HOSPITAL PHYSICIAN®

ONCOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

Metastatic Brain Tumors

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Table of Contents

Metastatic Brain Tumors

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INTRODUCTION

Systemic cancer can affect the central nervous system in several different ways, including direct tumor metastasis and indirect remote effects. Intracranial metastasis can involve the skull, dura, and leptomeninges (arachnoid and pia mater), as well as the brain parenchyma. Of these, parenchymal brain metastases are the most common and have been found in as many as 24% of cancer patients in autopsy studies.[1] It has been reported that metastatic brain tumors outnumber primary brain tumors 10 to 1.[2]

Metastasis to the brain generally occurs by hematogenous dissemination, with tumor cells having a propensity to lodge and grow at the gray-white junction. The distribution of brain metastases is proportionate to the cerebral blood flow, with 80% occurring in the supratentorial region, 15% in the cerebellum, and 5% in the brainstem.[1] Unlike primary brain tumors, such as glioblastoma, brain metastases do not typically involve the corpus callosum or infiltrate across the midline. The most common primary histologies include lung, breast, melanoma, renal, and colon cancer, and tumors of unknown primary (**Figure 1**).[3]

Brain metastases can present with a variety of symptoms (**Figure 2**), including focal neurological deficits, headache, and seizures. The sudden onset of symptoms may be related to intracranial hemorrhage associated with brain metastases. Given its relatively high incidence, lung cancer is the most common type of brain metastases to result in intracranial hemorrhage. However, other cancer primaries have, relative to their incidence, a very high propensity to spontaneously develop tumor-associated intracranial hemorrhage; they are melanoma, renal cell carcinoma, choriocarcinoma, thyroid, and germ cell. Ultimately, any brain metastasis has the potential for spontaneous hemorrhage.

Often, the presentation of brain metastasis occurs in a patient with established malignancy, in which case a clinical and radiological diagnosis is usually sufficient. Magnetic resonance imaging (MRI) with gadolinium contrast is preferred over computed tomography (CT) alone due to greater sensitivity in identifying additional lesions. For example, in approximately one-third of cases presenting with a single metastasis on CT, MRI will lead to the discovery of additional metastases (**Figure 3**).[4] Occasionally, brain metastasis can occur as the presenting feature in a patient not known to have

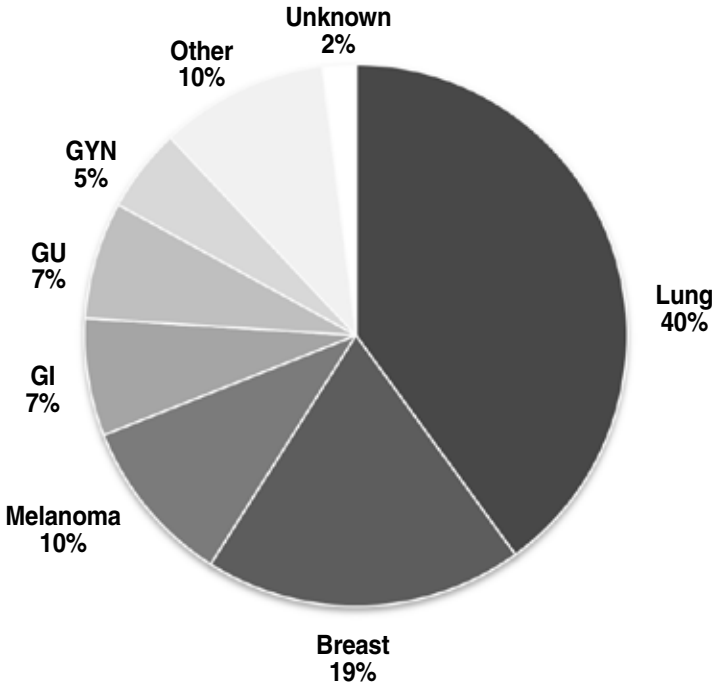

Figure 1. Malignancies most commonly associated with brain metastasis. GI = gastrointestinal; GU = genitourinary; Gyn = gynecologic. (Data from Posner.[3])

cancer. A thorough assessment is essential in identifying the associated systemic malignancy and in determining which site of disease is safest for tissue diagnosis. In the differential diagnosis, conditions apart from metastatic disease need to be considered (**Table 1**).

