The response of spinal cord ependymomas to bevacizumab in patients with neurofibromatosis Type 2

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OBJECTIVE People with neurofibromatosis Type 2 (NF2) have a genetic predisposition to nervous system tumors. NF2-associated schwannomas stabilize or decrease in size in over half of the patients while they are receiving bevacizumab. NF2 patients treated with bevacizumab for rapidly growing schwannoma were retrospectively reviewed with regard to ependymoma prevalence and response to treatment.

METHODS The records of 95 NF2 patients receiving bevacizumab were retrospectively reviewed with regard to spinal ependymoma prevalence and behavior. The maximum longitudinal extent (MLE) of the ependymoma and associated intratumoral or juxtatumoral cysts were measured on serial images. Neurological changes and patient function were reviewed and correlated with radiological changes.

RESULTS Forty-one of 95 patients were found to have ependymomas (median age 26 years; range 11–53 years). Thirty-two patients with a total of 71 ependymomas had scans appropriate for serial assessment with a mean follow-up of 24 months (range 3–57 months). Ependymomas without cystic components showed minimal change in MLE. Twelve patients had ependymomas with cystic components or syringes. In these patients, reductions in MLE were observed, particularly due to decreases in the cystic components of the ependymoma. Clinical improvement was seen in 7 patients, who all had cystic ependymomas.

CONCLUSIONS Bevacizumab treatment in NF2 patients with spinal cord ependymomas results in a decrease in the size of intratumoral and juxtatumoral cysts as well as adjacent-cord syringes and a decrease in cord edema. This may provide clinical benefit in some patients, although the changes do not meet the current criteria for radiological tumor response.

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KEY WORDS neurofibromatosis Type 2; ependymoma; bevacizumab; spinal tumor; oncology

NEUROFIBROMATOSIS Type 2 (NF2) is an autosomal-dominant condition that predisposes to the development of nervous system tumors (birth prevalence 1 in 25,000–33,000).¹² It is characterized by the presence of bilateral vestibular schwannomas alongside schwannomas of other craniospinal and peripheral nerves, craniospinal meningiomas, and ependymomas of the spinal cord. The

majority of these tumors are benign, but they can cause significant disability and shorten life expectancy,^{2,25} with the median life expectancy of patients with the more severe truncating NF2 mutations being 45.7 years.¹¹

In NF2, intramedullary lesions most commonly occur in the cervical spine and are often multiple.^{14,20} The majority of these spinal cord lesions are not resected in patients

ABBREVIATIONS MLE = maximum longitudinal extent; MRC = Medical Research Council; NF2 = neurofibromatosis Type 2; VEGF = vascular endothelial growth factor; VEGFA = vascular endothelial growth factor A; VEGFR = VEGF receptor.

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with NF2, but on the basis of previous imaging and pathological studies they are referred to as ependymomas.¹⁰ Rennie et al. observed a predominantly indolent course for small enhancing intramedullary lesions in a cohort of 11 NF2 patients with longitudinal radiological follow-up. However, in a minority of patients, some lesions grew significantly or developed cystic components with associated neurological deterioration.²²

Bevacizumab (a monoclonal anti-VEGFA antibody) has a beneficial effect on hearing and vestibular schwannoma growth in patients with NF2.^{17,20} More than 100 NF2 patients in the United Kingdom have been treated with bevacizumab for rapidly growing schwannomas since August 2010 as part of the nationally commissioned NF2 specialist multidisciplinary service. Spinal ependymoma in NF2 is not an approved indication for bevacizumab treatment in the United Kingdom.

The evidence for the use of bevacizumab in NF2-associated ependymomas is limited to positive individual case reports^{5,15} and a retrospective case series of 8 patients with symptomatic spinal ependymomas, all of whom reported subjective clinical improvement on a regimen of bevacizumab.⁸ Four of the 8 patients had a greater than 20% decrease in their spinal ependymoma length, which was reported to be mainly due to reductions in the size of ependymoma-associated fluid structures.

