Clinician awareness of neoplastic meningitis is important so that the disease is recognized and treated in a timely manner.

Clinical Presentation, Diagnosis, and Radiological Findings of Neoplastic Meningitis

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Background: Neoplastic meningitis is a complication of solid and hematological malignancies. It consists of the spread of malignant cells to the leptomeninges and subarachnoid space and their dissemination within the cerebrospinal fluid.

Methods: A literature review was conducted to summarize the clinical presentation, differential diagnosis, laboratory values, and imaging findings of neoplastic meningitis.

Results: Neoplastic meningitis is an event in the course of cancer with a variable clinical presentation and a wide differential diagnosis. In general, characteristic findings on gadolinium-enhanced magnetic resonance imaging and the presence of malignant cells in the cerebrospinal fluid remain the cornerstones of diagnosis. However, both modalities do not always confirm the diagnosis of neoplastic meningitis despite a typical clinical picture.

Conclusions: Clinicians treating patients with cancer should be aware of the possibility of neoplastic meningitis, especially when multilevel neurological symptoms are present. Neoplastic meningitis can be an elusive diagnosis, so clinician awareness is important so that this malignant manifestation is recognized in a timely manner.

Introduction

Neoplastic meningitis is a rare, late, and frequently terminal event in the course of malignancy. It occurs in 4% to 15% of solid tumors and up to 20% of lymphomas and leukemias, and it is associated with significant morbidity and short survival rates (range, several weeks to 8 months).1,2

Neoplastic meningitis is characterized by the diffuse involvement of the leptomeninges (pia and arachnoid), the subarachnoid space, and the cerebrospinal fluid (CSF) by malignant cells, and it occurs through the hematogenous invasion of the subarachnoid space and ventricles or through direct extension from bone and brain lesions, or, in some cases, with local spread through the dura along perineural and perivascular spaces.3 The most frequent primary solid tumors associated with neoplastic meningitis are breast cancer, non–small-cell lung cancer, and malignant melanoma.4 Neoplastic meningitis is typically a late event (70%) and is rarely (15%) a presenting finding in an undiagnosed malignancy.5 However, neoplastic meningitis is expected to occur more frequently in the future because longer cancer survival times allow tumor cells...
the time needed to penetrate so-called central nervous system (CNS) sanctuary sites. Molecular therapeutic agents, particularly monoclonal antibodies, generally do not penetrate the CNS, and their use could lead to increasing rates of neoplastic meningitis in patients receiving such agents. Use of improved neuroimaging techniques might also increase the diagnostic rate of neoplastic meningitis.

A diagnosis of neoplastic meningitis is generally suggestive of advanced disease, and the overall prognosis is affected by controlling leptomeningeal disease. However the prognosis, choice of therapy and patient outcomes depend on the state and extent of the systemic disease. Furthermore, a patient's general performance status is a core determinant of outcome, possibly because this value reflects the entire stage of the disease and its severity.

The dissemination of leptomeningeal cancer is a metastatic complication whose impact in clinical oncology is growing. Treatment advances have been hampered by difficulties in diagnosis and response assessment, as well as possible frustration from clinicians because of the poor prognosis of the disease, even with aggressive treatment. However, advances in therapeutic management have been achieved. In select patients, survival and time to neurological progression can be improved with therapy, making early diagnosis and a high index of suspicion very important.

**Clinical Presentation**

**Pathogenesis of Symptoms**

Neoplastic meningitis has a variable clinical presentation with multifocal and multilevel CNS involvement caused by multiple pathophysiological mechanisms, including the mass effect of tumor presence in the subarachnoid space, direct invasion of the leptomeninges and brain parenchyma, CSF circulation obstruction leading to increased intracranial pressure, and cranial or spinal nerve root impingement.