CASE PRESENTATION

INITIAL PRESENTATION AND EVALUATION

A 54-year-old woman presents with a left breast mass and is treated with a lumpectomy and axillary lymph node dissection. Her tumor is negative for hormonal receptors (estrogen receptor, progesterone receptor) and is also negative for HER2/neu (human epidermal growth factor receptor 2). She has positive lymph nodes and receives local radiation therapy and 8 cycles of adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil. There are no other sites of metastatic disease at diagnosis.

Eight months after her diagnosis, she develops right-sided headaches. She has an excellent performance status. CT of the brain without contrast reveals a right parietal hypodensity with significant mass effect. MRI with gadolinium contrast does not reveal any additional lesions (**Figure 4**). There is no evidence of any active extracranial disease.

- **What are important prognostic factors in brain metastasis?**

PROGNOSIS

Several factors have been validated as important prognostic factors in patients with brain metastasis. These include age, performance status, and extent of extracranial disease. These factors have been used to stratify patients into several prognostic

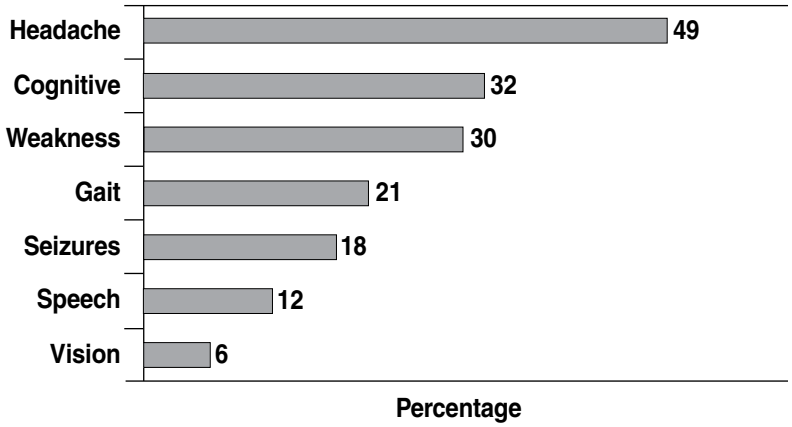

Figure 2. Common presenting symptoms of brain metastasis. (Data from Posner.[3])

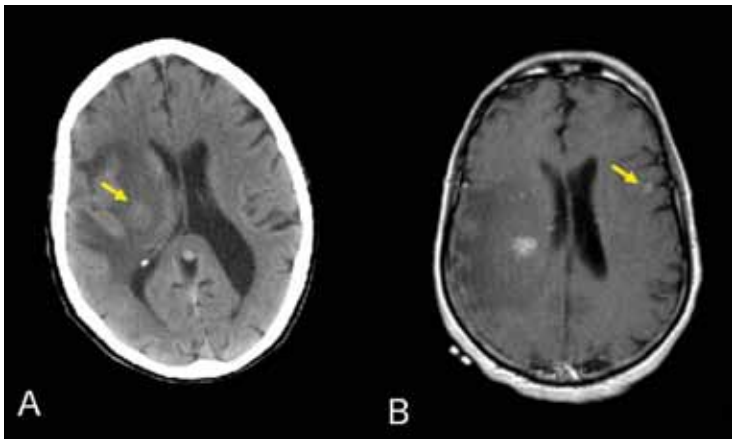

Figure 3. (**A**) Computed tomography of the brain reveals a single brain metastasis (*arrow*). (**B**) Magnetic resonance imaging with contrast reveals a second small site of metastasis in the contralateral hemisphere (*arrow*).

categories, known as RPA (recursive partitioning analysis) classes.[5] Discrete differences in survival have been demonstrated based upon this classification (**Table 2**). Poor performance status suggests a poor outcome (RPA class 3) regardless of the other factors. The patient in this case is in the most favorable group, RPA class 1.

Recently these prognostic categories were updated and a fourth prognostic element was incorporated: number of brain metastases. Known as *graded prognostic assessment* (GPA), this system scores patients from 0 to 4, with 4 corresponding to the most favorable prognosis.[6] The most recent update found that significant prognostic factors differed for each of the following tumor types: non–small cell lung cancer (NSCLC), breast cancer, melanoma, renal cell carcinoma, and gastrointestinal cancers.[7] In this analysis, patients with a low GPA score (0 to 1) tended to have a poor survival (of approximately 3 months) in all histologies examined. In addition, performance status was found to be an important prognostic factor in all groups.