Green et al. reported a radiographic response in sporadic intracranial ependymomas using combination chemotherapy plus bevacizumab.⁹ Sporadic spinal ependymomas have been reported to harbor mutations of the *NF2* gene, encoding merlin, a cytoskeletal protein involved in cell growth regulation.^{1,13} Pathological studies show vascular endothelial growth factor A (VEGFA) and VEGF receptors (VEGFRs) to be present in at least some ependymomas, particularly spinal ependymomas, raising the possibility of VEGF-mediated vascular proliferation.^{4,8,19}

As surgical intervention for NF2 patients with spinal ependymoma is potentially associated with postoperative neurological deterioration,²⁰ it is important to establish whether bevacizumab has a beneficial treatment effect on NF2-associated spinal ependymomas. Treatment with bevacizumab is associated with a number of side effects, including hypertension and proteinuria.^{17,20,23} In our cohort, the rates of proteinuria and hypertension are 24% and 17.5%, respectively.¹⁸ An understanding of the subtype of ependymoma most likely to exhibit a positive treatment response with bevacizumab and the time course of such an effect would therefore be helpful in the management of these complex patients.

In this study, we report the clinicoradiological effect of treatment with bevacizumab on both cystic and solid spinal ependymomas in patients with NF2 from the United Kingdom national bevacizumab cohort on treatment for rapidly growing schwannoma. The study was approved by the Westminster Ethics Committee as a multiple site study, and informed consent was obtained from all patients.

Methods

Population

The records of 95 NF2 patients who commenced treat-

ment between August 2010 and June 2015 with bevacizumab in the United Kingdom for rapidly growing schwannoma according to the national protocol previously described¹⁷ were retrospectively reviewed for imaging and clinical responses of coexisting spinal cord ependymomas. (Members of the UK NF2 Research Group are listed in the *Appendix*.) Given the patient population, intramedullary mass lesions with an enhancing component were considered to be ependymomas for the purpose of this study. Resection for pathological correlation was not performed in any of the patients due to the risk of potential subsequent neurological deterioration. One patient underwent resection of the cystic intramedullary spinal lesion prior to commencing bevacizumab treatment with the pathological report confirming an ependymoma. This ependymoma did not recur during the bevacizumab treatment period.

MRI Analysis

Accurate volumetric measurements could not be performed on the available spinal MRI scans because of the MRI slice thickness relative to the ependymoma size. Slight variations in slice placement at different time points would result in significant variance in volumes calculated due to insufficient slices through the tumor and partial volume averaging on the most laterally placed sagittal slices through the tumors.²⁴ In view of the retrospective nature of this study and consistent with previous published reports,⁸ ependymoma size was therefore calculated by measuring the maximum longitudinal extent (MLE) of the intramedullary tumor on sequential sagittal MRI scans of the spinal cord using the Centricity picture archiving and communication system (GE Healthcare). Due to the growth pattern of spinal cord ependymomas, this technique has the merit of measuring the longest diameter, particularly in larger tumors, and the superior and inferior margins of the tumors are least affected by partial volume averaging effects on sagittal images, resulting in the most accurately measurable diameter on sagittal images. A single rater measured all ependymomas, and all the scans for each patient were measured in a single reporting session. An experienced neuroradiologist reviewed all the measurements, and agreement was reached by consensus. Measurements were made blind to the clinical outcomes of the patient.

Ependymoma enhancement patterns were recorded using the classification suggested by Miyazawa et al. (subcategories: solid, patchy, heterogeneous with cyst, or nodule in cyst wall).¹⁶ Preference was given to T1-weighted, contrast-enhanced sequences. In some cases, the degree of enhancement within the ependymoma varied within a subject between time points. This may be due to differences in timing between contrast administration and image acquisition and/or the effect of bevacizumab on the tumor vasculature. Measurements were performed on sagittal T2-weighted images if contrast-enhanced scans contained within a patient's series were not suitable for technical reasons. T2-weighted images were used to further characterize the cystic components of lesions as required. Individual time points were excluded from measurement if the superior and/or inferior margins of a lesion could not be determined confidently on either the T1-weighted postcontrast or the T2-weighted sequence. For any given

patient, the same sequence was used throughout radiological surveillance to perform an assessment of the MLE over time.

