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BRIEF REPORT

Presentation and management of spinal meningioma and its association with breast carcinoma—case series and systematic review

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ABSTRACT

Objective: Benign spinal intradural tumors are rare entities and there have been relatively few case series describing the epidemiology and characteristics of these tumors. Here, we evaluate the presentation, demographics, pathology and outcomes associated with the surgical management of spinal meningioma in our unit over a 6-year period.

Results: A total of 68 cases presented to the operating surgeon during a 6-year period. Of these, over 80% ($n = 55$) were in females. Seventy-nine percent of the meningiomas were observed in the thoracic region ($n = 54$). Weakness and gait disturbance were the most common presenting complaints. Surgery significantly improved both motor outcome ($p < 0.001$) and health related qualities of life (SF36, $p < 0.01$).

Results: Seventeen percent of spinal meningioma cases ($n = 12$) had a preceding cancer diagnosis. Of these 75% ($n = 9/12$) were attributable to breast cancer. Overall, breast cancer preceded a diagnosis of a spinal meningioma in 16.4% of female cases (9/55). This is higher than expected number of breast cancer based on UK population and those reported in literature for breast cancer and intracranial meningioma.

Conclusion: Spinal meningioma is disproportionately over-represented in females. Patients present with neurological deficits and surgery improved both neurology and patient reported quality of life. Relative to the known UK prevalence of breast cancer, there is a significantly higher than expected association between spinal meningioma and a preceding history of breast cancer.

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Spinal meningioma; spinal intradural tumor; spinal meningioma and breast cancer

Introduction

Benign intraspinal tumors are rare entities with a reported incidence of around 0.7 per 100,000 per year in the USA,[1] although there are substantial variations in the reported incidence and distribution across different series.[1–3] Spinal meningioma accounts for 20%–40% of all intradural extramedullary tumors and exhibits a known female predominance.[3–5] The typical ratio of female to male patients at presentation is four to one.[3,6,7] Scattered case series have been published describing the epidemiology and treatment of these tumors. Most published series, since the advent of microsurgery, have included relatively small number of patients. Surgery is thought to be the treatment of choice for most patients, with complete resection (Simpson Grade I and II) thought to offer the best long-term prognosis.[6,8–11] Even in older populations (over 70 years old) with a substantial neurological deficit, surgery still offers a high chance of neurological recovery.[12]

Other organ malignancies such as breast cancer have been associated with intracranial meningiomas.[13–15] No such association has been reported with spinal meningioma to date. Here, we describe our single-surgeon experience on management of spinal meningioma within a tertiary neurosurgical unit in UK. We describe a previously unreported association between hormonal receptor positive breast carcinoma and spinal meningioma.

Methods

Study design

Prospective collection of data relating to all cases of spinal intradural tumors has been in place in our unit since 1 January 2014. Patient demographics (age and gender), tumor type, location and operative management were prospectively recorded in this database. Additional retrospective analysis on all patients over a 6-year period, from 1 January 2014 to 31 December 2019 was performed for this study with subset analysis of patients with spinal meningiomas. Database maintenance was performed by a dedicated member of staff (AH).

All patients were seen and assessed in clinic after diagnosis, where patients' symptoms on presentation and associated neurological deficit were recorded. Those patients who subsequently underwent surgery were then followed-up at 6 weeks by a spinal physiotherapist and at 3 months and beyond by the senior author. In addition to a 36-item Short Form Survey (SF-36)

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Supplemental data for this article can be accessed here.

Table 1. Histological subtypes and demographic characteristics of spinal intradural tumor within the case series.

	Total	Female	Male	Mean age	Cervical	Thoracic	Lumbar
Nerve Sheath tumor	108	41	67	58.5	21	40	45
Meningioma	68	55	13	72.5	13	54	1
Ependymoma	33	18	15	51	11	10	11
All tumors	258	147	111	59	55	122	74

questionnaire, patients' local and radiating pain was measured according to the Neuropathic Pain Score (NPS).[16] The MRC grading of muscle strength in the most affected limb, their walking ability as per the gait section of the Japanese Orthopedic Association's evaluation system for low back pain syndrome (JOA score),[17] the most significant presenting symptoms, patient's past medical history and Charlson Comorbidity Indices were also recorded.[18]

Further telephonic consultations of patients with previous history of malignancy were carried out. Data pertaining to the precise diagnosis, grading, staging and treatment received were documented.