With regard to breast cancer, there is emerging data that patients with hormone receptor–negative breast cancer may have increased risk of brain metastasis.[8] Elevated serum lactate dehydrogenase (LDH) also has been suggested as a predictor for developing brain metastasis.[9] The role of HER2/neu receptor status is unclear,[10] but the prognosis of patients with brain metastasis in the setting of HER2-positive disease may be more favorable due to better control of extracranial disease with trastuzumab.[11] Features of breast cancer which may increase risk for developing brain metastasis

Table 1. Differential Diagnosis of Brain Metastasis

Disease Process	Example
Demyelinating disease	Multiple sclerosis
Infection	Cerebral abscess
Primary brain tumor	Glioblastoma
Inflammatory/autoimmune	Neurosarcoidosis
Vascular	Hemorrhagic stroke
Idiopathic	Radiation necrosis

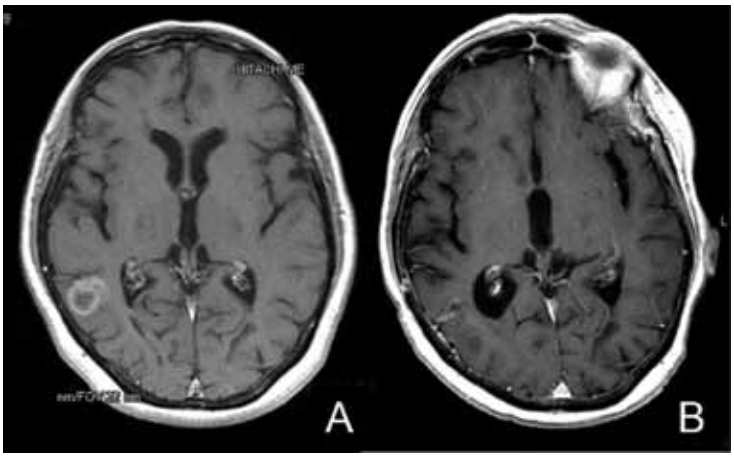

Figure 4. Right parietal brain metastasis from breast cancer. Magnetic resonance imaging of the brain with contrast (**A**) at diagnosis and (**B**) after surgical resection.

include age less than 50 years, high-grade histology, expression of basal cytokeratin CK5/6, overexpression of HER2 or epidermal growth factor receptor (EGFR), and the lack of estrogen receptors.[12] Stratification of breast cancer with gene expression arrays has identified subsets of breast cancer with varying prognoses.[13] Ongoing research is exploring the implications of these categories with regard to brain metastasis.

- **What treatment options are available for brain metastasis?**

TREATMENT

Surgery

Surgical resection is an important consideration for a patient with favorable prognostic factors (RPA class 1 or 2) and a single brain metastasis in a surgically accessible area. Several studies suggest improved functional independence and overall survival if surgical resection is performed in addition to whole brain radiation therapy (WBRT),[14–16] although one randomized study and a subsequent meta-analysis dispute this benefit.[17,18] Resection for several metastases is less well-established than resection for single lesions, although it appears that resection of all intracranial metastases confers an outcome similar to resection of a single brain metastasis.[19] Resection of recurrent brain metastasis after initial treatment has also been shown to be feasible in retrospective analyses.[20,21] Large tumor size, significant mass effect, noneloquent tumor location, and the need for diagnostic tissue are also considerations in making a decision to perform an operation.

Whole Brain Radiation Therapy

WBRT for brain metastases was described over 50 years ago by Chao and colleagues.[22] This modality, in contrast to the other local therapies, may address microscopic metastatic disease in the brain that is not yet clinically or radiographically evident. There is only one randomized study comparing WBRT and supportive care (with corticosteroids).[23] In this study, 46 patients were randomized to either WBRT or supportive care; median survival was slightly longer in the group receiving WBRT (14 weeks versus 10 weeks). However, neither brain imaging with CT or MRI nor statistical analysis was performed. Rates of local recurrence are significantly higher in patients who have WBRT withheld and only receive local therapy (either sur-

Table 2. Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) Prognostic Classification

RPA Class	Criteria	Median Survival (months)
1	KPS ≥70 Age <65 yr Controlled primary tumor No extracranial disease	7.1
2	All other situations	4.2
3	KPS <70	2.3

KPS = Karnosky performance status.

