Neoplastic Meningitis: A New Assessment of an Old Problem

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Abstract

Neoplastic meningitis (NM), also known as leptomeningeal carcinomatosis, is a complication of late stage malignancy, and is due to tumor infiltration of the leptomeninges and is found at autopsy in 5% of all cancer patients. The incidence of neoplastic meningitis is on the rise as the emergence of novel immunotherapeutic agents and continuous progress in modern cancer therapies increase overall survival rates of cancer patients. Diagnosis requires a high degree of clinical suspicion and is confirmed by the presence of leptomeningeal contrast enhancement on magnetic resonance imaging as well as confirmatory CSF cytology. Imaging may also reveal the presence of ventriculomegaly due to inflammatory changes inhibiting normal CSF circulation, resulting in a communicating hydrocephalus. Treatment is mainly palliative, primarily aimed at stabilizing patients' neurological status and prolonging a meaningful quality of life. Current treatment regimens include intrathecal delivery of chemotherapy with or without the addition of fractionated radiation therapy. Most patients with NM, due to the extent of their disease and poor prognosis, are generally excluded from most clinical trials and investigational treatment options are limited to case reports and small case series. However, several current preclinical and clinical investigations are underway to examine the safety and efficacy of several promising new intrathecal agents.

INTRODUCTION

Neoplastic meningitis (NM), also known as leptomeningeal carcinomatosis, is a complication of late stage malignancy, and is due to tumor infiltration of the leptomeninges and is found at autopsy in 5% of all cancer patients. First described by Eberth in 1870 and named "
meningitis carcinomatosa by Seifert in 1902, NM was thought to be a rare diagnosis, limited to several cases reported in the literature and diagnosed primarily on autopsy. However, the incidence of neoplastic meningitis is on the rise as the emergence of novel immunotherapeutic agents and continuous progress in modern cancer therapies increase overall survival rates of cancer patients [1]. New immunotherapeutic agents tend to have poor blood brain penetrance at doses used for the management of systemic malignancies, and though efficacious in the management of underlying malignancies, the longer survival times coupled with poor blood brain barrier penetrance creates a favorable environment for tumor cells to grow within the CNS and leptomeninges.

NM is found in 4-15% of solid tumors and in up to 20% of hematologic malignancies [1,2]. The most common primary malignancies are carcinomas of the breast, melanoma, leukemia and lymphoma [1, 6-10]. The clinical incidence of NM from particular tumors is 10-15% in small cell lung cancer, 5-15% in acute nonlymphocytic leukemia, 6% in Non-Hodgkin's lymphoma, 5% in breast cancer, 1% in head and neck cancer [9-16].

Diagnosis requires a high degree of clinical suspicion and is confirmed by the presence of leptomeningeal contrast enhancement on magnetic resonance imaging as well as confirmatory CSF cytology [3]. Imaging may also reveal the presence of ventriculomegaly due to inflammatory changes inhibiting normal CSF circulation, resulting in a communicating hydrocephalus [2,3].

Treatment is mainly palliative, primarily aimed at stabilizing patients neurological status and prolonging a meaningful quality of life. Current treatment regimens include intrathecal delivery of chemotherapy with or without the addition of fractionated radiation therapy [3]. Neurosurgeons may be consulted for neoplastic meningitis management, which may include placement of a ventricular-access device (for intrathecal chemotherapy) or a shunt for CSF diversion, because many patients have increased intracranial pressure due to communicating or obstructive hydrocephalus. When a shunt is placed, a programmable valve will allow for the intrathecal administration of chemotherapy by increasing pressure for several hours, and thus stop the flow, after infusion. Neurosurgeons should attempt to avoid iatrogenic neoplastic meningitis due to the spillage of tumor cells during brain and spinal cord tumor piecemeal resections. Radiotherapy is reserved for patients with bulky disease and as an adjunct to improve CSF flow abnormalities and help with the distribution of chemotherapeutic agents. Regional chemotherapy may include

methotrexate, but systemic myeloablative chemotherapy with or without stem cell transplantation or targeted agents (BRAF inhibitors) may also be utilized.