Spinal imaging was not performed according to a prospectively determined protocol since imaging on treatment was performed primarily to assess the patient's bevacizumab target tumor (intracranial schwannoma in 87 of 95 patients). However, the majority of patients underwent spinal scanning at 6- to 12-month intervals.

Clinical Assessment

Treating neurologists assessed global clinical function and neurological functioning of limbs and balance prior to treatment and while receiving bevacizumab. The neurological findings at each clinical assessment (every 3–6 months) were subsequently reviewed by the treating neurologist to determine if there had been clinical change during treatment with bevacizumab.

Patients could have several lesions (e.g., coexisting spinal or peripheral schwannomas) that potentially contributed to their clinical state. The treating neurologist made an assessment based on clinical judgment as to which tumor was most likely causing the observed signs and symptoms. If there was clinical change in the patient while receiving bevacizumab, the treating neurologist made a judgment as to whether the clinical change was due to the patient's spinal ependymoma. While the treating team had access to clinical scans, they were blinded to the MLE tumor measurements performed centrally as part of this study.

Genetic Analysis

The *NF2* genetic mutation was recorded for each patient, and severity was rated as previously described:¹⁷ 1) severe, full-germline truncating mutations in exons 2–13; 2) moderate, deletions not involving the promoter region or exon 1, splice-site mutations (exons 1–8), and mosaicism of truncating mutations in exons 1–13 in blood; and 3) mild, truncating mutations in exon 1, missense mutations, or an in-frame deletion, large deletions involving the promoter region/exon 1, splice-site mutations (exons 9–15) mosaicism (excluding moderate criteria), and no mutation identified on blood analysis.

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism (version 6). Baseline and maximum change measurements were compared using Wilcoxon matched-pairs testing.

Results

We identified 41 of 95 (43%) patients with intrinsic cord tumors consistent with spinal cord ependymomas. MRI scans technically adequate for serial radiological measurement were available in 32 of these 41 patients with a total of 71 spinal ependymomas. Ependymomas with cystic or fluid/syrinx elements were seen in 12 of 32 patients. The demographics and genetic severities of these patient groups are shown in Table 1. The reasons for excluding 9 of 41 patients with spinal cord ependymomas are de-

TABLE 1. Demographics and genetic severity

Variable	Entire Cohort	Patients w/ Ependymoma	Patients w/ Cystic Ependymoma
No. of patients	95	41	12
Median age (range), yrs	24 (11–66)	26 (11–53)	31 (14–52)
Sex (M/F)	53:42	26:15	7:5
Genetic severity*			
Mild	23 (24)	8 (19)	2 (17)
Moderate	31 (33)	19 (46)	6 (50)
Severe	40 (42)	13 (32)	4 (33)

Values are presented as the number of patients (%) unless indicated otherwise.

* One patient did not undergo genetic testing.

tailed in Table 2. The median follow-up after commencing treatment with bevacizumab was 24 months (range 3–57 months) in both the 32 patients suitable for radiographic assessment and in the 41 patients with ependymoma and 29 months (range 3–43 months) in the 12 patients with cystic or fluid/syrinx elements to their ependymoma.

The 12 of 32 patients who had a mixture of cystic and solid tumors (39 tumors, 1–9 tumors per patient) were collectively called the cystic-solid group. Within this group, the solid tumors were either in continuity with the cystic structure (5 tumors) or anatomically separate from the cystic component (21 tumors). The remaining 13 tumors were complex where the solid component could not be separately measured. A final group of 20 of the 32 patients who only had solid intramedullary tumors had a total of 32 tumors. The distributions of MLE at start of treatment for these subgroups are shown in Fig. 1.

The majority of spinal ependymomas were located in the cervical cord (54 of 71), with 15 of 71 and 2 of 71 ependymomas being located in the thoracic and conus regions, respectively.