Adapted from Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745–51.

gery or stereotactic radiosurgery; see below),[24–27] although overall survival appears similar, likely because death often results from extracranial disease. The effects of WBRT upon neurocognitive function and quality-of-life are conflicting; declines in neurocognitive function and quality-of-life have been attributed to poor tumor control[28–30] as well as to WBRT itself.[31] Acute radiation toxicity includes headaches, nausea, vomiting, fatigue, alopecia, ear fullness, dry mouth, and scalp irritation. Late toxicity from WBRT includes progressive cognitive impairment, ataxia, and urinary incontinence.[32,33] Using smaller fraction size (3 Gy or less) decreases the likelihood of such complications in the subset of patients who survive for a prolonged period of time.

Prophylactic cranial irradiation (PCI) of approximately 25 Gy of WBRT is considered standard of care in the treatment of chemotherapy-sensitive small-cell lung cancer (SCLC), as there is both a survival benefit and improved local control.[34] A randomized study found that higher doses of PCI (36 Gy) for SCLC led to increased neurocognitive toxicity without benefit.[35]

A trial of PCI for locally advanced NSCLC revealed a decreased risk of brain metastasis with increased neurocognitive toxicity.[36,37] This trial was closed prematurely due to poor accrual.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) involves techniques to precisely deliver high-dose radiation to a small area of brain in a single or small number of fractions. Theoretically, the surrounding tissue is spared most of the dose. Small spherical brain tumors are the ideal target for SRS. SRS has indications outside the cancer setting, such as trigeminal neuralgia and arteriovenous malformation. Depending on the technology, the dose is given either as a single fraction (most commonly) or over a small number of fractions. Use of a headframe may be a necessary part of the technique (eg, Gamma knife). A late and serious complication of SRS is radionecrosis. Multiple studies have confirmed the ability of SRS to achieve local tumor control,[38–42] even in radioresistant malignancies. SRS offers less morbidity than surgical resection in treating patients with multiple brain metastases, and it may be more cost effective.[43] Whether there is an upper limit to the number of brain metastases that can be treated with SRS is unclear; it appears feasible to treat patients with more than 10 metastases.[44] Randomized clinical trials evaluating surgical resection, WBRT and SRS for brain metastasis are summarized in **Table 3.**[14,15,17,24,26,27,38,42,45,46]

Pharmacologic Therapy

In randomized trials, traditional chemotherapy has demonstrated limited benefit in controlling metastatic brain tumors.[47–50] There may be several reasons for this. Most important, the blood-brain barrier limits the penetration of chemotherapy into brain and brain tumor tissue. Additionally, because

Table 3. Summary of Randomized Clinical Trials Regarding Treatments for Parenchymal Brain Metastases