Statistics

All statistics were performed through the Python statistics module (SciPy Stats), using the chi-squared test of independence for comparison of the MRC motor score in the most affected limb and JOA gait score; Student's t-test for the NPS. A probability of lower than 1 in 20 ($p = 0.05$) was considered to represent statistical significance.

The probability of an association between meningioma and a prior diagnosis of breast cancer was estimated with a chi-squared test for independence. The expected probability, assuming that breast cancer is independent from meningioma, was constructed from MacMillan cancer prevalence data (Macmillan-NCRAS cancer prevalence project),[19] the Central Brain Tumor Registry of the USA[3] and the UK census.[20] For detailed methods, see Supplementary materials.

Systematic review of literature

The systematic review was performed following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[21] The review protocol was registered with international registration database PROSPERO (Registration Number CRD42020161361). No ethical approval and patient consent were required. A literature search was performed to identify the English language publications that addressed the association between breast cancer and meningioma. The detailed literature search and systematic review were included in Supplementary materials.

Results

Characteristics of spinal meningioma and treatment outcome

Over a 6-year period, a total of 258 patients presented with intraspinal tumors to our unit, including 68 patients with spinal meningiomas (Table 1), 108 patients with nerve sheath tumors and 33 ependymomas. Spinal meningiomas were the primary focus of this current paper and within this subset most patients were female (55) with a mean age of presentation 72.5 (±12.5) years old. Meningiomas were most commonly encountered within the thoracic spine (54 patients). Three patients were treated expectantly with radiological monitoring and did not undergo a surgical intervention.

Table 2. Operative outcomes in spinal meningioma.

	Pre-op	Post-op
Motor		
MRC grade most affected limb	4 (0–5)	5 (0–5)***
Gait		
JOA gait score	1 (0–3)	2 (0–3)**
Pain		
NPS	25.5 ± 16.0	15.8 ± 12.7**
Quality of Life		
Physical	32.8 ± 31.9	67.8 ± 33.8***
Limitation (physical)	17.3 ± 29.9	68.1 ± 40.6***
Limitation (emotional)	43.1 ± 42.4	78.6 ± 35.0***
Vitality	49.1 ± 12.1	56.3 ± 11.0**
Mental health	54.9 ± 15.0	65.6 ± 13.5***
Social	47.6 ± 26.7	76.4 ± 25.0***
Pain	47.5 ± 30.6	71.2 ± 28.2***
General health	52.7 ± 15.6	59.6 ± 14.1*

For motor function, the median MRC grade of most affected limb before and after surgery was recorded (range of MRC grade of most affected limb, chi-squared test of independence). For gait function, the median Gait score as according to gait section of the Japanese Orthopedic Association's evaluation system for low back pain syndrome (JOA score) before and after surgery is recorded (range of Gait score, chi-squared test of independence). For neuropathic pain, the pre and postoperative mean NPS is recorded (±SD, Student's t-test). For quality of life assessment, the mean pre and post-operative 36-item Short Form Survey (SF-36) questionnaire score was recorded (±SD, Student's t-test). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Pre-operatively, the median Charlson comorbidity index was 3 (77% estimated 10-year survival). The most common presenting symptom was weakness (38.5%), followed by pain (26.9%). The median power in the most affected limb was MRC grade 4. The mean pre-op NPS was 25.5 out of 100. Daily activities were commonly affected: the median pre-op JOA gait score was 1 (unable to walk further than 500 m). At the time of diagnosis, the patient's quality of life as per the SF-36 questionnaire was severely compromised (mean score 17.5 − 52.3 across different aspects of the SF-36 score).

Surgical resection of the spinal meningioma significantly improved all patient parameters assessed. Weakness improved in 35 patients and worsened in 2 patients only. The median MRC motor score in the most affected limb post-op improved to 5 ($p < 0.001$, chi-squared test of independence); mean NPS was 15.8 out of 100 ($p = 0.002$, Student's t-test); median JOA gait score was 2 ($p = 0.002$, chi-squared test of independence). With these improvements, all eight aspects of SF-36 quality of life score improved significantly (Table 2).

Incidence of concurrent breast cancer in patients diagnosed with meningioma

A preceding history of breast cancer was observed in 9 of 55 female patients with spinal meningiomas. In the absence of a control population for direct comparison, over 16% of our case series had a diagnosis of breast cancer, which is significantly higher proportion than would be expected from established matched prevalence data for the UK (expected prevalence of 4.98%, $p < 0.001$). In addition, out of the 41 female patients diagnosed with nerve sheath tumors in our series, only 3 patients had a prior diagnosis of breast cancer (7.32%, $p = 0.01$), significantly less than those with spinal meningiomas.