The Effect of Treatment With Bevacizumab on Solid Ependymomas

Radiographic Effect

Fifty-three of the 71 spinal ependymomas identified were solid with no associated cysts or syringes. These solid ependymomas had a median pretreatment MLE of 8.9 mm (range 2.6–21.7 mm) and did not experience a sig-

TABLE 2. Reasons for excluding patients identified as having ependymoma that could not be assessed on serial imaging

Reason for Exclusion	No. of Patients
Extrinsic lesion preventing adequate view of ependymoma	2
Ependymoma excised prior to treatment w/ bevacizumab; no recurrence of tumor throughout follow-up	1
Artifact	3
<10-mm intrinsic spinal lesion seen only at 1 time point on serial imaging	1
Follow-up spinal imaging awaited	2

nificant change in MLE during treatment with bevacizumab (median change -0.2 mm, range -3.0 to 4.2 mm; or -2% , range -22% to 76% , $p = 0.8$). Only 1 of these 53 solid tumors (in a patient with only solid tumors) decreased by over 20% in MLE.

Clinical Effect

Of the 20 of 32 patients with only solid ependymomas, 2 had relevant clinical signs that could be reassessed to determine the clinical effect of treatment. These 2 patients did not experience an improvement in their clinical state during treatment with bevacizumab (median MLE 8.3 mm, range 6.2 – 13.7 mm). In the remaining 18 patients with only solid ependymoma, 13 were asymptomatic from their ependymoma (median MLE 10.6 mm, range 2.6 – 19.6 mm) and 5 patients had tandem pathology (e.g., brainstem compression from bilateral vestibular schwannoma) that could have explained their clinical signs (median MLE 10.1 mm, range 5.5 – 16.3 mm).

The Effect of Treatment With Bevacizumab on Ependymomas Associated With Cysts or Syringes

Ependymomas with cystic or fluid/syrinx elements were seen in 12 of 32 patients. The clinical and radiological details of these 12 patients are described in Table 3. This subgroup of 12 patients had a total of 39 ependymomas (both solid and cystic ependymomas combined).

Clinical Effect

Seven patients (58%) experienced a relevant clinical improvement. Two cases are presented in detail below.

Radiographic Effect

When only ependymomas with either cystic components or associated syringes were evaluated (12 patients, 16 ependymomas), treatment with bevacizumab was associated with a significant decrease in the MLE (median decrease in length of -4 mm or -21% [range -27 mm to 4 mm; or -100% to 43%], $p < 0.0001$; Fig. 2). There was a greater than 20% decrease in MLE in a total of 16 of 18 ependymomas and syringes (8 of 12 patients), and this decrease was sustained while on treatment. In some cases complete obliteration of the fluid structures was observed. There was no significant decrease in the MLE of solid components of these 12 patients ($p = 0.21$).

Patients in Cases 3, 4, 8, and 12 had breaks in treatment of over 3 months' duration. Patients in Cases 3 and 8 had breaks in treatment with bevacizumab of over 6 months' duration that were associated with a reexpansion of cystic structures on imaging and a worsening of clinical state during the period of time off treatment (Table 3).

In 5 patients who underwent scanning at 3-month intervals, decreases in the size of their tumors were initially seen at 3 months with a maximum response being seen up to 9–12 months while receiving bevacizumab prior to a plateau in radiological response.

Illustrative Cases

Case 1

This 31-year-old man had experienced progressive clin-

FIG. 1. MLE of ependymomas in patients with solid tumors only (SP), and in patients with cystic and solid tumors (CSP). CSP tumors are divided into solid tumors separate from any fluid structures (s-SEP), solid tumors associated with an adjacent cystic structure (s-CONT), and cystic tumors including complex structures and fluid structures including syrinx and cysts associated with solid tumors.

ical deterioration over the 12 months preceding the start of treatment with bevacizumab. Treatment was commenced for a rapidly growing vestibular schwannoma. Coexistent extensive cervical cord ependymomas were deemed by the treating neurosurgical team to be surgically unfavorable due to their longitudinal extent (Fig. 3). In the 12 months prior to treatment the patient had developed a profoundly weak and flaccid right arm and an asymmetrical paraparesis, leaving him wheelchair bound. Sphincter function was intact.