Study	Clinical Situation	All Received	Randomized Intervention	*N*	Conclusions
Patchell et al (1990)[14]	Single brain metastasis	WBRT	Surgical resection	48	Undergoing surgical resection prior to WBRT improved local control at original site of metastasis, overall survival, and functional independence
Vecht et al (1993)[15]	Single brain metastasis	WBRT	Surgical resection	63	Undergoing surgical resection prior to WBRT improved local control at original site of metastasis, overall survival, and functional independence,* particularly in patients with well-controlled extracranial disease
Mintz et al (1996)[17]	Single brain metastasis	WBRT	Surgical resection	84	Undergoing surgical resection prior to WBRT *failed* to demonstrate an improvement in overall survival or functional independence
Patchell et al (1998)[24]	Single brain metastasis	Surgical resection	WBRT	95	The addition of WBRT following surgical resection decreased the risk of intracranial relapse and risk of neurologic death, but did not improve overall survival or functional independence
Kondziolka et al (1999)[42]	2–4 brain metastases	WBRT	SRS	27†	Adding SRS to WBRT was well tolerated and improved local control, but did not improve overall survival
Andrews et al (2004)[38]	Unresectable 1–3 brain metastases (RTOG 9508)	WBRT	SRS	333	In patients with a single unresectable brain metastasis, adding SRS to WBRT led to improved overall survival. The SRS group experienced improved performance status. In subset analysis, patients with favorable histology (NSCLC), RPA class I, and age <50 also experienced a survival advantage with the addition of SRS to WBRT.
Aoyama et al (2006)[26]	1–4 small (<3 cm) brain metastasis	SRS	WBRT	132	Omitting WBRT after SRS increased the risk of local recurrence, but did not change overall survival. There were no significant differences in neurological function and toxicity between the 2 groups.
Muacevic et al (2008)[45]	Single resectable brain metastasis	–	Resection + WBRT versus SRS alone	33†	The group treated with SRS alone experienced an increased rate of distant intracranial relapse, although these distant sites could be salvaged with additional SRS. Other conclusions are difficult to make due to limited accrual to the study.
Kocher et al (2011)[27]	1–3 brain metastases (EORTC 22952)	Either resection or SRS	WBRT	359	Omitting WBRT after local therapy (with either surgery or SRS) led to increased risk of intracranial relapse and neurologic death; however, there were no significant differences in overall survival or functional independence. Separately published analysis demonstrated improved QOL in the group that did not receive WBRT.‡
Sperduto et al (2013)[46]	1–3 brain metastases (RTOG 0320)	WBRT and SRS	3-arm study of concurrent/adjuvant: temozolomide versus erlotinib versus none	126†	The study was underpowered to derive conclusions; however, there was a suggestion of improved survival and improved time to CNS progression in the control group,* that is, the group that received radiotherapy without drug.

CNS = central nervous system; NSCLC = non–small cell lung cancer; QOL = quality of life; RPA = reverse partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

*Trend, but not statistically significant.

†Study terminated early.

‡Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol 2013;31:65–72.

brain metastasis can develop as a late feature in the course of cancer, the tumor may have already been treated with several chemotherapy regimens, leading to some degree of chemoresistance in the metastatic tissue.

However, systemic chemotherapy does play an important role in controlling extracranial disease. For example, patients with brain metastasis from HER2-positive breast cancer may have improved survival compared to patients with brain metastasis associated with HER2-negative disease due to the efficacy of agents such as trastuzumab in controlling extracranial disease.[51] Trastuzumab itself has no significant penetration across the blood-brain barrier.[52]

Newer agents with better penetration into the central nervous system, such as temozolomide,[46,53,54] capecitabine, lapatinib,[55] and erlotinib,[46] have been investigated as treatment options for brain metastasis, and as potential radiosensitizers. Many such agents are small-molecule compounds with relatively favorable toxicity profiles. The optimal role of chemotherapy in the treatment of brain metastasis is still evolving.

The histology of the primary tumor is an important consideration when selecting drug therapies. In patients with metastatic melanoma and brain metastasis, ipilumimab does not appear to contribute to toxicity and may warrant further exploration.[56,57] Sorafenib may decrease the incidence of brain metastasis in patients with renal cell carcinoma.[58]

EGFR mutations predict response to therapy with anti-EFGR agents such as erlotinib. Systemic resistance may occur while the metastatic disease in the central nervous system remains sensitive;[59] higher concentration of drug might be achievable in the central nervous system via weekly "pulsatile" dosing of erlotinib. Finally, in HER2-positive breast cancer, responses are observed (objective response rate of 38%) with the combination of lapatinib plus capacitabine.[55] Experimental therapies for brain metastasis include the placement of BCNU (bis-chloroethylnitrosourea)–impregnated wafers into the resection cavity at the time of surgery for single metastasis.[60]

Radiation Sensitizers

Another approach in treating brain metastasis is to utilize agents that may serve as a radiosensitizer. Agents tested in a randomized controlled fashion include lonidamine,[61] metronidazole,[62] thalidomide,[63] misonidazole,[64] bromodeoxyuridine,[65] gefitinib,[54] and motexafin gadolinium.[66] None of these agents has been shown to prolong overall survival in brain metastases, but motexafin gadolinium has been shown to improve time to neurological progression as well as neurocognitive function in the subset of patients with NSCLC.[67,68] Based on the success of the concurrent use of temozolomide with radiation therapy in glioblastoma,[69] temozolomide and erlotinib were separately tested as radiosensitizers in a randomized controlled trial (RTOG-0320) for patients with 3 or fewer brain metastases from NSCLC. All arms of the study included SRS and WBRT. Patients were randomized to either temozolomide, erlotinib, or no chemotherapy during the period of radiotherapy and were allowed to continue the drug as adjuvant therapy. Unfortunately, the study was terminated early due to poor accrual, and it appeared that overall survival was in fact worsened by adding 1 of the 2 agents compared with SRS/WBRT alone, although the study was underpowered to confirm this trend.[46]