Of the nine patients, eight had estrogen receptor positive breast cancers, four cases of invasive ductal carcinoma, two cases of invasive lobular carcinoma and one nonspecific invasive

Table 3. The Breast cancer characteristics of the nine spinal meningioma patients with a preceding diagnosis of breast cancer.

Age	Gender	Meningioma level	Histology	TNM	ER	Her-2	Years since diagnosis	Treatment			
								Surgery	Chemotherapy	Radiotherapy	Hormone
58	F	C2	Nonspecific invasive carcinoma	T2N0M0	+	–	6	Yes	Yes	Yes	Yes
68	F	T11	Invasive Ductal Carcinoma	T2N1M0	+	–	5	Yes	Yes	Yes	Yes
76	F	T7	Invasive Ductal Carcinoma	T1N0M0	+	–	3	Yes	No	Yes	Yes
74	F	T5	Infiltrating Lobular Carcinoma	T1N0M0	+	–	13	Yes	No	Yes	Yes
52	F	T7	Multifocal Invasive Ductal Carcinoma	T2N1M0	+	–	5	Yes	Yes	Yes	Yes
77	F	T11	Invasive Ductal Carcinoma	T1N0M0	+		18	Yes	No	Yes	Yes
77	F	T5	Invasive lobular carcinoma	T3N0M0	+	–	18	Yes	No	Yes	Yes
78	F	C4	High Grade Multifocal DCIS	Tis	–		5.5	Yes	No	No	No
85	F	C1	Invasive Ductal Carcinoma	T2N0M0	+	–	9	Yes	No	No	Yes

carcinoma. The mean age of diagnosis of their breast cancer was 61.8 years and the mean time between the two diagnoses (breast cancer to meningioma) was 8.98 years. All eight patients were treated surgically for their breast cancer, followed by radiotherapy in seven patients and hormonal therapy for all eight patients, and all were in remission by the time of their spinal meningioma diagnosis (Table 3). The other patient had high-grade ductal carcinoma *in situ* (DCIS) and received surgical treatment only. The location of these nine meningioma was spread out across neuroaxis (C1 to T11).

Other visceral malignancies were also observed sporadically throughout our series. One patient who presented with thoracic meningioma had a history of pancreatic cancer. In the nerve sheath tumor patient population, in addition to patients with a prior diagnosis of breast cancer, there was one patient with a history of prostate and renal cancer, one with melanoma and one with caecal carcinoma.

Association of breast cancer and meningioma—review of literature

To our knowledge, a relationship between breast cancer and spinal meningioma has not previously been reported in the literature. Although, historically an association between breast cancer and intracranial meningioma has been observed.[13–15,22,55] This link, however, remains controversial and most of the published literature is limited to case reports and case series. We performed a systematic review of literatures according to the PRISMA protocol to enable comparison between our series and published literature.

We identified 44 English language literatures discussing association of breast cancer with meningioma. This included 27 case reports and 3 case series reporting a total of 38 cases. All patients were female apart from one where the sex of the patient was not specified, the mean age is 60 (23–79). Six were reports of co-existence of breast cancer and meningioma,[23–28] whilst the rest were reports of breast cancer metastasing to existing meningioma.[54] Five of the cases were of spinal meningiomas,[23,26,29–31] whereas the rest are intracranial meningiomas.

We found 14 population-based cohort studies that addressed the risk of developing both breast cancer and meningioma. Two of the articles explicitly compared the prevalence of both diagnosis within their cohort against the background population (Table 4).[13,14] Custer et al.[13] was a study based on the Washington State cancer registry between 1992 and 1998 which looked at 598 female patients with meningioma and found the 1.83% were diagnosed with breast cancer following the meningioma diagnosis (11 patients). The expected number of cases was calculated to be 7.16, giving a relative risk ratio of 1.54 (95% Cl 0.77–2.75). Rao et al.[14] used five American cancer registries between 1995 and 2004 and looked at four separate cohorts. Expected number of cases was calculated using annual incidence rate. It was found that of the 6103 females diagnosed with meningioma, 219 then went onto develop breast cancer, when the expected number was only 3.77, giving a relative risk of 58 (95% Cl 51–67), which is several folds higher than those reported elsewhere; however, the breast cancer cases were recorded during the entire study period and the expected number did not appear to correct for this.