The types of symptoms in neoplastic meningitis arise because of involvement of the different anatomical areas and may, at times, depend on the type of primary cancer. A normal reduction of CSF circulation and the effect of gravity may be why CSF obstruction is seen in the lumbar region and may explain why gross tumor involvement is typically present at the base of the brain (basilar cisterns or posterior fossa), the Sylvian fissures, and the cauda equina. Tumor cells can also reach the leptomeninges through the blood or by invasion into the perineural or perivascular spaces and vascular alterations due to tumor growth. Parenchymal metastases may be present, but neurological symptoms that cannot be attributed to a single area of the CNS may be the result of neoplastic meningitis; thus, the clinician must have a high index of suspicion.

Patients with neoplastic meningitis subacutely present with symptoms that can emerge over days or weeks and can include multifocal neurological impairment, meningismus with headache, vomiting, and nuchal rigidity. These symptoms may be difficult to attribute to neoplastic meningitis because they are nonspecific. Signs and symptoms of neoplastic meningitis can be categorized according to where the disease manifests within the 3 anatomical areas of the CNS: cerebrum (15%), cranial nerve/brainstem (35%), and spinal cord (60%).

A retrospective study of 187 patients found that 34% of study patients had signs in 1 anatomical area, 39% in 2 anatomical areas, and 25% in all 3 anatomical areas. Two percent of those study patients had no clinical features, although other researchers have shown that an even higher percentage of patients are asymptomatic.

In all anatomical areas combined, the most common symptoms are headache, nausea, vomiting, paresis, paralysis, confusion, diplopia, cerebellar dysfunction, and back pain (Table 1).

### Cerebral Symptoms

Cerebral symptoms include headache, dizziness/vertigo, confusion, fatigue, gait instability, aphasia, ataxia, and falls. Such symptoms are attributed to high intracranial pressure and may be associated with papilledema. Headaches are often described as worse when awakening or lying down and can interfere with sleep. Other patients present with seizure and altered mental status, seizure (although rare), hemiparesis, and numbness. Of these, headache is the most common among all 3 anatomical areas of the CNS. These symptoms are attributed to high intracranial pressure and may be associated with papilledema.

### Cranial Nerve and Brainstem Symptoms

Cranial nerve and brainstem symptoms include visual disturbances (eg, loss of visual acuity, diplopia), facial muscle weakness, hearing loss, nausea and vomiting, dysphagia and dysarthria, hoarseness, decreased hearing, and facial pain or numbness. A related symptom encountered in breast cancer is that of a “numb” or “frozen chin” (ie, presence of hypesthesia in the chin). Visual loss and ocular mobility deficits with diplopia are the most frequently occurring ocular symptoms.

Cerebellar involvement can cause an unsteady gait, diplopia, ataxia, and falls. Such symptoms are present in 65% of patients; nausea, vomiting, and diplopia are the most frequent symptoms.
Spinal Cord Symptoms

Spinal nerve root involvement may cause lumbar pain, limb paresis or paralysis, bowel and bladder dysfunction, and loss of reflexes that may lead to cauda equina or cauda medullaris syndrome.8,14,15 Paresis or paralysis was the initial finding in 41% of patients presenting with neoplastic meningitis secondary to breast cancer and is a commonly seen symptom.8,14,16 At our clinic, 1 patient presented with painful, unprovoked muscle spasms who, after investigation, was diagnosed with neoplastic meningitis.

Physical Examination

Findings on physical examination may reflect the multi-level CNS involvement and typically consist of neurological signs. Neurological examination may show visual loss or ocular motor nerve palsies, with abducens nerve being the most commonly affected followed by oculo-motor and trochlear nerves.5

Oculomotor nerve palsy causes diplopia accompanied with ptosis and mydriasis, whereas the patient with trochlear palsy diplopia may notice it when descending stairs; abducens palsy causes horizontal diplopia. Facial and trigeminal palsy may cause facial weakness and hypesthesia, and vestibular and cochlear nerve involvement may cause hearing impairment, vertigo, and instability. Lower cranial nerve (IX, X, XI, XII) palsies lead to impaired speech and swallowing.

