8 Clinical Presentation of Central Nervous System Metastases

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Introduction

Central nervous system (CNS) metastases are associated with significant morbidity and mortality and remain one of the most challenging complications of systemic cancer. While intraparenchymal brain metastases represent the most common site of CNS disease, other potential locations in the brain include the pituitary gland, ventricular system and choroid plexus, as well as the spinal cord and leptomeninges [1]. In this chapter we provide an overview of the clinical presentation of CNS metastases including diagnostic workup and initial management.

Brain Metastases

Brain metastases are the most common intracranial malignancy, occurring ten times more frequently than primary brain tumors [2]. The reported incidence of brain metastases varies, ranging from 6% to 30% across various studies [3–6]. The incidence is thought to be increasing, in part due to improved imaging techniques as well as more effective systemic therapies resulting in longer overall survival [3]. The CNS is considered a sanctuary site for disease. While there have been advances in the treatment of certain types of CNS metastases with targeted therapies or checkpoint inhibitors, the majority of chemotherapeutic agents have limited blood-brain barrier penetration [7, 8]. Survival varies greatly depending on the underlying cancer subtype, burden of systemic disease, and other patient-associated factors such as age and performance status [9].

Brain metastases can present at any point along the disease course. The Surveillance, Epidemiology, and End Results (SEER) database recently added information regarding the presence or absence of brain metastases at the time of initial diagnosis. Based on these data, the incidence proportion of brain metastases in all patients with newly diagnosed cancer was calculated to be about 2%. Brain metastases at diagnosis were most common (>10%) in small cell and non-small cell lung cancer regardless of cancer stage. Conversely, among all patients with breast cancer, melanoma, and renal cancer, the incidence at diagnosis was relatively low (0.4%, 0.7%, and 1.5% respectively). Compared to patients with any stage cancer diagnosis, patients with systemic metastases at baseline carried an increased incidence of brain metastases at 12.1%. In this population, the incidence of brain metastases was

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highest in patients with melanoma (28.2%), lung adenocarcinoma (26.8%), small cell lung cancer (23.5%), and renal cancer (10.8%) [10].

The presentation of brain metastases varies dramatically, ranging from incidentally discovered, asymptomatic lesions found during a staging workup to acute neurologic decompensation requiring emergent intervention, particularly in the case of hemorrhagic metastases. Depending on the location, number, size, and degree of surrounding edema, they can present with a diversity of symptoms [11].

Focal Neurologic Deficits

Focal neurologic deficits are the presenting symptom in 20–75% of patients with brain metastases [11, 12]. The specific deficit depends on the location of the tumor. Intraparenchymal metastases are most often found along the grey-white junction or in watershed regions. This is thought to reflect hematogenous dissemination of disease with seeding of distal capillaries by tumor microemboli [13, 14]. While some studies suggest the majority of brain metastases (70–80%) are supratentorial, other autopsy studies have found nearly equal rates of disease in the posterior fossa and cerebellum [15, 16]. Compared to other cancers, breast and lung cancer metastases seem to have a predilection for the cerebellum [17]. Although limited by small sample size, a recent study quantifying the spatial distribution of brain metastases found that metastases were more common along branches of the anterior cerebral artery, particularly in the paracingulate gyrus [18].

Supratentorial metastases can involve any lobe of the brain. Patients with symptomatic tumors in the frontal lobes can present with contralateral hemiparesis as well as personality changes ranging from abulia to disinhibition. When the dominant hemisphere is involved, a Broca's-type aphasia, characterized by difficulty expressing language, can occur. Due to the spatial arrangement of motor function along the homunculus, weakness from cortical lesions may be very specific, such as isolated hand weakness from a metastasis in the hand knob. Lesions in the medial motor cortex often affect the leg, while more lateral lesions tend to involve the arm and face to a larger degree [19].

The temporal lobes include the hippocampus, limbic system, portions of the visual pathways, and Wernicke's area. Temporal lobe metastases, particularly bilateral lesions, can present with short-term memory impairment. If the dominant hemisphere is affected, Wernicke's aphasia, characterized by an inability to comprehend language (also known as receptive aphasia), can result. On exam, a contralateral superior quadrantanopia may be detected if the optic tracts are involved; however, this is not always reported by the patient. Seizures are also very common, particularly with medial temporal lobe lesions [11, 19].

Patients with right parietal lesions often present with visual spatial disturbance, specifically left neglect. This may manifest itself as bumping into things on the left or, in more extreme cases, neglecting the left side completely. Patients may report forgetting to close the car door on the left or improperly clothing the left side of their body. Often there is a lack of awareness of the deficit, or anosognosia, seen with non-dominant parietal lesions. Left parietal lesions can present with acalculia. Contralateral hemisensory loss or visual field deficits, specifically an inferior quadrantanopia, can also be seen. Occipital lesions also present with a contralateral visual field cut, typically involving the entire contralateral hemifield. Complex visual hallucinations have also been reported [11, 19].

