Describing Symptom Burden and Functional Status at the Diagnosis of Leptomeningeal Metastasis

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OBJECTIVES: To investigate the associations of primary cancer, tumor characteristics, and cancer treatment with symptom burden and functional status.

SAMPLE & SETTING: 52 patients with leptomeningeal metastasis (LM) at the University of Texas MD Anderson Cancer Center in Houston.

METHODS & VARIABLES: Records of 52 patients were reviewed, and presenting symptoms were recorded. Mean differences in number and specific symptoms and functional status were explored. Correlations between age and overall number of symptoms with specific symptoms were assessed with Pearson correlations.

RESULTS: Pain was the most frequently reported symptom. Hormonal ablation therapy within six months of LM diagnosis was associated with a higher number of symptoms. Receiving biotherapy more than six months prior to an LM diagnosis was associated with pain, and cerebrospinal fluid leukocytosis was associated with a poor Karnofsky Performance Status score.

IMPLICATIONS FOR NURSING: Nurses caring for patients with advanced cancer can help ensure the highest possible quality of life by obtaining a careful history, assessing symptoms, and noting any changes since the last encounter.

KEYWORDS leptomeningeal; metastasis; central nervous system; symptom burden; functional status

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Cancer brings physical and psychosocial challenges to patients. However, when cancer metastasizes to the leptomeninges and cerebrospinal fluid (CSF), a unique symptom burden arises that is further complicated by the site of primary cancer, sites of metastasis, cumulative treatment toxicities, and neurologic symptom burden because of tumor involvement in the neuroaxis. Patients with leptomeningeal metastasis (LM) typically undergo multiple treatment regimens and may have multiple metastatic sites. In addition, multifocal symptoms frequently occur because of the involvement of unrelated sites along the neuroaxis (Olson, Chernik, & Posner, 1974), creating an unusual neurologic burden that may include cognitive and other neurologic symptoms, such as radicular pain, weakness, or cauda equina syndrome.

Neurologic Symptoms of Leptomeningeal Metastasis

The presence of multifocal neurologic symptoms is a hallmark of LM and frequently leads to testing and diagnosis (Olson et al., 1974). Neurologic symptoms may be referable to the cerebrum, cranial nerves, meninges, or spinal nerve roots. However, many patients experience symptoms in more than one of these areas. For example, patients have reported cerebral symptoms in combination with cranial nerve symptoms (Chamberlain & Kormanik, 1997), as well as symptoms referable to the cerebrum, cranial nerves, and spinal nerves in combination (Duan, Li, & Sun, 2014). Frequently, symptoms may be identified in two or three locations along the neuroaxis (Duan et al., 2014; Wasserstrom, Glass, & Posner, 1982). Recognizing neurologic signs or symptoms related to the involvement of multiple sites along the neuroaxis is key to the diagnosis of LM.

Studies to date describe variation of presenting symptoms in patients with LM. Cerebral symptoms often appear first and remain conspicuous throughout the course of the disease (Olson et al., 1974). Mental status changes, headaches, radicular pain, impaired ambulation, and cranial nerve deficits are also frequent findings and lead to imaging studies (Little, Dale, & Okazaki, 1974; Theodore & Gendelman, 1981). Symptoms described in case reports of LM include sensorineural hearing loss (Asadollahi, Shayanfar, Rezaiyan, & Hasibi, 2012; Duan et al., 2014; Hiraumi, Yamamoto, Sakamoto, & Ito, 2014), facial palsy (Hiraumi et al., 2014), dementia, dysarthria, gait disturbances (Jadav et al., 2012), extremity weakness (Asadollahi et al., 2012; Duan et al., 2014; Jadav et al., 2012; Quadri, Sobani, Enam, Enam, & Ashraf, 2011; Sim et al., 2014), incontinence, aphasia (Jadav et al., 2012), tinnitus (Asadollahi et al., 2012), diplopia and other visual deficits (Madgula, Hemmerdinger, & Clark, 2014; Pan et al., 2014), and urinary retention (Sim et al., 2014).