PATHOPHYSIOLOGY

Studies show that cancer cells in the CSF upregulate the production of complement component C3 resulting in a disruption of the blood brain barrier, allowing for entry of plasma growth factors into the CSF, which in turn promote the growth of cancerous cells [1]. The possible pathways by which tumor cells infiltrate the leptomeninges have been described throughout the literature—tumor infiltration can occur as a result of direct extension from tumors of the brain/spinal cord parenchyma, dura or bone or secondly, via hematogenous spread through the venous plexi and/or along perineural or perivascular structures within the central nervous system, or via hematogenous invasion of the subarachnoid space and ventricles [1,4,5].

CLINICAL PRESENTATION

Neoplastic meningitis generally presents late in the course of advanced stages of malignancies and is rarely seen as an initial presentation in newly diagnosed malignancies. Patients with leptomeningeal involvement, present with relatively acute onset of symptoms arising over days to weeks. Clinical signs and symptoms vary depending on the area of neuraxial involvement, however the majority of patients present with multifocal neurological symptoms, consistent with the diffuse histopathological pattern of tumor infiltration. Signs and symptoms can be referable to portions of the neuraxis afflicted—cerebral, cranial nerve and/or spinal cord/nerve root involvement. Clarke et al. describes 187 patients with NM, of which 150 patients had a primary solid tumor, and 37 patients with hematologic malignancy. Of the 150 patients with solid tumor, headache was the most common presenting symptom in 39%, followed by nausea and vomiting (25%), lower extremity weakness (21%), cerebellar dysfunction (17%), altered mental status (16%), diplopia (14%), facial weakness (13%) [17,18].

Headache is the most common initial presenting symptom in NM and is seen in 30-50% of patients, and is a sign of cerebral involvement [2,17,19]. The headache may be bifrontal, diffuse or at the base of the skull and radiating into the neck and shoulders. The cause of the headache can either be secondary to elevated intracranial pressures or secondary to meningeal irritation. A thorough history and physical exam can help distinguish the underlying cause of the headaches. Patients with meningeal irritation will generally complain of meningitic symptoms—headaches, photophobia and nuchal rigidity. Whereas nausea, vomiting, dizziness and episodic changes in headache severity associated with positional changes (supine to sitting/standing) are more consistent with elevated ICP's. In such patients, physical exam may reveal papilledema on funduscopic examination. Patients with cerebral involvement may also present with encephalopathy with varying degrees of

mental status alteration. Altered mental status can result from a combination of diffuse cerebral dysfunction, hydrocephalus as well as seizures.

Approximately 25% of patients experience some form of cognitive dysfunction, and about 50% of patients with NM have some form of difficulty with recent memory or concentration on a detailed mental status examination [17,18,19].

Patients may also present with a mild gait apraxia, which is usually multifactorial in cause [19,20, 21]. Patients will present with a broad-based stance and difficulty lifting feet from the floor upon ambulation.

Spinal cord and/or nerve root involvement can result in a broad range of symptoms including back pain, radiculopathy, peripheral limb paresis, bowel and bladder dyfunction, cauda equina syndrome. Spinal symptoms are seen in over 50% of patients with NM. Symptoms can arise from direct invasion of nerve roots, resulting in radicular pain, weakness and/or paresthesias. Patient may also present with signs of meningeal irritation due to invasion of the leptomeninges [19].

DIAGNOSIS

The diagnosis of NM requires one of the following three National Comprehensive Cancer Network criteria: (1) cytologic findings demonstrating tumor cells in the CSF, (2) radiologic findings of NM irrespective of clinical findings, or (3) clinical examination findings consistent with NM and abnormal laboratory findings in the CSF (low glucose level and elevated white blood cell and protein counts) in a patient with a history of cancer [22].

Imaging

The diagnosis of NM requires a high degree of clinical suspicion as well as confirmatory findings on magnetic resonance imaging and CSF cytology analysis. If there is any suspicion of a clinical diagnosis of NM, T1-weighter MR images with paramagnetic contrast is indicated as the first diagnostic test of choice with a reported sensitivity of about 71-88% [23,24,25]. Contrasted computed tomography should only be done in patients with an absolute contraindication to MRI. Though the gold standard for definitive diagnosis of NM is CSF analysis with positive cytology, an MRI should be done prior to performing a lumbar puncture, to avoid intracranial hypotension which can result in pachymeningeal enhancement on MRI and can result in misdiagnosis of NM [19,26,27,28]. Similar to NM, intracranial hypotension can result in an elevated cell count and elevated protein on CSF analysis [29].

Neoplastic meningitis is often diagnosed at the same time as parenchymal CNS disease in 38-83% of cases [19]. However, many times, the patients symptomatology is not well explained solely by the mass lesion, thus prompting further investigation with CSF analysis.

