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Diagnosis and Management of CNS Metastases

MRINAL KANTI ROY, DIPANKAR SIRCAR

INTRODUCTION

The cases of CNS metastases are increasing because of increase in incidence of cancer in the general population, with longer survival due to improved patient care services in the field of oncology, surgery and radiotherapy. It is also partly due to the earlier diagnosis of small tumors by improved technology in the field of imaging. In clinical practice, therefore, CNS metastases have become a common problem.

Metastases from a primary site can involve any part of the neuraxis. Common sites of involvement are brain, meninges, and spinal cord, commonly epidural and intramedullary spaces. Metastases from lung (9.7% to 64%)[1] followed by breast (2-25%)[2], melanoma (4-20%), colorectal and genitourinary tract and sarcoma (1%) are in order of descending frequency. Primary site is unknown in up to 15% of patients with brain metastases[3]. The relative distribution of brain metastases tends to occur in a pattern proportional to the blood flow to specific brain areas. In that regard, the great majority of brain metastases (approximately 80%) occur in the cerebral hemispheres, while the cerebellum and brainstem are less involved (10-15% and 2-3%) respectively[4].

Clinical evidence of leptomeningeal metastases (LM) is evident in 8% of patients with metastatic solid tumors; at necropsy, the prevalence is as high as 19%[5]. The frequency is highly dependent on the type of primary cancer. LM is especially common in patients with lymphoma, leukemia, breast and small cell lung cancer (SCLC) as well as melanoma. However, most patients with LM encountered in clinical practice will have either lung or breast cancer. Diffuse histiocytic and lymphocytic lymphomas (high grade), adenocarcinoma of breast, SCLC a have special predilection for LM. Primary brain tumors, while rare, compared to systemic malignancies have a relatively high frequency of leptomeningeal dissemination.

Spinal cord may be compressed by metastatic lesions, and commonly seen in the epidural spaces, which reflect the propensity of solid tumors to metastasize to the vertebral column, probably due to abundance of bone marrow in the axial skeleton. Lung, breast and prostatic cancer each account for about 20% of all cases of epidural spinal cord compression (ESCC). Non-Hodgkin's lymphoma, multiple myeloma, renal cell and colorectal carcinoma are frequent causes[6,7]. In children, the most common causes of ESCC are sarcomas and neuroblastomas[8]. The most common tumors that spread to the spinal cord are the small cell lung cancer (SCLC), followed by breast cancer. Though uncommon, intramedullary spinal cord metastases (ISCM) are encountered more in recent times, due to advent of MRI. Lung cancer, followed by breast, renal cancers, lymphoma, and melanoma are main causes. ISCM can be a complication of widespread metastatic disease.

Clinical Presentation

Cerebral Metastases

Most of the brain metastases are detected after the detection of the primary tumor (>80%). Less frequently, brain metastases may be the first manifestation of disease. The median interval from the diagnosis of the primary to the onset of the neurological symptoms varies from 3 to 12 months according to the type of the primary tumor[9]. Metastatic brain tumors usually present with the features of increased intracranial pressure, and focal neurological deficits with focal irritation. Headache at

presentation is more common with metastases in the posterior fossa, and may be mild. It often awakens the patient at night, or is present in the early morning. In posterior fossa tumors, it is aggravated by bending down or lifting. Some patients report nausea, vomiting, confusion and lethargy. Seizures may be focal or generalized. It is a presenting symptom in approximately 10% of patients. Seizures are common in patients with multiple lesions. Ataxia, motor weakness, aphasia, sensory and visual field defects are other focal neurological manifestations. An acute stroke-like presentation may occur and often is caused by hemorrhage into the tumor. Hemorrhage is common in metastases resulting from melanoma, choriocarcinoma, renal cell, thyroid carcinoma and bronchogenic carcinoma[10]. Papilledema is rarely seen.

Leptomeningeal Involvement

LM is suspected in the background of a known malignancy elsewhere in the body, especially when a patient presents with symptomatology suggestive of involvement of multiple levels in the nervous system. Frequently, signs are more widespread than symptoms, as for example, an absent ankle jerk in a patient complaining of diplopia. Headache, back or radicular limb pain, nausea, vomiting, weakness, sensory disturbance (mainly lower extremities and saddle distribution), altered mental status, diplopia, incoordination, seizures, sphincter disturbance, dysphonia, dysphagia, dysarthria, papilledema and diminished visual acuity, meningismus may present in combination or in isolation.[11] However, multiple cranial nerve involvement is the rule rather than the exception. Hydrocephalous is a common sequelae.