Objective

Most LM studies are case studies, have small samples, and are concerned with efficacy and tolerability of treatment; symptom burden and functional status are often not primary outcomes. Describing symptom burden and functional status at the diagnosis of LM is important for personalized symptom management, treatment planning, the design of future studies aimed at symptom control, and the development of interventions to address systemic, neurologic, and psychosocial symptom burden. The purpose of this study was to identify the most prevalent symptoms at the diagnosis of LM and to investigate associations between Karnofsky Performance Status (KPS) scores and number of symptoms at diagnosis, type of symptoms, and patient characteristics (such as location of LM tumor or imaging characteristics).

Methods

Sample and Setting

The study was undertaken at the University of Texas MD Anderson Cancer Center (MDACC) in Houston. A retrospective chart review from January 2009 to December 2011 was completed. The protocol was approved by the MDACC and the University of Texas Health Science Center at Houston institutional review boards.

The authors reviewed the medical records of 52 patients who had been newly diagnosed with LM and were planning to undergo treatment at the MDACC Anne C. Brooks Brain and Spine Center from January 2009 to December 2011. Patients were included in the study if they were aged at least 18 years, had LM from any solid tumor except a primary brain tumor, and had either radiographic or cytological evidence of LM. Data were collected at LM diagnosis only.

Data Collection

Data were collected on gender, age, type of primary cancer, sites of metastasis (other than LM), site(s) of LM (brain, spine, or both), imaging characteristics of LM, history of prior cranial or spinal radiation, history of other treatments (chemotherapy, biotherapy, hormonal therapy, surgery, radiation other than to the central nervous system [CNS]), CSF characteristics (protein, glucose, cell counts, pathology), CSF pathway obstruction, KPS score, and type and number of symptoms. Imaging characteristics of interest were the presence of linear and nodular enhancement of the CNS to determine if either was associated with worse symptom burden or functioning. Linear enhancement refers to thin lines of enhancement along the leptomeninges, whereas nodular enhancement refers to bulky disease. Thirty-one patients did not have a KPS score at diagnosis. Therefore, a KPS score was estimated based on recorded signs and symptoms, ambulatory status, ability to perform daily activities, and cognitive status by the primary investigator of this study, who is a clinician at the brain and spine center. Based on evidence previously reported on patients with primary brain tumors (Armstrong et al., 2006), the current authors dichotomized KPS scores as good (90 or greater) or poor (less than 90).

Instruments

LM can involve the brain and the spine, so identification of symptoms associated with lesions in both locations is needed. No instrument has been developed specifically for assessing symptoms in LM. Therefore, the MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) and MD Anderson Symptom Inventory–Spine (MDASI-SP) were used to collect information on the presence or absence of symptoms from the chart review.

The MDASI-BT is a self-report Likert-type scale of symptom burden and life interference. Evidence of validity and internal consistency (Cronbach alpha > 0.7) have been reported in patients with brain tumors (Armstrong et al., 2006, 2009). Part one of the MDASI-BT has 22 items. Part two consists of a life interference subscale with six items. Scoring is conducted on an 11-point Likert-type scale ranging from 0

TABLE 1. Sample Characteristics and Symptoms (N = 52)

Characteristic	$\bar{X}$	SD	Range
Age (years)	51	12.26	24–76
Number of symptoms	1.87	1.3	0–6
Characteristic			**n**
Gender			
Female			41
KPS score			
Poor (less than 90)			30
Location of leptomeningeal metastasis			
Brain			23
Spine			8
Both			21
Cerebrospinal fluid pathway obstruction			
Yes			1
Primary cancer			
Breast			29
Lung			7
Melanoma			5
Other			11
Metastatic site[a]			
Brain			33
Bone			22
Liver			14
Lymph node			13
Lung			12
Other			10
None (other than leptomeningeal metastasis)			2
Symptom experienced[a]			
Pain			24
Numbness or tingling			14
Vision changes			12
Nausea or vomiting			8
Problems with comprehension			5
Arm or leg weakness			4
Memory problems or aphasia			4
Fatigue			2
Bowel or bladder control			1
Disturbed sleep			1
Dyspnea			1
Seizures			1

[a] Some participants reported more than one.
KPS—Karnofsky Performance Status

(not present) to 10 (as bad as you can imagine). Items are then summed, and the mean of the total score is calculated. The life interference subscale can be scored separately in the same fashion. Higher scores indicate greater symptom burden and life interference.