Infratentorial disease can present with ataxia or gait impairment. Cerebellar hemispheric lesions can cause ipsilateral dysmetria and incoordination. Lesions affecting the cerebellar vermis are more likely to contribute to truncal instability instead of classic dysmetria. Given the high density of motor and sensory pathways as well as cranial nerve nuclei that run through the brainstem, even small lesions can be highly symptomatic. Brainstem lesions can cause contralateral hemiparesis and hemisensory loss of the face, arm, and leg. If the lower pons (below the facial nucleus) or medulla are affected, patients may present with crossed find-

ings including ipsilateral weakness of the face and contralateral weakness in the body [19].

In the setting of intratumoral hemorrhage, these deficits may be acute in onset; however, in many patients, they progress over the course of days to weeks. Progressive focal neurologic deficits in any patient with known systemic cancer should trigger additional workup for CNS metastases.

Cognitive Impairment

While not often considered a true focal neurologic deficit, cognitive impairment is also common in patients with brain metastases [11]. This can manifest as disorientation, confusion, memory impairment, and/or executive dysfunction. One study evaluating whole brain radiotherapy in patients with lung cancer found that 65% of patients with brain metastases had cognitive dysfunction prior to treatment [20]. In patients with primary brain tumors, cognitive impairment is one of the leading causes of disability and caregiver distress. In caregivers of patients with brain metastases, cognitive impairment was associated with worse coping strategies, which can negatively impact quality of life [21]. While delirium or acute mental status changes are common in cancer patients, this is a less common presentation of brain metastases. In a series of 132 patients requiring neurology consults for altered mental status, brain metastases were the underlying etiology in only 15% of cases [22].

Headaches

Headaches are another common symptom of brain metastases, reported by approximately 25–60% of patients, particularly in the setting of multiple lesions [1, 11]. These can result from increased intracranial pressure (ICP) as well as traction on the dura which contains pain fibers [23]. The classic headache resulting from a brain tumor is focal, worse in the morning, and exacerbated by lying flat or Valsalva maneuvers. These headaches may also be associated with nausea and/or vomiting [24]. However, a prospective study of over 100 patients at Memorial Sloan Kettering Cancer Center with brain tumors (both primary and metastatic) found that the majority (77%) described a tension-type headache that was most often bifrontal or ipsilateral. Unlike classic tension-type headaches, these were more frequently associated with nausea (40%) and worsened with bending over (32%). In this series, the classic morning headache was uncommon [25].

Headaches are also very common in the general population, with an annual prevalence approaching 60% [26]. In a cancer patient with an underlying headache disorder, a change in the frequency, severity, or character of their typical headaches should prompt additional evaluation to exclude brain metastases.

Seizures

Up to one-third of patients with brain metastases present with seizures. In one retrospective study of over 500 patients with surgically resected metastases, multiple lesions, temporal and occipital locations, and bone involvement were all associated with preoperative seizures. Large tumors (>5 cm) and those in locations other than the frontal lobes were associated with uncontrolled seizures preoperatively (defined as requiring more than one antiepileptic drug (AED)). Headaches and cognitive dysfunction were also commonly seen with seizures. In this cohort, subtotal resection, >3 metastatic lesions, temporal lobe location, local recurrence, and no postoperative chemotherapy were all associated with seizures in the postoperative setting [27, 28].

While some studies have suggested the presence or absence of seizures has no impact on overall survival with brain metastases, they can significantly impair quality of life. Each state has laws limiting driving after seizures. Patients also need to be maintained on AEDs, sometimes indefinitely. Poorly controlled seizures are associated with worse outcomes in patients with brain metastases [29].

Numerous studies have demonstrated no benefit to prophylactic AEDs in the primary preven-

tion of seizures, with an increased risk of adverse events [30, 31]. For this reason, the American Academy of Neurology recommends against prophylactic AED use for patients with brain tumors, including metastases [32]. Despite this, prophylactic AED use remains common in practice [33]. Many of the original studies focused on older AEDs with more side effects, while newer drugs such as levetiracetam are often better tolerated with a more favorable risk-benefit profile [34, 35]. There are also data to suggest that primary prophylaxis may be beneficial in a high-risk subset of patients or in the perioperative period to decrease the rate of early postoperative seizures [36, 37]. However, randomized controlled trials are limited and this remains an area of controversy.

Uncommon Intracranial Metastases

Pituitary Metastases

Metastases to the pituitary gland are rare, accounting for 0.14–3.6% of intracranial metastases, although in autopsy series, the incidence has been reported as high as 28%. Breast and lung cancer are the most common cancers to metastasize to the pituitary gland, but many other cancers have been reported. Unlike adenomas, which affect the anterior pituitary gland, metastases tend to have a predilection for the posterior pituitary [38, 39].

Over 80% of pituitary metastases are asymptomatic. In patients who present with symptoms, visual impairment has been reported in almost 50% of cases. The most common visual field deficit seen with pituitary lesions is a bitemporal hemianopia due to compression of the optic chiasm, which overlies the pituitary gland. Endocrine dysfunction, specifically diabetes insipidus (DI) and panhypopituitarism, was reported in over one-third of cases each. Patients with diabetes insipidus often present with increased thirst and urine output. Panhypopituitarism can be more difficult to diagnose as symptoms may be nonspecific including fatigue, lethargy, and orthostasis. Headaches were also common, occurring in 35% of patients. Pituitary apoplexy is a life-threatening emergency characterized by hemorrhage into the pituitary gland. While this is of concern with pituitary adenomas, it is rarely seen with metastases [39].