With drastic improvement in current neuroimaging technology and improved visualization of the subarachnoid spaces on

MRI, imaging has become in many cases the initial, and often sole diagnostic modality for the diagnosis of NM [17]. Contrast enhancement on MRI indicates areas of disruption of the Blood-CSF barrier, a hallmark of the pathophysiology of NM.

CSF analysis

CSF studies with cytology is the most definitive diagnostic modality for NM [31,31,32]. If there is any suspicion of intracranial or spinal mass lesions, an MRI should be obtained for confirmation, and if a mass is present, the lumbar puncture should be put off for several days until the patient's ICP's are well controlled on steroid therapy to avoid the possibility of causing a herniation. For most accurate results, it is imperative to obtain a large enough CSF sample with a minimum of 4cc, but preferably 10 cc, available for cytology evaluation [19,33]. The most common findings expected on CSF analysis in patients with NM is an elevated opening pressure, elevated cell count, elevated protein levels, low CSF glucose and positive cytology. However, it is rare to see the full spectrum of expected CSF abnormalities and thus, a detailed comprehensive cytological evaluation is imperative [34]. Though uncommon, it is possible to have normal CSF studies, particularly in patients with leukemic leptomeningeal disease [34].

An elevated opening pressure (>160mm H20) is found in at least 50% of patients and is secondary to obstruction of the normal CSF absorptive pathways by the leptomeningeal disease. It is not infrequent to see elevated opening pressures in the absence of radiographic evidence of hydrocephalus. However, in a patient with underlying malignancy, one must also take into consideration other causes of elevated ICP's. Intracranial pressure is a function of cerebral venous pressure, which in turn is reflective of systemic venous pressure, thus, other comborbidities seen in malignancies such as compression of the SVC or jugular vein by tumor or development of congestive heart failure can result in elevated cerebral pressure as well. Patient's with underlying lung cancer can develop elevated ICP in the setting of respiratory failure, due to the exponential elevation of ICP with rising PCO2 [19].

More than 50% of patients with NM will exhibit elevated WBC cell count on CSF analysis with a predominantly lymphocytic pleocytosis. Eosinophilia has been reported in a number of patients with NM from Hodgkin disease, lymphoma and in one case of epithelial tumor [35,36,37].

Total CSF protein levels are usually elevated as well (>50mg/dL) secondary to passage of serum protein across a disrupted blood-CSF barrier, as well as break down product of lysed tumor cells and inflammatory mediators and leukocytes [19].

Glantz et al. conducted a study of 532 patients with leptomeningeal metastatic disease who underwent lumbar puncture for CSF cytology and identified positive cytology in 71, 86, 90 and 98% respectively after 1, 2, 3 or ore samples per patient [33]. The first sample may show positive malignant cells in only 50-70% of patients,

thus if clinical suspicion is high, at least one additional CSF samples should be obtained. False negative cytological studies do occur and are more likely in patients with more sparse leptomeningeal infiltration by tumor cells or in cases where tumor cells are tightly adherent and do not exfoliate into the CSF [31].

Differential Diagnosis

When considering a patient with NM, one must consider a broad range of other possible diagnoses and causes of subacute meningitis in their differential including neoplastic, infectious and autoimmune conditions affecting the leptomeninges and neural structures. In fact, metastatic disease in CNS compartments adjacent to the meninges, such as the skull base and dura, can elicit symptoms similar to NM, and therefore patients should be further evaluated for such potential etiologies. One must also consider imaging artifact such as differentiating between normal vascular markings versus true leptomeningeal enhancement. Neurosarcoidosis, infectious meningitis, Guillan Barre Syndrome can present with very similar patterns of linear leptomeningeal enhancement, thus, in a patient without any history of underlying malignancy, a broad spectrum of differential diagnoses must be considered [2,19,38].