The MDASI-SP is scored with a self-report Likert-type scale. Evidence of validity and internal consistency (Cronbach alpha = 0.9) have been reported in patients with spinal tumors (Armstrong et al., 2010). Part one of the MDASI-SP has 18 items. Part two consists of a life interference subscale with six items.

Because this study was retrospective, the authors collected information regarding the presence of symptoms from medical records and dichotomized symptoms as present or not present rather than rate them on a scale of severity. Therefore, reported symptoms that corresponded to the MDASI-BT or MDASI-SP were extracted from the medical records for analysis.

Statistical Analysis

Exploratory analysis was conducted using IBM SPSS Statistics, version 22.0. Descriptive statistics were employed to describe the sample; independent sample t tests and one-way analysis of variance were performed to explore the mean differences in specific symptoms, number of symptoms, and functional status as measured by KPS scores. Pearson correlations were performed to assess relationships between age and overall number of symptoms with specific symptoms. Associations between categorical data were assessed using a chi-square test.

Results

Sample Characteristics

Table 1 provides a description of the sample, including symptoms experienced at the diagnosis of LM, and Table 2 provides patient disease characteristics. Fifty-two patients were included in the study, and ages ranged from 24–76 years (median = 51 years). Most patients were women with breast cancer, and lung cancer and melanoma were the second and third most frequent primary cancers. More than half the patients had a KPS score of less than 90 (poor). Most patients had parenchymal brain metastasis, and many had received cranial radiation. LM was detected mostly in the brain. CSF studies at diagnosis revealed malignant cells in most patients. A review of CNS imaging revealed that most participants had nodular enhancement of the leptomeninges as opposed to linear enhancement. Two patients' medical records did not indicate CNS imaging.

Number of Symptoms

Patients reported, on average, 1.9 symptoms at diagnosis, with a range of 0–6 symptoms. The most common symptom at diagnosis was pain, followed by numbness or tingling and vision changes. As with KPS scores, most clinical and demographic characteristics were not associated with the number of symptoms overall. Of note, significantly fewer symptoms were reported by patients with bone metastasis (t = [44.25]2.77, p = 0.008) and by those who received biotherapy six months or less prior to the diagnosis of LM (2–6 months: t = [50]2.42, p = 0.02; 1 month or less: t = [44]3.74, p = 0.001). Hormonal ablation therapy received six months or less prior to LM diagnosis was associated with significantly more symptoms (2–6 months: t = [50]–2.38, p = 0.02; 1 month or less: t = [50]–2.54, p = 0.02).

Eight patients reported that symptoms were associated with a significantly higher number of symptoms overall, including memory problems (t = [50]–4.52, p < 0.001), vision changes (t = [50]2.5, p = 0.03), any type of pain (t = [50]–2.53, p = 0.02), vomiting (t = [50]–2.79, p = 0.007), difficulty with comprehension (r = [50]0.29, p = 0.04), aphasia (r = [50]0.45, p = 0.001), sleep disturbance (r = [50]0.45, p = 0.001), and dyspnea (r = [50]0.45, p = 0.001).

Functional Status

Table 3 provides a detailed summary of associations with KPS scores. Most patients with CSF leukocytosis (elevated level of white blood cells) had poor KPS scores (χ^2 = [1]4.12, p = 0.04). One of the seven patients who had undergone any type of cancer surgery 2–6 months prior to the diagnosis of LM had a poor KPS score (χ^2 = [1]4.06, p = 0.04). However, no significant associations between KPS scores and demographic characteristics, symptoms, or tumor characteristics were observed in this sample.