Findings on neurological examination may also reveal weakness in the extremities, hypesthesia, deficits of higher mental functions with altered mental status (confusion, lethargy, personality changes), gait instability, ataxia and dysmetria in cerebellar tests, and asymmetry in tendon reflexes. Funduscopy may or may not reveal papilledema. Nuchal rigidity and the presence of the Lhermitte sign — although considered to be typical signs — are not common.

Patient performance status is important in the setting of neoplastic meningitis. In a study of leptomeningeal metastases from breast cancer and a study of neoplastic meningitis due to several different primary tumors, researchers found that the median Karnofsky performance status was approximately 70%.8,16

Differential Diagnosis

The clinical presentation of neoplastic meningitis can be mimicked by a variety of conditions. The differential diagnosis of patients with symptoms suggestive of neoplastic meningitis is less laborious in patients with a diagnosed malignancy than in those without a diagnosis of cancer because a wide range of infectious and noninfectious causes of meningitis-like symptoms will need to be vetted.

In patients with cancer, metastatic disease in compartments of the CNS adjacent to the meninges may provoke clinical features similar to those seen in neoplastic meningitis. The bone structures surrounding the CNS, with special attention paid to the base of skull
as well as the dura and brain parenchyma, must be evaluated for metastatic disease that may or may not coexist with neoplastic meningitis.21

Paraneoplastic syndromes are a group of disorders that can present in patients with cancer; many of these syndromes have symptoms resembling neoplastic meningitis. Cerebellar degeneration, sensory neuropathy, limbic encephalitis, myasthenia gravis, and Eaton-Lambert myasthenic syndrome are the most common paraneoplastic neurological syndromes, and their manifestation can precede a cancer diagnosis by years.22

A list of infectious agents should be included in the differential diagnosis of meningitis, with special interest paid to those causing more chronic forms of meningitis. This is because acute infections are generally less difficult to rule out based on their typical clinical and laboratory findings. However, the clinician must keep in mind that patients with leptomeningeal disease can also have acute infectious meningitis.

Bacteria that can cause chronic meningitis include *Listeria monocytogenes*, *Rickettsia rickettsii*, *Tropheryma whippelii*, and species of Actinomyces, *Brucella*, *Ehrlichia*, and *Nocardia*. Tuberculosis and spirochetal infections due to *Borrelia burgdorferi*, *Treponema pallidum*, and *Leptospira* species are also included in the differential diagnosis of chronic meningitis, as are many viral infections (HIV, cytomegalovirus, Epstein-Barr virus, human T-cell lymphotropic virus types 1 and 2, herpes simplex virus [HSV; typically type 2 because type 1 causes encephalitis], varicella zoster virus, *Enterovirus*, paramyxovirus, West Nile virus, St Louis encephalitis virus, and lymphocytic choriomeningitis virus).23 Fungal infections should be acknowledged in the differential diagnosis and include the fungi *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Coccidioides immitis*, as well as parasitic infections with *Taenia solium*, *Angiostrongylus cantonensis*, *Toxoplasma gondii*, and *Acanthamoeba* species.24

Viral encephalitis or partially treated bacterial meningitis may have persistent symptoms that may be misleading. Recurrent meningeval inflammation (usually related to HSV type 2 infection) has also been described as Mollaret meningitis, with more than 3 episodes of fever and meningismus lasting less than 1 week and spontaneously resolving.24 Noninfectious, recurrent meningeval irritation may be related to an epidermoid cyst or other intracranial cystic abnormalities, because they can lead to the intermittent leakage of irritating squamous material into the CSF.25

Infection of structures adjacent to the meninges, such as an epidural or subdural abscess, sinusitis, or otitis, should be ruled out. Occasionally, systemic infections may have CNS complications such as brain microabscesses in bacterial endocarditis.