Efaproxiral, an allosteric modifier of hemoglobin, demonstrated improved survival and quality of life when randomly assigned to 106 patients with breast cancer receiving WBRT and supplemental oxygen.[70]

Supportive Care

In addition to selecting definitive treatment of the central nervous system neoplasm, managing neurological symptoms is an important aspect of care of patients with metastatic brain tumors. There are several measures which can be taken to improve quality of life.

Cerebral edema and mass effect from the tumor may result in many neurological symptoms. Surgical resection of tumor, when feasible, is the most direct way of ameliorating this problem. Corticosteroids improve vasogenic edema and are a mainstay in treating cerebral edema from primary or metastatic brain tumors. A typical dose of dexamethasone consists of an intravenous bolus of 10 to 20 mg followed by 4 to 24 mg/day in divided doses. Vigilance is needed for side effects including hyperglycemia, peptic ulcer disease, weight gain, edema, psychosis, immunosuppression, and proximal weakness due to steroid myopathy. Corticosteroids are often continued until tumor control is achieved with definitive treatment (eg, surgery or WBRT) and should then be tapered.

Seizures can occur in patients with brain metastasis. However, anticonvulsants should be reserved for patients who have actually experienced a seizure.[71] Anticonvulsants that do not induce hepatic enzymes, such as levetiracetam, valproate, gabapentin, and pregabalin, are less likely to interact with chemotherapy and are preferred.

CASE 1 CONTINUED

The single metastasis is surgically resected without significant neurological sequelae (Figure 4). The pathological review is consistent with metastatic breast cancer. The patient then receives WBRT to a total dose of 30 Gy in 15 fractions. She receives surveillance brain MRI with gadolinium every 3 months. She remains clinically and radiologically stable 6 months after the completion of WBRT. After the eighth month, she reports impaired balance and urinary incontinence. Contrast MRI of the brain reveals sulcal enhancement within the cerebellum. MRI of the spine shows leptomeningeal enhancement near the conus medullaris (**Figure 5**). Lumbar puncture is performed; cerebrospinal fluid (CSF) analysis reveals elevated protein (121 mg/dL) and the presence of malignant cells on CSF cytology. These cells are consistent with the primary cancer cells.

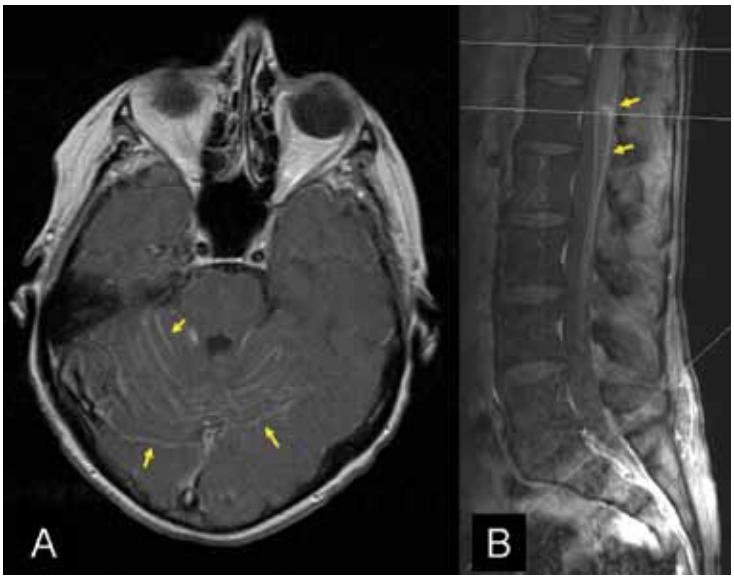

Figure 5. (**A**) Sulcal enhancement of the cerebellum (*arrows*) on brain magnetic resonance imaging (MRI), consistent with leptomeningeal metastasis. (**B**) Leptomeningeal metastasis on lumbar spine MRI with enhancement near the conus medullaris (*arrows*).