Specific Symptoms

Table 4 provides a detailed summary of associations between specific symptoms with demographic characteristics, clinical characteristics, and number of symptoms. Seizures were not associated with LM tumor characteristics, parenchymal brain metastasis, or treatment modalities. However, 1 of 10 patients with metastasis to organs other than the brain, lung, bone, liver, or lymph nodes reported seizures (χ^2 = [1]4.28, p = 0.04). Fatigue was associated with having received spinal radiation (χ^2 = [1]19.55, p < 0.01) and the presence of CSF lymphocytosis (χ^2 = [2]14.19, p < 0.01). Interestingly, no associations existed between fatigue

TABLE 2. Sample Disease Characteristics (N = 52)

Characteristic	n
Treatment prior to LM diagnosis	
Chemotherapy more than 6 months prior	45
Surgery more than 6 months prior	39
Chemotherapy 2–6 months prior	26
Biotherapy more than 6 months prior	24
Cranial radiation	21
Radiation more than 6 months prior[a]	21
Chemotherapy 1 month prior	20
Biotherapy 2–6 months prior	19
Hormonal therapy more than 6 months prior	15
Biotherapy 1 month prior	13
Surgery within 6 months prior	7
Hormonal therapy within 6 months prior	6
Radiation within 6 months prior[a]	6
Spinal radiation	5
Imaging characteristic	
Nodular enhancement	31
Linear enhancement	18
No findings or missing	3
Location of tap	
Lumbar	35
Ventricular	13
No tap documented	4
CSF protein[b]	
Normal (≤ 50 mg/dl)	28
High	21
CSF glucose[b]	
Normal (45–80 mg/dl)	30
High	10
Low	9
CSF white blood cells[c]	
Normal (0–5 cells/mcl)	28
High	22
CSF neutrophils[c]	
Normal (0%–5% of white blood cells)	35
High	15
CSF lymphocytes[c]	
Normal (28%–96% of white blood cells)	40
Low	8
High	2

[a] Other than cranial or spinal
[b] Missing = 3
[c] Missing = 2
CSF—cerebrospinal fluid; LM—leptomeningeal metastasis

and other treatment modalities. Comprehension was the only cognitive symptom to show significant associations with treatment modalities or LM tumor characteristics, including ventricular tap (as compared to lumbar tap) (χ^2 = [2]11.6, p = 0.01), negative CSF pathology (χ^2 = [1]4.66, p = 0.03), and radiation to any organ (other than CNS) more than six months prior to LM diagnosis (χ^2 = [1]8.2, p < 0.01). Younger patients were more likely to have vision (r = [50] –0.31, p = 0.03) and sensory (r = [50]–0.34, p = 0.02) changes. In addition, patients with CSF leukocytosis were more likely to report extremity weakness (χ^2 = [1]5.53, p = 0.02).

TABLE 3. Associations Between KPS Score and Number of Symptoms

	Poor KPS Score		
	Present	Absent	
Characteristic	n	n	p
CSF leukocytosis	17	13	0.04
Surgery 2–6 months prior to LM diagnosis	1	6	0.04
	Number of Symptoms		
	Present	Absent	
Characteristic	$\bar{X}$	$\bar{X}$	p
Symptom			
Aphasia	6	1.8	0.00
Dyspnea	6	1.8	0.00
Memory	4.7	1.7	0.00
Memory problems	4.67	1.69	< 0.001
Pain	2.33	1.46	0.02
Sleep disturbance	2.3	1.5	0.02
Vision changes	2.92	1.55	0.03
Vomiting	3.5	1.73	0.007
Treatment prior to LM diagnosis			
Biotherapy two to 6 months prior	1.32	2.18	0.02
Biotherapy within 1 month	1.08	2.12	0.001
Hormonal ablation therapy within 1 month	3.2	1.72	0.02
Hormonal therapy 2–6 months prior	3	1.72	0.02
Other			
Bone metastasis	1.36	2.23	0.008