In patients who are immunocompromised by their underlying disease or therapy, opportunistic infections must always be ruled out. Fungal meningitis, such as that resulting from *Cryptococcus neoformans*, is the most common cause of subacute infectious meningitis in the immunosuppressed patient. Patients generally present with mild or no signs of meningeal irritation and with signs and symptoms of a subacute meningoencephalitis. Low-grade fever generally is seen in only 30-50% of patients, and patients typically present with headaches, lethargy, personality changes and memory loss over several weeks. Diagnosis can be challenging due to the subacute nature of nonspecific symptoms, and Cryptococcosis should be considered in any immunocompromised patient with fever, headaches or any signs or symptoms relatable to the nervous system. CSF analysis, similarly to patients with NM, will demonstrate high opening pressures, elevated protein and hypoglycorrhachia. In HIV-negative patients, cell counts will generally be high, however, there will be a mononuclear cell predominance rather than the lymphocytic pleocytosis seen with NM. Definitive diagnosis requires culturing the organism from the CSF; cultures are positive in 90%. Examination of the CSF with India Ink stain demonstrates encapsulated yeast in 75% of HIV patients and only 50% of HIV-negative patients [38].

Neurosyphilis is another cause of meningitis which is intimately linked to immunocompromised patients. An estimated 1.1 million persons in the US at the end of 2015 were living with HIV infections, and approximately 1% of those patients have serological evidence of neurosyphilis. 95% of cases occur in the first year following the primary infection, and symptoms include

malaise, fever, stiff neck and headache, with facial and vestibulocochlear nerve involvement being common. Diagnosis is determined by positive Fluorescent Treponemal Antibody (FTA) blood testing and reactive CSF-VDRL, though CSF-VDRL may be negative in patients with neurosyphilis and AIDS. [19,38]

Tuberculous meningitis is yet another infectious etiology of meningitis in the immunocompromised, and typically results from seeding of mycobacteria into the subarachnoid space from an old tuberculous focus. Tuberculous meningitis is often the only active manifestation of the disease in adults, while it is often indicative of active progressive disease in pediatric patients. Prodromal symptoms typically last 2-3 weeks, and include apathy, anorexia, malaise, and intermittent headaches. Moreover, CSF analysis may yield similar results to NM, and so definitive diagnosis requires PCR, Ziehl-Neelson staining, or culture on Lowenstein medium.

There are a number of other infectious etiologies that can result in a chronic meningitis picture mimicking the presentation of leptomeningeal metastatic disease, even in the immunocompetent patient. Bacteria that can cause chronic meningitis include: *Listeria monocytogenes*, *Rickettsia rickettsii*, *Trophyrema whippelii*, *Actinomyces spp., Brucella spp, Ehrlichia spp, and Nocardia spp.* Listeriosis and brucellosis should be suspected in a patient with a history of exposure to unpasteurized milk products or contact with farm animals. CSF analysis in brucellosis typically shows low glucose levels in nearly half of cases, and other findings can be strikingly similar to those of tuberculous meningitis. Diagnosis is typically confirmed with blood and CSF cultures, serology, and PCR [38].

Borrelia burgdorferi is a spirochete that is transmitted by the *Ixodes* tick, and is the cause of Lyme disease. Meningitis is the most common neurological manifestation of Lyme disease, with presentation typically occurring weeks to months after the initial dermatological manifestation of erythema migrans. Approximately 15% of patients who have untreated primary disease will progress neurological involvement. CSF analysis typically shows an elevation of mononuclear cells, with normal glucose and a mild elevation of protein with frequent oligoclonal bands, however Oligoclonal bands can also be seen in patients with multiple sclerosis. Diagnosis of neuroborreliosis is via IgM and IgG antibodies detected by ELISA.

Intracranial hypotension, such as post lumbar puncture, can result in pachymeningeal enhancement which can be misinterpreted as leptomeningeal enhancement. Pachymeningeal enhancement generally appears as thickened linear or nodular enhancement along the undersurface of the calvarium, falx and tentorium [39,40]). Leptomeningeal enhancement on the other hand tends to follow the convolutions of the gyri and is most commonly present in the basal cisterns, within the cerebellar folia and/or linear or nodular enhancements along the nerve roots of the cauda equina [23,24].

Systemic causes of meningitis include sarcoidosis, Behcet's disease, SLE, among others. Although CNS-sarcoidosis is preceded or combined with systemic lesions in 25-70% of cases, isolated neurosarcoidosis does exist. Granulomatous lesions frequently involve the cranial nerves, optic chiasma, and hypothalamus. CSF findings include a modestly decreased glucose, moderate increase of lymphocytic cells, and increased protein with occasional oligoclonal fractionation of IgG. Cerebral lupus occurs in 25-50% of patients with SLE, though the incidence of chronic meningitis is only 1%. CSF is characterized by lymphocytosis, and oligoclonal fractionation in 50% of patients. Glucose is typically normal, as a decreased glucose is more indicative of transverse myelitis [2,19,38].