Subsequent to commencing bevacizumab at a dose of 7.5 mg/kg every 3 weeks, the patient experienced a significant improvement in function. After 3 months of treatment, he had Medical Research Council (MRC) Grade 4/5 power in his previously flaccid arm and was able to stand and walk 10 m in 23 seconds unaided. After 6 months of treatment, he was able to feed himself with his previously flaccid right arm. At his most recent review at almost 9 months since the start of treatment, previous pressure sores on his feet had healed, his mood and outlook on life had improved and he could walk 10 m in 17 seconds.

Over the same time period, MRI of his spinal cord showed little change in the longitudinal extent of the solid components of the ependymomas but a significant decrease in the size of the cystic components of the ependymomas. Particular note was made of the reduction in size of the syrinx that extended throughout the thoracic spinal cord with a reduction in the neighboring parenchymal edema (Fig. 3).

While receiving treatment, the patient developed 2+ proteinuria, but creatinine clearance and 24-hour urinary protein remained within normal limits. Otherwise treatment was well tolerated.

TABLE 3. Ependymomas with cystic components and juxtatumoral cysts

Case No.	Location & Description of Lesion	Baseline MLE (mm)	Max Change From Baseline (mm)	Max MLE Change (%)	Time to Max Change (mos)	Length of FU (mos)	Cyst Behavior	Clinical Progress
1	C-2	11	1	7	3	7	Adjacent cyst thins	Dramatic improvement in function from hemiparesis & chair bound to self-feeding & walking
	C3-4	40	-7	-17	7		Decreases	
	C-5 (solid)	4	1	21	7		NA	
	C5-6 (solid)	9	1	8	7		NA	
	C-6 (solid)	9	-1	-16	3		NA	
	C-7 composite (solid)	16	1	7	7		NA	
	C6-7 cyst	4	-2	-38	7		Decreases	
	T-10 (solid)	14	0	-3	3		NA	
	Thoracic complex cystic/syrinx	109	-21	-19	7		Decreases	
	AP caliber at T-4	7	-4	-64	7			
2	C-5	41	-10	-23	15	24	Intratumoral cyst decreases until 9 mos then stable; peritumoral edema resolves	Improvements in power from 3 mos & continued to 2-yr FU
	C-5 cyst	22	-7	-31	15			
	Thoracic (solid)	12	-1	-10	15			
3	C-3	27	-6	-22	6	31	Decreases while on Tx	Tandem pathology; initial improvement but then had break in Tx for surgery; schwannomas likely contribute most to symptoms, particularly a deterioration in gait
	C-5 w/ cyst	22	1	6	18		Lesion consistently smaller while on Tx; cyst variable visibility	
	C-7	38	-13	-34	3			
4	C1-2 (solid)	22	4	20	29	43	NA	Tandem pathology; pain improved but continues to require assistance for mobility
	Cervical	83	-13	-15	12		Complex lesion w/ multiple small cystic components which vary over time	
	C-4 large intratumoral cyst	14	6	43	12		Varies over time but generally larger	
5	C1-2	21	5	25	25	42	Solid component returned to baseline size at final FU	Minor initial improvement in rt leg function attributed to cystic ependymoma decrease but remains chair bound & very dependent for care. Subsequent rt UL deterioration likely multilevel including peripheral schwannomas
	Juxtatumoral cyst	12	-12	-100	12		Decreases then disappears	
6	Whole cervical lesion	61	-4	-7	15	36	Decrease in edema & cyst caliber	Clinically stable w/ minor improvements also due to musculoskeletal & peripheral lesions
	Central solid core of cervical lesion	40	-3	-7	24			
	Supratumoral cyst	24	-11	-44	24		Decreases	
	Syrinx	62	-24	-30	24			
7	Solid cervicomedullary	25	1	4	24	32	Cysts decrease then disappear at 24 mos	Asymptomatic
	Cyst adjacent to cervicomedullary	16	-15	-100	24			
	C3-7 w/ cyst in wall	69	-20	-29	24			
8	C-1 (solid)	5	2	43	23	30	Syrinx not visible at 10 mos then reappears (smaller in width & length than at baseline) after 6-mo break in treatment; regresses again on Tx	Patient reported deterioration in gait during Tx break; subjective benefit on restart of treatment although examination largely unchanged; tandem brachial plexus lesion
	C-2 (solid)	12	-1	-9	18			
	C4-6 (solid)	38	-4	-9	3			
	Syrinx below C-6 (3 spinal segments)	27	-27	-100	15			