Autoimmune diseases are important to the differential diagnosis of neoplastic meningitis. Sarcoidosis, systemic lupus erythematosus, granulomatosis with polyangitis, Behçet disease, CNS vasculitis, and Vogt-Koyanagi-Harada syndrome can all present similarly to neoplastic meningitis.26 The same is true for multiple sclerosis, Creutzfeldt-Jakob disease, and other neurodegenerative diseases with a protracted clinical course.27

Drug-induced meningitis is another entity to rule out in the differential diagnosis. Symptoms and signs of aseptic meningitis can be induced by a number of medications, including nonsteroidal anti-inflammatory drugs, certain antibiotics (eg, trimethoprim/sulfamethoxazole), intravenous immunoglobulin, cetuximab, and antiepileptic drugs.28-31 In addition to drug-related symptoms and findings that mimic neoplastic meningitis, a neoplastic meningitis–like presentation can occur as a complication of treatment (radiation-induced nerve root dysfunction with thickening).

**Workup**

In patients presenting with symptoms suggestive of neoplastic meningitis, particularly if a diagnosis of cancer has not been established, the clinician must obtain the patient’s medical history. A travel history should also be taken, which could indicate an endemic infection such as coccidiomycosis if the patient has recently traveled to the southwestern United States or Mexico. Animal or arthropod exposure can lead the clinician to suspect conditions such as Lyme disease or lymphocytic choriomeningitis, and a history of unpasteurized dairy product consumption, contact with cattle, or both may point to brucellosis.

Involvement in risky sexual behaviors and intravenous drug use could suggest infection with HSV type 2, HIV, or syphilis, and a history of contact with other individuals with suspect symptoms or conditions (eg, enterovirus infection, tuberculosis) can be helpful for the differential diagnosis. A medication list must also be obtained (eg, nonsteroidal anti-inflammatory drugs, immunoglobulin).

Scrutiny in the review of systems may reveal symptoms indicative of an etiology other than neoplastic meningitis. Patients who are acutely ill with fever are more likely to have bacterial meningitis or a form of aseptic meningitis than neoplastic meningitis, which, in turn, would be expected to have a more insidious presentation. If the non-neurological systemic symptoms present are not related to a known cancer diagnosis, the likelihood of neoplastic meningitis is low. Uveitis, iritis, or both are suggestive of sarcoidosis, Behçet disease, or Vogt-Koyanagi-Harada syndrome (as well as vitiligo and poliosis for the latter). Diabetes insipidus and peripheral facial nerve palsy are also indicative of sarcoidosis. Recurrent genital ulcers related
to Behçet disease and herpetic skin and genital lesions may precede neurological signs in herpetic meningo-encephalitis. Skin rash and purpura are typical skin findings in Neisseria meningitides infection. Enteroviral infection, primary HIV infection, or syphilis may present with a diffuse maculopapular rash. Salivary gland inflammation is seen in mumps, and pharyngeal inflammation in conjunction with sores and encephalopathy are signs of primary HIV infection.

**Laboratory Tests**

CSF cytology is the diagnostic cornerstone of neoplastic meningitis because it has a high rate of specificity. In rare cases, viral infections can cause false-positive results when a patient is evaluated for neoplastic meningitis as a result of a hematological malignancy, but not for solid tumor–related neoplastic meningitis. A negative finding on cytology does not exclude neoplastic meningitis if the clinical presentation and findings on imaging are suggestive of the disease, but it is unusual to have neoplastic meningitis in conjunction with a normal CSF cell count and normal findings on biochemistry.