Spinal Cord Compression

It may be one of the manifestations of metastases from solid tumors. The vertebral column is the commonest site, and most neoplasms in adults are epidural in origin. Thoracic cord is the most commonly involved site. Pain is the initial symptom, which may be aching or localized, sharp and radiating in quality. Coughing, sneezing or movement can increase the pain. Patients often awaken at night due to pain. Pain of recent onset, persistent and boring, especially in the thoracic region may be a manifestation of vertebral metastasis in some cases. Pain is present in 83-96% of ESCC cases. Duration may be a few hours to several months. The site of pain corresponds often poorly to the localization of ESCC on MRI. Most patients experience motor deficits at the time of diagnosis. Upper motor neuron type weakness with disproportionate affection of iliopsoas muscle may be found when ESCC arises at or above the level of the conus. Spinal sensory levels are unreliable for localizing epidural tumors, though the sensory deficits are found in the majority of patients at diagnosis. Thoracic ESCC commonly presents with back pain and bilateral leg weakness, whereas radicular pain and sensory changes may be a common manifestation of lumbosacral ESCC. Pain typically precedes signs of cord compression by weeks or even months[4]. Spinal cord compression may give rise to weakness, sensory loss and autonomic dysfunction in the form of urinary urgency and incontinence, fecal incontinence, and sexual impotence in men. Once signs of spinal cord compression appear, they tend to progress rapidly.

Patients with ISCM can present with sensory alteration, pain, weakness, and gait unsteadiness or sphincter dysfunction. Hemicord dysfunction may be the initial clinical presenting feature.

Diagnosis

Diagnosis of CNS metastases is often easy in a patient with a known primary cancer. However, it is difficult when the primary site is unknown, and a high degree of suspicion is necessary. Clinical symptomatology, including a thorough history, general and systemic—with special emphasis on neurological—examination is a necessary initial step. A meticulous treatment history especially for the primary tumor, is essential. An examination may reveal neurologic changes that are specific to the location of the tumor. Signs of increased pressure within the skull are very common. Some tumors may not show symptoms until they are very large. Then, they suddenly cause rapid decline in the person's neurologic functioning. The original primary tumor may already be known, or it may be discovered after an examination of tumor tissues from the brain, indicating that it is a metastatic type of tumor.

Contrast enhanced MRI should be the imaging modality of choice. Contrast enhanced MRI detects 2-3 times as many lesions as contrast CT, especially lesions <5 mm in diameter. In addition, approximately 20% of patients with solitary metastatic lesions on CT show multiple lesions on MRI. When MRI is not available or is contraindicated, CT scanning can evidence the lesion. Most brain metastases appear as ring enhancing lesions surrounded by edema at the gray-white matter junction. Rarely do small metastases enhance, but they may be evident on T2-weighted MRI images. Metastatic brain tumors must be differentiated from primary brain tumors, abscess, infarction, radiation necrosis,

granuloma and demyelination. Cancer patients often present with immune suppression related to therapy received, and opportunistic infection is common, and should be considered in the differential diagnosis[12]. One study has demonstrated that even when contrast MRI is used, 11% of cancer patients with a single brain lesion have a false-positive diagnosis[13]. PET scanning is also a sensitive tool for detecting unknown primary tumors in patients with confirmed cerebral metastases[14]. Furthermore, magnetic resonance spectroscopy, comparing the different relative intensities of lactate, lipids, choline and N-acetyl aspartate may distinguish normal brain from edema, neoplasia, necrosis or demyelination[15].

In the diagnosis of LM, lumbar puncture is a useful procedure. To yield maximum information, repeated CSF studies on various occasions may be needed. CSF may demonstrate malignant cells in cytological examination. Lymphocytic pleocytosis, increased protein levels, and normal or low CSF glucose are characteristic CSF findings. In selected cases, meningeal biopsy can also help in diagnosis. MRI can demonstrate nodular tumor deposits in the meninges. Diffuse meningeal enhancement is a characteristic finding. Hydrocephalus may sometimes be evident on MRI study.

In evaluating cases of spinal cord metastases, plain radiographs of the spine and radionuclide bone scans have only a limited role in diagnosis because they do not identify 15-20% of the metastatic vertebral lesions and fail to detect paravertebral masses that reach the epidural spaces through the intervertebral foramina[16]. MRI is superior to CT and myelography in the diagnosis of spinal tumors especially of epidural masses. Differential diagnosis includes epidural abscess, tuberculoma, and epidural hemorrhage. On T1 weighted MRI scans, vertebral metastases are usually hypointense relative to a normal bone marrow signal. If contrast is given, there may be enhancement and this may "normalize" the appearance of tumor by increasing its intensity to that of the normal tissue. Disc spaces are usually preserved in metastatic lesions. MRI can also detect ISCM. Apart from radiological methods, in SCLC patients, an elevated CSF calcitonin strongly suggested CNS metastases and an elevated mammalian bombesin was very suggestive of the presence of meningeal carcinomatosis[17].

Prognosis

The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) describes three prognostic classes, defined by age, Karnofsky Performance Score (KPS), and disease status, which is a measure of how well a patient functions. It is commonly used by physicians to classify impairment of functions. It rates patients from 0 to 100, with 100 being no complaints with normal functioning and 0 being deceased. In Class 1 are patients with KPS > or = 70, < 65 years of age with controlled primary, no systemic disease and no extracranial metastases; in Class 2, the KPS $\geq$ 70 with at least one of the following: age $\geq$ 65 years, uncontrolled primary tumor, or presence of systemic disease; in Class 3, KPS < 70. The best survival (median: 7.1 months) was observed in patients < 65 years of age with a Karnofsky Performance Status (KPS) of at least 70, and a controlled primary tumor with the brain the only site of metastases. The worst survival (median: 2.3 months) was seen in patients with a KPS less than 70. All other patients had relatively minor differences in observed survival, with a median of 4.2 months[18]. Treatment modalities also influence survival. Patients with higher performance status, RPA class I, and treated with surgery followed by whole brain radiotherapy (WBRT) had better survival[19]. Patients with hematological malignancies usually fare better than patients with solid tumor metastases.

