinal	n.a.	5	Spinal	20	IC			
	F	8	Spinal	n.a.	6	Spinal					
Yu et al. [21]	F	12	Spinal	3	8	Spinal					
Carrà et al. [22]	M	18	Spinal	n.a.	60	Spinal					
Ide et al. [23]	F	24	IC	11	60	IC					
Ahn et al. [12]	F	7	IC	15–20	72	IC					
Dhall et al. [3]	F	32	IC	n.a.	36	Spinal					
Liu et al. [24]	M	2	Spinal	n.a.	60	Spinal					
Jain et al. [5]	M	18	IC	2	24	n.a.					
	M	47	IC	2	36	n.a.					
Ohba et al. [25]	M	60	IC	1.7	14	n.a.					
Prayson et al. [26]	F	27	IC	4.3	96	n.a.	125	n.a.			
	M	58	IC	6.2	14	n.a.	65	n.a.			
	F	40	IC	6.3	54	n.a.					
	M	72	IC	22.4	15	n.a.	50	n.a.			
	F	35	IC	30.2	20	n.a.					
	M	76	IC	5.7	16	n.a.					
	F	56	IC	36.9	43	n.a.					
	F	80	IC	8.6	27	n.a.					
	M	49	IC	13.9	39	n.a.					
	F	69	IC	10.4	39	n.a.	78	n.a.	97	n.a.	
Deb et al. [27]	M	48	IC	n.a.	Around 120	IC					

F female, *M* male, *IC* intracranial

form the origin of a distant tumour recurrence. New distant recurrences can happen even after a long time, as seen in this case after 6 years. MRI follow-up surveillance should take place once a year and should encompass the complete neuroaxis.

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