Three additional articles discussed the relative risk of having both diagnosis without explicitly discussing the reference data for background population.[32–34] These three studies looked at populations in Swedish and Norway cancer registry and reported an increased prevalence of meningioma in breast cancer patients with a relative risk of 1.57–1.75, and an increased prevalence of breast cancer within meningioma patients with a relative risk of 1.54. Nine other cohort studies of varying size investigated the prevalence within their cohorts without discussing how this would compare against the sporadic rate of both diagnoses.[35–43]

Discussion

Benign spinal intradural tumors are relatively rare, and studies so far have been confounded by the small number of patients in each series. In our unit, we treated 258 patients with spinal intradural tumors over a 6-year period, representing an incidence of 1.5 per 100,000, which is similar to, or slightly higher than, other reported figures in literature.[1,44] The two most common pathologies were nerve sheath tumor (41.9%) and meningioma (26.4%). The two pathologies represented distinct populations, with meningioma seen in older and predominantly female patients. Most of our patients with spinal meningiomas were managed surgically. The slow growing nature of these tumors, and their rarity, mean that these patients often present insidiously and are frequently initially misdiagnosed. At the time of diagnosis, we found that patients' quality of life was severely compromised, as demonstrated by their SF36 scores. Surgical resection of the spinal meningioma led to improvement in all aspect of outcome measures, with improvement in neuropathic pain, motor score and quality of life. In particular regarding muscle strength, most patients recovered to a power of MRC grade 5 (42 out of 68 patients who had a motor deficit on presentation). With these improvements, patients' reported quality of life also increased. Although different outcome measures are used, our result is in keeping with published case series.[6,8,9,12]

Historically, an association between breast cancer and intracranial meningioma has been observed and reported. However, to our knowledge a relationship between breast cancer and spinal meningioma has not previously been reported in the literature.

Table 4. The Cohort studies identified in systematic review of literature addressing association of breast cancer with meningioma and comparison with current spinal meningioma case series.

Publications	Study type	Data source	Population	Years studied	Breast cancer cases	Meningioma cases	Expected no of cases	Relative risk (CI)	% Breast cancer in meningioma	% Meningioma in breast cancer
Custer et al.[13]	Cohort Study	Western Washington State cancer registry data	Meningioma patients - subsequent breast cancer	6	11	598	7.16	1.4 (95% CI 0.67–2.58)	1.84%	
			Breast cancer patients - subsequent meningioma	6	21,551	10	7.13	1.54 (95% CI 0.77–2.75)		0.05%
Rao et al.[14]	Cohort Study	Arizona, Colorado, Massachusetts, New York, Texas state cancer registries	Meningioma patients - subsequent breast cancer	9	219	6,103	3.77	58 (95% CI 51–67)	3.59%	
			Breast cancer patients - subsequent meningioma	9	153,276	320	4.03	80 (95% CI 72–89)		0.21%
Malmer et al.[33]	Cohort study	Swedish cancer registry	Breast cancer patients - subsequent meningioma	36	154,414	150	120.8	1.57 (95% CI 1.36–1.81)		0.10%
Helseth *et al.*[34]	Cohort Study	Norway National Cancer Registry	Meningioma patients - subsequent breast cancer	31	22	907	14.26	1.54 (95% CI 0.97 – 2.34)	2.43%	
			Breast cancer patients - subsequent meningioma	31	42,414	21	11.99	1.75 (95% CI 1.08 – 2.68)		0.05%
Ji et al.[32]	Cohort study	Swedish cancer registry	Female with breast cancer pre tamoxifen 1961 – 1987	27	98,681	145		1.54 (95% CI 1.3 – 1.81)		0.15%
			Female with breast cancer post tamoxifen 1988 – 2010	22	128,854	78		1.06 (95% CI 0.84 – 1.32)		0.06%
			Overall female with breast cancer	49	227,535	223				0.10%
Our series	Case series		Meningioma patients with breast cancer	6	9	55	2.74		16.40%	

We have identified five cohort studies, which reported the relative risks of breast cancer and intracranial meningioma. The first two articles explicitly compared the prevalence of both diagnosis within their cohort against the background population. Three additional articles discussed the relative risk of having both diagnosis without explicitly discussing the reference data for background population.