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TABLE 3. Ependymomas with cystic components and juxtatumoral cysts

Case No.	Location & Description of Lesion	Baseline MLE (mm)	Max Change From Baseline (mm)	Max MLE Change (%)	Time to Max Change (mos)	Length of FU (mos)	Cyst Behavior	Clinical Progress
9	C1–2	12	–2	–16	26	27	Cyst disappears over 2 yrs	Tandem pathology affecting UL function; multifactorial improvement in gait
	Cyst btwn C-1 & C-2 lesions	20	–20	–100	26			
	C-2	9	–3	–27	6			
	C5–6 (solid)	5	2	42	6			
	C-6 (solid)	7	3	40	26			
	C-7 (solid)	6	5	76	26			
10	T-10 solid component	9	3	32	12	17	Both cysts decrease at 3 mos & disappear at 6 mos	Well-functioning throughout FU; patient reported improved ataxia & power on treatment
	T-10 including superior & inferior cysts	27	–12	–45	12			
11	C-1 (solid)	4	0	–8	3	3	NA	Asymptomatic
	C-2 (solid)	3	0	–9	3		NA	
	C-2 (2nd tumor; solid)	7	–1	–16	3		NA	
	C-4 (solid)	7	1	15	3		NA	
	C7–T1	15	–2	–11	3		Slight decrease	
	T-2 (solid)	6	0	–7	3		NA	
	T-10 (solid)	8	–1	–11	3		NA	
	T10–11 (solid)	5	0	0	3		NA	
12	Cervical	30	1	4	15	15	No objective change	Previous ependymoma surgery confounds examination; some arm cramp & examination improvements but bladder & LL spasticity unchanged; ambulatory status unchanged/worse
	Thoracic (solid)	8	2	18	15		NA	

AP = anteroposterior; FU = follow-up; LL = lower limb; NA = not applicable (solid tumor); Tx = treatment; UL = upper limb.

MLE at baseline, maximum change in MLE after commencing bevacizumab, and time of the last available radiological follow-up are shown along with clinical progress.

Case 2

This 31-year-old man was dependent on a wheelchair prior to treatment with bevacizumab for an enlarging vestibular schwannoma. He commenced treatment with bevacizumab at 5 mg/kg every 2 weeks for 6 months and then was subsequently treated with 5 mg/kg every 4 weeks as maintenance therapy. The target vestibular schwannoma was stable with a maximum decrease of 15% compared with baseline volume. Ependymomas were seen in the cervical and thoracic cord.

He was unable to perform a 10-m walk at baseline or at 3 months but at 6 months could walk 10 m in 34 seconds with the assistance of a rail and a family member. After 9 months of treatment, his timed 10-m walk had further improved to 18 seconds. At his most recent clinical examination (Month 30), he was able to complete the walk test in 18 seconds.

After 3 and 6 months while receiving treatment, the power in the patient's limbs had progressively improved from MRC Grade 2–3/5 distally in his arms and MRC Grade 3–4/5 in his legs to normal strength. He subsequently maintained good limb strength and function throughout treatment.

The patient developed hypertension after 6 months of treatment, requiring a 1-month delay in the dosing schedule alongside the commencement of an angiotensin-converting enzyme inhibitor. Treatment was otherwise well tolerated. A further dose of bevacizumab was postponed by 1 month to allow wound healing from an accidental burn to the patient's finger.

Discussion

This study has shown that treatment with bevacizumab is associated with a reduction in the MLE of NF2-associated spinal ependymomas and that this radiological response is largely driven by the effect of bevacizumab on spinal ependymomas with cystic components. Our analysis of the 12 patients with cystic tumors showed that this subgroup of patients exhibited the greatest radiological treatment effect, with a median reduction of 21% in tumor MLE.