Pleocytosis in CSF has been observed in many clinical entities resembling neoplastic meningitis. In 1 study, a CSF neutrophilic white blood cell count of 1180 cells/μL, a protein level above 220 mg/dL, and a glucose level below 34 mg/dL were suggestive of bacterial meningitis in the appropriate clinical setting. It is possible that different white blood cell populations could indicate the diagnosis without being a hallmark for it. Fungal infections (eg, nocardiosis, actinomycosis, aspergillosis), autoimmune disease (eg, systemic lupus erythematosus), and chemical or drug-induced meningitis are related to predominantly neutrophilic CSF pleocytosis. In 1 study using flow cytometry immunophenotyping to describe the distribution of the main leukocyte populations in patients with neoplastic meningitis, solid tumor–related neoplastic meningitis showed prominent neutrophilic pleocytosis when compared with lymphoma-associated neoplastic meningitis.

A high CSF lymphocyte count can be seen within 24 hours of enteroviral infection. Eosinophils increase when the following are present: parasitic and bacterial infestations (eg, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Rickettsia rickettsii), hematological malignancies (acute lymphocytic leukemia, Hodgkin lymphoma), subarachnoid hemorrhage, and obstructive hydrocephalus. Mononuclear pleocytosis can be seen in tuberculosis, cryptococcal infections (with a low CSF white blood cell count), and coccidiodymycosis. Traumatic lumbar puncture or subarachnoid bleeding can cause generalized transient seizures and an increase in the white blood cell count.

CSF should be sent for routine Gram stain, which has rates of sensitivity and specificity of 97% and 80%, respectively, for bacterial meningitis; cultures should be obtained for aerobic, anaerobic, and fungal infections; blood cultures and other samples should also be collected as clinically indicated. Additional CSF tests to consider include β-D-glucan for Candida meningitis, mycobacterial cultures with acid-fast bacilli smear, and other tests based on the differential diagnosis (eg, polymerase chain reaction), fungal and parasitic assays (eg, Cryptococcus, Toxoplasma, Taenia), and serology and virus-detection assays.

Biochemistry of the CSF can also be helpful. CSF lactate concentration may differentiate bacterial from viral meningitis better than white blood cell count, glucose level, and protein concentration, although CSF lactate may be elevated in patients with other CNS diseases. The level of protein can be elevated in many infectious and noninfectious diseases as well as in traumatic lumbar puncture and subarachnoid bleeding. Creatinine kinase and lactate dehydrogenase (LDH) CSF levels are also high in pyogenic or tubercular meningitis.

Typically, the presence of xanthochromia is assessed to distinguish a traumatic tap from subarachnoid hemorrhage, but it can also be found in neoplastic meningitis from malignant melanoma.

Oligoclonal bands may suggest multiple sclerosis, although they are also present in other conditions (eg, Lyme disease, autoimmune diseases, brain malignancies, lymphoproliferative diseases). CSF Tau proteins and 14-3-3 protein levels can help in the diagnosis of Creutzfeldt-Jakob disease. Detection of paraneoplastic syndrome–related antibodies in the serum or CSF may help reach a diagnosis. Anti-Yo, anti-Hu, anti-Ri, anti-N-methyl-D-aspartate receptor antibody, anti-Musk, or antibodies against acetylcholine receptors or voltage-gated calcium channels may also be helpful.

The level of CSF glucose is typically low in neoplastic meningitis, similar to other pathological conditions (bacterial meningitis and mycobacterial, mycoplasma and fungal CNS infections, meningoencephalitis due to mumps, infection with enteroviruses, lymphocytic choriomeningitis virus, HSV, or varicella zoster virus, subarachnoid hemorrhage, and neurosarcoidosis).