Management

Symptomatic Treatment

Antiepileptic drugs (AED) are used when patients have seizures. There is no role of prophylactic AED in cerebral metastases[20]. In cerebral metastases, corticosteroids are the first line in management of patients with peritumoral edema. Dexamethasone is usually started at a dose of 10-16 mg/day and continued every six hours. Patients with small, completely asymptomatic lesions, may not need steroids.

Corticosteroids are effective in treating and ameliorating neurological symptoms and deficits resulting from LM and ESCC in most of the cases, especially headache and radicular pain. A dose in the wide range of 16-100 mg of dexamethasone per day is probably appropriate; with higher dosages requiring a rapid taper if toxicity is to be minimized. Non-steroidal anti-inflammatory agents are often used for bone pain. Other supportive measures including care of bowel, bladder, skin, nutrition, etc. should be given due consideration. Prophylaxis against DVT should be considered. Spinal braces are sometimes advocated though they are uncomfortable for the patient.

Surgical Management

Surgical intervention in brain metastases establishes the diagnosis, prevents mass effects, and allows the local

control of the tumor. Patients with single brain metastasis, who received resection followed by WBRT, did better than those given WBRT alone, and the surgical group presented with less frequent recurrence, a significantly longer overall survival, and a longer functional independence than the radiation group[21]. Bindal, in a retrospective study, found that patients with multiple brain metastases who underwent complete surgical resection had significantly longer survival than patients who underwent partial resection[22]. Although the role of surgery in the management of brain metastases is still controversial, surgery is strongly advocated for patients with single brain metastases whose primary disease can be controlled.

Indications for surgery in ESCC are considered if there is spinal instability, compression of the spinal cord, worsening of the neurodeficit during, or following radiotherapy, highly radioresistant epidural tumors and limited tumor elsewhere, and, diagnosis in doubt. Overall prognosis of surgery in ESCC is not satisfactory. Decompressive laminectomy with or without postoperative radiotherapy is usually undertaken.

Radiotherapy in Cerebral Metastases

WBRT is the treatment of choice for most patients, because 70% of patients present with multiple metastases. Median survival after WBRT alone is 3-6 months, but most patients die from the systemic disease and not from the brain metastases. Survival of 2 years or more have been found in RTOG RPA class 1 and 2 patients and those with single brain metastases[23]. A relatively short course of radiation therapy is used, with a 30 Gy total dose, given in 300 cGy fractions five times a week. High total doses have not been proven to be of benefit. With WBRT, control of the presenting neurological problems has been achieved in 70-90% of patients without acute neurological side effects[24]. However, long-term safety is unknown. This is not an issue in patients with cerebral metastases because of their short survival. Possible long-term adverse effects can be dementia, ataxia, urinary incontinence, and can be fatal. Radiation sensitizers or hyperfractionated radiotherapy have not improved survival.

Prophylactic cranial irradiation (PCI) may be considered in tumors, which have a high propensity to spread to the nervous system, although doubts about its efficacy in prolonging survival remain. Prophylactic cranial irradiation has been shown, in one study, to decrease the incidence of metastasis, but without any effect on long-term survival[25].

Radiation in Spinal Cord Disease

In many patients, this form of therapy offers a well-tolerated and effective means of ameliorating pain and stabilizing neurological status. Further tumor growth and neurological damage are prevented in most of the cases by radiotherapy. Pain associated with ESCC can be relieved to a great extent by radiotherapy. In many studies, it has been shown that patients with ESCC treated with radical direct decompressive surgery plus postoperative radiotherapy regain the ability to work more often and maintain it longer than those patients treated with radiation alone.

Treatment of LM

The main goal of treatment is pain relief and prevention of neurological morbidity. Steroids are used for pain and focal deficits. Intrathecal chemotherapy with radiation to the area of maximum symptomatology is the mainstay of treatment. Prior to intrathecal chemotherapy, all patients should have a CSF study. Methotrexate and cytarabin are the most commonly used and best-studied intrathecal agents. Cytarabin can cause chemical meningitis while methotrexate may cause necrotizing leukoencephalopathy—especially in combination with radiotherapy. Systemic chemotherapy may be indicated in selected cases. Patients with symptomatic hydrocephalus should be offered a shunt if justified by reasonable performance status and life expectancy.

Stereotactic Radio Surgery (SRS)

The most recent evidence shows that both gamma knives and linear accelerators achieve similar excellent clinical results. The risk of side effects increases with the treated volume; so SRS is generally utilized only for lesions 3.0 cm or less in diameter. Results of a current open phase 3 randomized trial by the American College of Surgeons Oncology Group is addressing the role of WBRT in addition to SRS in patients with one to three brain metastases are still awaited.

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