CSF—cerebrospinal fluid; KPS—Karnofsky Performance Status; LM—leptomeningeal metastasis

Discussion

The results of this study provide insight into presenting patient and tumor characteristics of LM and add support for the occurrence of multiple and varied symptoms in the LM population. LM affected functional status in the sample. Although most patients (n = 30) had poor functional status at diagnosis, many patients (n = 22) had KPS scores of at least 90, indicating high functional capacity. Higher performance status in 22 patients may be related to the recent diagnosis of LM, the relatively recent onset of associated neurologic symptoms, or factors related to patient referral, such as preselection of patients with high functional status. This finding emphasizes the considerable variability in the functional presentation of LM. Low KPS scores may be related to many factors, including symptoms of advanced systemic disease and cumulative toxicities from multiple treatments.

The findings of this study are congruent with the findings of Olson et al. (1974), who found that neurologic symptoms at baseline may not be significant and may worsen over time in patients with LM. It is also possible there is a preselection of patients with higher performance status when referring patients to neuro-oncology service for treatment, because patients with low performance status may be transitioned to hospice prior to the actual diagnosis of LM or the first treatment for LM. Early detection of LM by healthcare providers may partly explain higher performance status as well. In addition, a KPS score is a measure of overall performance. As such, cumulative effects from advanced cancer and treatment toxicities may be of greater significance to the score than neurologic deficits that are specific to LM.

Patients with CSF leukocytosis were more likely to have a poor KPS score. White blood cells are a marker of inflammation (Illán et al., 2014); therefore, it is possible that CNS inflammatory processes affected the patients' ability to function. In addition, although KPS score was unrelated, many patients who reported arm or leg weakness had CSF leukocytosis, suggesting that this weakness may be related to CNS inflammation. It is unclear whether this inflammation is an immune reaction targeting malignant cells in the CSF or an immune response to the disruption of the blood–brain barrier by metastatic disease or radiation.

Surprisingly, no significant associations existed between KPS score and number of symptoms, presence of LM in the brain and spinal cord, presence of nodular disease, or specific symptoms. This may be because of the small sample size, lack of indication of the severity of symptoms, and under-reporting of symptoms in the

medical record, indicating a need for prospective studies using validated self-report instruments.

Pain was reported most frequently in the sample. This is congruent with the findings of Little et al. (1974). Type of pain was not differentiated in the current study. Several associations existed between specific symptoms and disease characteristics and treatment modalities; however, they did not always reveal expected associations. For example, problems with comprehension were not associated with past chemotherapy, which is incongruent with findings in the literature (Miao et al., 2016; Wefel, Saleeba, Buzdar, & Meyers, 2010), particularly because evidence supports that cognitive deficits are present early in the course of disease, possibly related to the cancer itself and chemotherapeutic regimens (Komaki et al., 1995). Similarly, the lack of comprehension problems in patients who had undergone radiation to the brain was unexpected, because brain radiation is associated with worsening cognitive functioning (Grosshans, Meyers, Allen, Davenport, & Komaki, 2008). Evidence supports that stereotactic radiosurgery is less damaging to cognitive function than whole-brain radiation (Brown et al., 2016); however, the current study did not differentiate between the two modalities. In addition, formal neurocognitive testing was not conducted in the sample. Quantifying cognitive function through formal testing might prove important in adequately describing presenting cognitive function in patients with LM and serve as a baseline in longitudinal studies.

In the current study, patients receiving biotherapy had significantly fewer symptoms if received less than six months prior to LM diagnosis, possibly because of the anti-inflammatory properties of many monoclonal antibodies (Brennan, Chantry, Jackson, Maini, & Feldmann, 1989; Maneiro, Salgado, & Gomez-Reino, 2013) that may target proinflammatory cytokines, which are important factors in cancer symptom burden (Myers, 2008; Wang et al., 2010, 2012). Why significantly fewer symptoms were reported by patients with bone metastasis is unclear. Fatigue was present in 40% of patients with spinal radiation, which is congruent with other studies investigating fatigue and spinal radiation (Amsbaugh et al., 2012; Katsoulakis et al., 2013; Zeng et al., 2012).