TREATMENT

There is a limited role for neurosurgical intervention in the management of NM and the mainstay of treatment remains nonsurgical. However, a neurosurgical consultation is often required for consideration of Ommaya reservoir placement for intrathecal drug delivery as well as possible palliative CSF diversion procedures. Chemotherapy and radiation remain the mainstay treatment options in NM. Treatment is guided by underlying malignancy and the extent of systemic disease, patient age, history of prior CNS therapy, and the presence or absence of abnormal CSF flow. Treatment is primarily palliative rather than curative, as NM is generally a late complication of advanced systemic disease and survival after diagnosis is generally under 6 months. However, in patient with lymphomas, leukemias or breast cancer, prognosis tends to be more favorable. However, the main limitation in the treatment of NM is the necessity to target the entire neuraxis which in turn can carry with it a high morbidity [41,42].

Due to its diffuse nature, the treatment of NM must be directed at the entire neuraxis. Corticosteroids may provide temporary symptomatic relief in patients with mass lesions and resultant edema resulting in elevated intracranial pressures. Chemotherapy can help reduce symptoms, especially if started early and if pain is the predominant complaint. However, early diagnosis and intervention are imperative. Once neurological deficits arise, treatment has limited role in reversing neurological dysfunction.

Systemic chemotherapy often fails due to poor penetrance of chemotherapeutic agents across the blood brain barrier. To circumvent the limitations imposed by the blood brain barrier on drug penetrance, two options exist—administration of high doses systemic administration of the desired chemotherapeutic agent to achieve cytotoxic levels within the CSF, or via direct infusion of agents into the intrathecal space via lumbar puncture or Ommaya reservoir. The benefit of high dose systemic drug administration is that it allows for a more uniform distribution of the drug throughout the entire CSF, longer maintenance times of desired drug concentration with prolonged

infusions as well as better penetration of the drug into deep perivascular spaces [42]. However, the use of high-doses of chemotherapeutic agents is limited by systemic drug toxicity. Thus, to overcome the risk of drug toxicities, direct intrathecal infusion via an Ommaya reservoir is another option. Due to the small volume of distribution and low clearance of drugs from the CSF, the desired cytotoxic doses can be attained with a fraction of the systemic dosage, thus minimizing the risk of systemic drug toxicities. The antimetabolites methotrexate and cytarabine, either alone or in combination with hydrocortisone (triple intrathecal chemotherapy), are the most commonly used agents for intrathecal administration. However, due to the need for neurosurgical intervention for the placement of a ventricular access device, intrathecal drug therapy is generally reserved for more overt cases of leptomeningeal disease [19,42].

Most patients with NM, due to the extent of their disease and poor prognosis, are generally excluded from most clinical trials and investigational treatment options are limited to case reports and small case series. However, several current preclinical and clinical investigations are underway to examine the safety and efficacy of several promising new intrathecal agents.

Dabrafenib has demonstrated intracranial antitumor activity in patients with BRAF V600E or V600K-mutant melanoma brain metastases [43]. Intrathecal trastuzumab has been shown is several studies to be safe and effective for patients with ERBB2-positive breast cancer NM, delaying the need for WBRT.

Some targeted immunotherapy agents have been studied in some prospective trials, including Ipilimumab, an anti-CTLA-4 monoclonal antibody, in treating melanoma-associated NM. However, there is still very limited data available to support the use of monoclonal antibodies in the treatment of patients with NM [42,43].

Radiotherapy has been shown to be beneficial in both treatment and prevention of highly radiosensitive tumors such as leptomeningeal leukemia and lymphoma. Whole brain radiotherapy has been utilized in some cases to prevent the progression to leptomeningeal leukemia in patients with high risk of CNS relapse [44]. However, for tumors that are relatively insensitive to radiation, such as NSCLS, radiotherapy is generally reserved for targeted treatment of symptomatic or bulky disease. In patients with predominantly cranial neuropathies, low dose fractionated radiotherapy targeted at the skull base can be utilized. However, whole brain radiation carries with it high morbidity, and is associated with significant risk for cognitive impairment and encephalopathy in a delayed fashion. Patients who receive craniospinal irradiation are also at risk of bone marrow suppression and acute GI toxicities [41,42]. Thus, due to the high rate of complications associated with radiotherapy, other treatment options should be explored.

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