The underlying link remains unknown, however several theories have been proposed, including a role for hormonal receptors such as estrogen and progesterone receptors.[45–48] The ability to make an association has most likely been confounded by the fact that spinal meningioma is a rare entity. In this case series, we have identified, and reported a significantly increased prevalence of breast cancer in female patients with spinal meningiomas. Overall, nine female patients were previously diagnosed with breast cancer. Out of 55 female patients, this represented a proportion of 16.4%. This is significantly higher than baseline prevalence of breast cancer in female population ($p < 0.001$) after accounting for age, size of population and incidence of spinal meningioma, and in direct contrast with the lower rate of breast cancer within the female patients with nerve sheath tumors (7.32%). It is difficult, however, to interpret the true significance of this without comparing our data with established literature. We therefore performed a systematic review of the English language literature. Although there has been a wealth of literature reporting the association between intracranial meningioma and breast cancer, most are case reports and case series. We found five studies looking into the relative risk against a background population.[13,14,32–34] However, only two of these articles directly discussed the background population used and importantly the expected rate of disease within the background population.[13,14] Both studies extracted data from state cancer registry in the USA. The Washington study[13] looked at the incidence of breast cancer in meningioma patients (1.84%) over a 6 years period and vice versa (0.05%) and their expected incidence were calculated based on 5-year age group specific incidence taking into account of patient-year at risk, giving a relative risk of 1.54 for developing breast cancer in meningioma patients. Similarly, Rao et al.[14] used data from five of the state registries, recording an incidence rate of 3.59% for breast cancer in female meningioma patients and 0.21% for the reverse population over 9 years. However, they calculated their expected incidence from annual incidence rather than taking into account of the 9 years of the primary data, which resulted the very high relative risk of 58 for breast cancer in meningioma which was several magnitude higher than reported elsewhere.[13,32–34] This most likely demonstrates bias within this study rather than true risks. Three other studies found also reported relative risk ratio including two based on Swedish cancer registry and one of Norway national cancer registry.[32–34] These studies, however, did not discuss the background population used for comparison. The relative risk of developing meningioma in a breast cancer population was reported as 1.54 and those of breast cancer in meningioma population were 1.57–1.75. Combining the data and excluding the one outlier,[14] the relative risk ratio of developing meningioma in patients with breast cancer were between 1.54 and 1.75,[13,32–34] with 1.54 being the most commonly reported value. Similarly, the relative risk ratio of developing breast cancers in patients with meningioma was reported as 1.4 and 1.54. Given these studies used data from different countries over different time periods and using different data recording method, this is remarkably consistent. The reported prevalence of breast cancer within meningioma population was 1.63% to 8.33%. In comparison, in our series of spinal meningiomas, the prevalence of breast cancer is 16.4% and substantially higher to those reported in literature for intracranial meningioma.

No mechanistic link between meningioma and breast cancer has been proven. We note, however, that in our case, series most patients had estrogen receptor positive breast cancers and received surgery, radiotherapy and hormonal therapy.

Intracranial meningiomas are thought to be hormone responsive.[45,49] This is supported by evidence that women receiving hormone replacement therapy may be at an increased risk of intracranial meningioma;[47–51] the rapid increase in sizes of meningioma during pregnancy that is sometimes observed and a possible association with women using oral contraceptives and meningioma.[47,52,53] Intracranial meningiomas have also been known to express both estrogen and progesterone receptors.[45,46,48] There have been studies linking tamoxifen exposure to reduced risk of meningioma, however given that in our series all patients had received hormonal treatment, this link seems to be less clear. The only demonstrated risk factor to date for intracranial meningioma is ionizing radiation.[46–48] Seven of the patients in our series were treated with radiotherapy. However, modern radiotherapy is focused on the breast area and the location of the spinal meningiomas in these patients were spread over a much broader area across the neuro-axis including two high cervical tumors at C1/2, one at C4, two cases at T5, T7 and T11 each, making a link unlikely. Any such link can only be rigorously evaluated through a much larger case series, or experimental models of spinal meningioma. In our unit, prospective data collection involving patients with spinal meningioma and a concomitant diagnosis of breast cancer remains *in situ* with a new pathway set up to analyze hormone receptor profiles of both tumor types. Given the small number of patients presenting with this condition, we encourage other neurosurgical units to publish their own case series so that a larger number of cases can be examined through meta-analysis and the link between spinal meningioma and breast cancer confirmed or denied with confidence. Although large-scale screening of breast cancer patients is unlikely to be cost effective, knowledge of this association should prompt greater vigilance especially given the observed/recognized delay in diagnosis.

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Disclosure statement

The authors declare that they have no conflict of interest. No patient specific information is included with this study. Patient cannot be identified via the article.

Presentation

Manuscript has been presented at SBNS Autumn Meeting 2018 as an oral presentation.

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