Clinical improvement thought likely to be attributable to a reduction in the size of the patient's spinal ependymoma occurred in 22% of the entire ependymoma cohort and was driven by the clinical improvement observed in

FIG. 2. MLE of each cystic ependymoma and associated fluid structure at the start of treatment and after maximum change in MLE (the minimum MLE on treatment).

58% of patients with cystic spinal ependymomas. In some cases, this clinical improvement was associated with a significant gain in daily functioning. A lack of standardized score for improvement (MRC sum score or walk time) that improved in every patient is a limitation of this study due to its partially retrospective nature. The potential for clinical improvement in this group of patients is extremely important as spinal ependymomas can cause significant clinical disability and, as previously noted, can be extremely challenging to manage surgically.^{5,8,15}

The beneficial effect of bevacizumab on cystic spinal ependymomas reported in our study is consistent with previous individual case descriptions^{5,15} and a smaller series report⁸ that described either radiological or symptomatic benefit in this patient group. In addition, our larger study and detailed analysis of the radiological changes observed has permitted a wider appreciation of both the different types of ependymomas and their clinical consequence (including asymptomatic patients) and also the complex structure of these tumors within an individual.

It is not clear why bevacizumab appears to have a greater radiological effect on the cystic components of spinal ependymomas in NF2 patients. It has been postulated that this is due to an antiedema effect. However, VEGFR-2 has been shown to be distributed throughout the spinal ependymomas in a recent immunohistochemical analysis of 5 NF2 spinal ependymomas and VEGFR-1 to be present in 4 of these 5 tumors.⁸

FIG. 3. Case 1. Sagittal T2-weighted MR images obtained at baseline (A, cervical spine; C, thoracic spine) and after 7 months of treatment with bevacizumab (B, cervical spine; D, thoracic spine) showing a decrease in cord swelling and the size of the intrinsic cord cysts and the longitudinally extensive thoracic syrinx on treatment. This imaging change was clinically paralleled by the return of ambulation and the ability of the patient to feed himself again following the recovery of a previously flaccid right arm.

Our study identified spinal ependymomas in 43% of the original patient cohort being treated with bevacizumab for rapidly growing schwannomas. The higher prevalence of patients with spinal ependymoma in our cohort when compared with a previous study²² may reflect the fact that patients receiving treatment with bevacizumab in the United Kingdom generally have a relatively high disease burden. Indeed, 34% of the patients identified as having a spinal cord ependymoma had a severe genotype that has been associated with an increase in spinal tumors and severity of disease manifestation.^{3,6,7} The predominantly cervical location of the ependymomas observed in our study is in keeping with previous reports.^{21,22}

The radiological assessment of spinal ependymomas in our retrospective study was constrained by the limited available MRI sequences performed as part of the routine imaging follow-up. To further understand the effect of bevacizumab on ependymomas in NF2 patients, prospective scanning with detailed volumetric protocols of the ependymoma will be important.

In this patient group with multiple nervous system tumors, it is often difficult to determine the clinical manifestations specifically attributable to a particular tumor. This is a limitation to both prospective and retrospective studies of clinical outcomes in this population. This may in part account for the lack of clear correlation between the extent of clinical and radiological change respectively observed both in our study of 32 patients with ependymoma and also reported in a previous study of 8 NF2 patients

with symptomatic spinal ependymomas treated with bevacizumab.

Conclusions

Pragmatically, our data suggest that patients with symptomatic cystic ependymomas may obtain clinical benefit from treatment with bevacizumab and that associated changes in ependymoma size and/or clinical improvement may be seen within the first 3–6 months of treatment. In contrast, the lack of significant change in the size of the solid ependymomas observed while on treatment with bevacizumab, coupled with the potential toxicity^{17,18,20,23} from treatment with bevacizumab, may suggest that patients with this subgroup of spinal ependymoma are less likely to benefit overall.

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Appendix

English Specialist NF2 Research Group Members

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Disclosures

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