- **What is the significance of these findings?**

LEPTOMENINGEAL METASTASIS

The clinical, radiological, and laboratory findings are suggestive of leptomeningeal metastasis (LM). LM refers to infiltration of the leptomeninges (arachnoid and pia mater) with neoplastic cells. Synonyms for this condition include neoplastic

Table 4. Signs and Symptoms of Leptomeningeal Metastasis at Initial Presentation

Symptoms	Percentage	Signs	Percentage
Cerebral			
Headache	38	Papilledema	12
Mental change	25	Abnormal mental state	50
Nausea and vomiting	12	Seizures	14
Gait difficulty	46	Extensor plantar response	50
Dysarthria/dysphagia	4	Diabetes insipidus	1
Loss of consciousness	6		
Cranial nerve			
Visual loss	8	Optic neuropathy	2
Diplopia	8	Ocular motor paresis	30
Facial numbness	0	Trigeminal neuropathy	12
Hearing loss	6	Facial weakness	25
Dysphagia	2	Hearing loss	20
		Hypoglossal neuropathy	8
Spinal			
Pain	25	Nuchal rigidity	16
Back	18	Straight leg raising	12
Radicular	12	Absent reflex	60
Paresthesias	10	Dermatomal sensory loss	50
Weakness	22	Lower motor neuron weakness	78
Bladder/bowel dysfunction	2		

Adapted from DeAngelis LM, Boutros D. Leptomeningeal metastasis. Cancer Invest 2005;23:145–54.

meningitis, meningeal carcinomatosis, and leptomeningeal disease. The presence of malignant cells on CSF cytology is considered the diagnostic gold standard for this condition and is highly specific; however, a single negative cytology does not necessarily exclude the diagnosis. Three serial lumbar punctures for CSF analysis has a sensitivity of approximately 90%.[72] CSF protein is commonly elevated. When unequivocal evidence of LM is noted on MRI, a radiographic diagnosis of LM may be made without CSF.

Simultaneous involvement of multiple levels of the neuroaxis is a clinical hallmark of LM. Cerebral, cranial nerve, and spine involvement are common and each may be associated with a specific set of signs and symptoms (**Table 4**).[73] Elevated intracranial pressure may result in headache, nausea, vomiting, and confusion. Hematological malignancies are frequently associated with LM, as are many types of solid malignancies and primary brain tumors (**Table 5**).[74]

The disease process may be diffuse or nodular. Diffuse LM may be difficult to detect on MRI. Nodular LM can cause symptoms due to mass effect and can result in spinal cord compression. Use of intra-CSF chemotherapy may have limited benefit for bulky leptomeningeal tumors greater than 2 mm in size due to limited penetration of drug.[75–77] MRI findings in LM are noted in **Table 6**.[78,79]

Table 5. Malignancies Associated with Leptomeningeal Metastasis

Malignancy	Frequency (%)
Non-CNS solid tumors	
Lung	
SCLC	15
NSCLC	1
Breast	5
Melanoma	5
Gastrointestinal	1
Head and neck	1
Hematologic malignancies	
Leukemia	5–15
Lymphoma	6
Primary CNS tumors	
PCNSL	42
Glioma	14

CNS = central nervous system; SCLC = small cell lung cancer; NSCLC = non-small-cell lung cancer; PCNSL = primary CNS lymphoma.

Adapted from Kesari S, Batchelor TT. Leptomeningeal metastases. Neurol Clin 2003;21:27

Table 6. Magnetic Resonance Imaging Findings in Leptomeningeal Metastasis

Finding	Frequency (%)
Brain	
Parenchymal volume loss	93
Sulcal (pial) enhancement	57
Enhancing nodules	36
Ependymal enhancement	21
Communicating hydrocephalus	7
Spine	
Cauda equina nerve root thickening	20
Lineal pial enhancement	32
Enhancing subarachnoid nodules	Not reported

Adapted from Chamberlain MC, Sandy AD, Press GA. Leptomeningeal metastasis: a comparison of gadolinium-enhanced MR and contrast-enhanced CT of the brain. Neurology 1990;40(3 Pt 1):435–8; *and* Collie DA, Brush JP, Lammie GA, et al. Imaging features of leptomeningeal metastases. Clin Radiol 1999;54:765–71.