TABLE 4. Significant Associations Between Symptoms and Characteristics

Characteristic	Symptom Present $\bar{X}$	Symptom Absent $\bar{X}$	p
Numbness or tingling			
Age (years)	44	53	0.02
Vision changes			
Age (years)	44	52	0.02
Characteristic	**n**	**n**	**p**
Seizure			
Other metastases[a]	1	9	0.04
Fatigue			
Spine radiation	2	3	0.00
CSF lymphocytosis	–	2	0.00
Comprehension			
Lumbar tap	–	35	0.01
Radiation[b]	5	16	0.00
Ventrical tap	4	9	0.01
Negative CSF pathology	1	11	0.03
Arm or leg weakness			
CSF leukocytosis	12	3	0.02
No metastasis	1	1	0.02
Pain			
Biotherapy[b]	6	18	0.01
Numbness or tingling			
Breast primary	11	18	0.04
Hormonal therapy[b]	7	8	0.04
Vomiting			
No metastasis other than LM	1	1	0.02

[a] Other than lung, bone, liver, lymph nodes, or brain
[b] More than 6 months prior to LM diagnosis
CSF—cerebrospinal fluid; LM—leptomeningeal metastasis
Note. The n values indicate patients who have experienced the symptom and select characteristic.

Limitations

The retrospective design of this study limited the amount and quality of the data available for collection. For example, symptoms may have been under-reported in the medical record, skewing the findings on functional status and symptom burden. More women were represented in the study, reflective of breast cancer being the most common primary cancer in the sample. This makes it difficult to interpret findings related to gender. In addition, the study had a small sample size and included only patients who were presenting for initial intrathecal treatment; therefore, patients with worse performance status or higher disease burden may not have been referred for therapy.

Implications for Nursing

Patients with advanced cancer like LM benefit from careful symptom assessment and proactive management to improve quality of life. Nurses caring for patients with advanced cancer can help ensure the highest possible quality of life by obtaining a careful history; assessing symptoms, including a physical assessment; and noting any changes since the last encounter. Appropriate nursing interventions should be initiated, along with collaboration with an advanced practice provider or physician to provide necessary diagnostic testing or medical interventions. The patient and family should be educated about symptom reporting and control, including indications for hospital emergency assessment and consultation.

Conclusion

The findings of this descriptive study indicate that the symptom burden, number of symptoms, and performance status of patients with LM vary widely at diagnosis, with a surprising number of patients presenting for treatment with high functioning and low to moderate symptom burden. Prospective studies exploring measures to reduce the occurrence of symptoms and preserve function during the disease course are needed. Patients with LM have a unique symptom burden consisting of symptoms referable to neurologic disease, possibly at multiple points along the neuroaxis; systemic disease; and cumulative treatment toxicities. Although this study provides needed insight into the symptom burden of patients with LM, no instrument is dedicated to measuring symptom burden in this population. Neither the MDASI-BT nor the MDASI-SP has been validated in patients with LM. The symptoms of patients with LM should correspond to items on one or both instruments. Therefore, the development of a dedicated instrument for measuring symptom burden in patients with LM and the validation of these instruments are warranted.

Although most patients demonstrated a KPS score of less than 90, many demonstrated good performance status. Prospective studies aimed at evaluating whether poor performance status is related more to the cumulative effects of advanced cancer or to rapid neurologic decline related to a new diagnosis of LM, and its effects on the CNS, would help to clarify these findings.

KNOWLEDGE TRANSLATION

- Patients with leptomeningeal metastasis (LM) present with variable symptoms that may progress over time.
- Inflammation within the central nervous system is associated with extremity weakness and lower functional status.
- Most patients with LM report poor functional status at diagnosis.

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