Leptomeningeal Disease

The leptomeninges include the pia mater, subarachnoid space, and arachnoid membrane surrounding the brain and spinal cord [19]. Metastases to this space are typically a late-stage complication of cancer. While leptomeningeal disease (LMD) is most common in adenocarcinomas and hematologic malignancies, almost any cancer can metastasize to the leptomeninges [40, 41]. As the cerebral spinal fluid (CSF) flows throughout the entire leptomeningeal space, bathing the brain and spinal cord, the presentation of LMD is highly variable and can range from symptomatic hydrocephalus to isolated cranial neuropathies, multifocal deficits, and/or seizures.

When LMD involves the cerebral leptomeninges, patients often present with signs of elevated ICP. Leptomeningeal metastases can interfere with CSF reabsorption through the arachnoid granulations, causing hydrocephalus, or limit ventricular compliance such as in the setting of diffuse subarachnoid tumor, resulting in elevated ICP without radiographic hydrocephalus [42]. Patients often present with positional headaches, worse in the morning or when bending over. These can be associated with nausea or vomiting and sometimes with neck pain and stiffness [43]. Vision changes including blurry vision or horizontal diplopia from a partial cranial nerve VI palsy may also be seen. As ICP increases, patients may become increasingly lethargic [41]. Other alterations in consciousness include seizures or abrupt unresponsiveness precipitated by changing position, a phenomenon known as pressure or plateau waves [42].

Cranial nerve involvement from leptomeningeal disease can manifest as vision changes, numbness over the face, facial weakness, hearing loss, tinnitus, or hoarseness [42, 43]. Involvement of the spinal cord and cauda equina nerve roots can contribute to radicular pain, bowel or bladder dysfunction, or focal numbness or weakness

in the legs [41, 42]. A combination of symptoms affecting multiple levels of the neuro-axis should raise suspicion for LMD in a patient with metastatic cancer [1].

Spinal Metastases

Tumors involving the spine are divided into three categories based on location: extradural, intradural extramedullary, and intradural intramedullary. The vast majority of metastases are extradural [44]. Extradural tumors often arise from the vertebral bodies, most commonly in the thoracic spine, and extend into the extradural space [42, 44]. Initially, these lesions may present with severe back pain. Pain is often severe, worse at night, and may wake the patient from sleep. Both extradural and intradural extramedullary lesions can present with cord compression. As the spinal cord becomes compressed, patients can develop focal neurologic deficits including weakness, numbness, bowel or bladder dysfunction, or gait impairment [43]. Approximately 5% of patients with metastatic cancer initially present with cord compression [45].

Intramedullary metastases are rare, with an incidence of <2%. Although they may be the presenting symptom of disease, intramedullary metastases are typically seen in the setting of known brain metastases or leptomeningeal disease [46]. Patients may present with spinal cord syndromes, such as a Brown-Sequard syndrome, characterized by ipsilateral weakness and vibratory/proprioceptive loss and contralateral loss of pinprick and temperature below the level of the lesion. Pain, weakness, and sensory changes are the most commonly reported symptoms; however, bowel or bladder dysfunction and spasticity can also be seen. Typically patients have a relatively rapid decline as the lesion increases in size, but it is possible for diagnosis to be delayed [47].

Workup and Management

The imaging modality of choice for CNS metastases is gadolinium-enhanced magnetic resonance imaging (MRI) [12]. For patients presenting with focal neurologic complaints, imaging can be focused to the area of highest concern, such as the brain alone or a particular spinal level. In the case of patients with parenchymal brain metastases identified on imaging, full CNS staging is not always necessary if the patient is otherwise asymptomatic. For patients presenting with leptomeningeal disease, workup should include complete imaging of the neuro-axis including brain and total spine, with and without contrast. When there is clinical suspicion for LMD but negative imaging, the gold standard for diagnosis is a lumbar puncture for CSF analysis. Multiple lumbar punctures may be necessary as the sensitivity of CSF cytology does not exceed 90% until after three studies [48]. Extradural spinal metastases arising from the vertebrae rarely occur in isolation, so imaging the entire spine is recommended [49]. Once CNS metastases are identified, systemic restaging is recommended as this has implications for both prognosis and treatment options.

The initial management of a patient with symptomatic brain metastases includes high-dose dexamethasone to decrease edema and reduce symptom burden. Steroids may not be necessary in asymptomatic brain metastases without significant edema. Treatment options for patients with brain metastases have evolved and may include a combination of radiation, surgery, chemotherapy, immunotherapy, or targeted agents. These will be discussed extensively in the later chapters of this book; however, the appropriate approach to the management of each patient depends on the burden of CNS disease, the extent of systemic disease, and the options available for systemic treatment [2, 50, 51].

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