The prognosis of LM is poor and survival is typically less than 6 months. However, a small subset of patients with LM (including those with breast cancer) may experience prolonged survival of 1 year or greater.

- **What treatment options are available for patients with LM?**

Treatment options for patients with LM are palliative and include intrathecal chemotherapy, systemic chemotherapy, and radiotherapy.

Chemotherapy

Intra-CSF chemotherapy can be delivered via lumbar puncture (intrathecal) or via a ventricular catheter connected to a reservoir placed under the scalp (Ommaya reservoir). While complications are possible from an Ommaya reservoir, it offers a means of delivering intra-CSF chemotherapy as well as obtaining CSF sampling with greater convenience than serial lumbar puncture. A radionucleotide CSF flow study (cisternogram) may be performed prior to delivering intrathecal chemotherapy to identify any sites of obstruction to CSF flow; these areas may be treated with focal radiotherapy to restore normal flow patterns.[80] Agents which may be administered into CSF for LM are listed in **Table 7**. Arachnoiditis, a common acute complication of intra-CSF chemotherapy, may present within 72 hours of drug administration as headache, nausea, and vomiting, and is treated with systemic cortico-steroids.

Systemic chemotherapy may play a role in treating LM as well as managing the extracranial malignancy (**Table 8**).[81] Supportive care for patients with LM includes CSF shunting,[82] corticosteroids, and anticonvulsants.

Radiation therapy can also be used to palliate LM. The extent of the central nervous system

Table 7. Agents That Have Been Administered into Cerebrospinal Fluid for Leptomeningeal Metastasis

Methotrexate
Cytarabine (ara-C)
Liposomal cytarabine (DepoCyt)
Thiotepa
Topotecan
Trastuzumab*
Rituximab*
Interleukin-2

*Perissinotti AJ, Reeves DJ. Role of intrathecal rituximab and trastuzumab in the management of leptomeningeal carcinomatosis. Ann Pharmacother 2010;44:1633–40.

Table 8. Chemotherapy Options in Leptomeningeal Metastasis.

Drug	CSF–Plasma Ratio (%)
Antimetabolites	
Methotrexate	3
6-Mercaptopurine	25
Cytarabine	20
Capecitabine*	Unknown
Alkylating agents	
Thiotepa	>90
Temozolomide†	20

*Rogers LR, Remer SE, Tejwani S. Durable response of breast cancer leptomeningeal metastasis to capecitabine monotherapy. Neuro Oncol 2004;6:63–4.

†Ostermann S, Csajka C, Buclin T, et al. Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. Clin Cancer Res 2004;10:3728–36.

Adapted from Berg SL, Chamberlain MC. Systemic chemotherapy, intrathecal chemotherapy, and symptom management in the treatment of leptomeningeal metastasis. Curr Oncol Rep 2003;5:29–40.

treated may vary and can range from very limited radiation therapy to irradiation of the entire neuroaxis (craniospinal radiation therapy). This decision may depend on many factors including the sites involved, neurological symptoms, functional status, extent of extracranial disease, and likelihood of response to other therapies.

CASE CONTINUED

Treatment consisted of radiation therapy to the caudal equina area with improvement in urinary incontinence. Following radiation therapy, intrathecal liposomal cytarabine was administered via an Ommaya reservoir with clearing of CSF cytology after 3 doses. The patient remained neurologically stable, but developed new lung metastases which were unresponsive to salvage treatment and resulted in significant functional impairment. She decided to pursue comfort care and died shortly thereafter.

CONCLUSION

Metastatic disease to the central nervous system is an issue that has become more significant as patients survive longer with cancer. Brain metastases and leptomeningeal metastases are 2 types of central nervous system metastases which require careful selection of treatment modalities for each individual patient. The prognosis is generally poor for both conditions, but prognostic factors have been identified which help to stratify patients and determine the appropriateness of available therapies. In addition to treatment of malignancy, management of neurological complications is important in managing these patients. More effective therapies for these conditions are essential, as they represent a critical obstacle to the overall progress of cancer treatment.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic.
Go to www.turner-white.com and select Oncology from the drop-down menu of specialties.

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