Although it is not routinely recommended, meningeval biopsy can be performed for diagnostic purposes if findings on both cytology and imaging are negative in a patient with a strongly suggestive clinical syndrome. The findings can be diagnostic, especially if taken from an area of contrast enhancement on magnetic resonance imaging (MRI). Pathology will show macroscopically diffuse, fibrotic thickening of the affected area of the brain and spinal cord as well as layering of the nerve roots with tumor tissue. Microscopic examination shows local fibrosis with tumor cells covering the blood vessels and nerves, either as a single layer or as aggregates.
Imaging in Differential Diagnosis

MRI of the craniospinal axis with paramagnetic contrast is useful in detecting neoplastic meningitis and has a sensitivity rate of up to 88% in solid tumors.10

Findings on MRI do not confer a definitive diagnosis because they are nonspecific. Neurosarcoidosis, chronic meningitis, Guillain-Barre syndrome, and many infectious cases of meningitides can cause the linear leptomeningeal enhancement seen on MRI.49 Bacterial and viral meningeal inflammation tends to appear as linear enhancement, whereas fungal inflammation is generally nodular.50 Primary nerve sheath tumors in the subarachnoid space may also appear as areas of nodular enhancement.50 In addition, lumbar puncture can indicate false-positive meningeal enhancement seen at the level of puncture and at higher levels and can persist for months, so it is important to obtain MRI prior to performing lumbar puncture.51 Dural metastases, intracranial hypotension, granulomas, and meningiomas can appear as pachymeningeal linear or nodular enhancement that can be falsely interpreted as neoplastic meningitis.50

Radiology

Typically, the diagnosis of neoplastic meningitis is based on findings from symptomatology, CSF cytology, and neuroimaging studies (eg, gadolinium-enhanced MRI of the brain and spine). Gadolinium-enhanced MRI is the first study obtained in a patient with a systemic malignancy and neurological symptoms. Frequently, neoplastic meningitis is discovered at the same time as parenchymal CNS disease (38%–83%).52 In many such cases, radiological findings in the brain parenchyma are not explained by the neurological symptoms, thus leading to further investigation with CSF cytology.

Historically, imaging to investigate neoplastic meningitis involved computed tomography (CT) with a myelogram; however, since the advent of MRI — which is more sensitive than CT — CT is only used in patients who have a contraindication to MRI. MRI performed to investigate the CNS for neoplastic meningitis should be multiplanar, obtained before and after the administration of gadolinium 0.1 mmol/kg in at least a 1.5 Tesla scanner (gadolinium-enhanced MRI), preferably with thin cuts in the brainstem, and should include the entire neuraxis. Revealing sequences include contrast-enhanced fluid-attenuation inversion recovery and contrast-enhanced T1-weighted sequences.2

Findings

Not all patients with neoplastic meningitis demonstrate positive findings. In 1 study, 66% of patients with neoplastic meningitis demonstrated findings on MRI.14 Such findings include ependymal, leptomeningeal, and dural enhancement. Observations seen the cranium may include enhancement or thickening of the cranial nerves, small superficial metastases in the sulci, linear enhancement of the leptomeninges of the cerebellum or the basal cisterns, or ventricular dilation consistent with communicating (nonobstructive) hydrocephalus. In the vertebral column, intradural, nodular enhancement — particularly but not exclusively in the cauda equina — is the hallmark of neoplastic meningitis (Fig 1).53 Lumbar or sacral nerve roots may appear thickened and associated intramedullary disease may be present. Irritation of the meninges can lead to meningeal enhancement, so lumbar puncture should be performed following MRI.8 Other false-positive results can occur because of ischemia, infection, inflammation, hemorrhage, irritants, radiotherapy, chemotherapy, granulomas, trauma, or hypoxia (Fig 2). Previous therapy with bevacizumab can affect enhancement.3 Atypical presentation in the form of symmetrical, curvilinear, band-like edema along the surface of the brain stem has also been described.53

Results from a study showed that findings on MRI differ according to clinical presentation.12 Thus, study patients with no neurological symptoms or signs were unlikely to have radiological findings (14%), whereas study patients with cranial nerve (33%), spinal cord

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**Fig 1.** — Positive findings of neoplastic meningitis seen on MRI of the spine of a woman aged 45 years with metastatic melanoma. She had been receiving ipilimumab therapy and had been in remission for 5 years when she presented with headache, diplopia, twitching, and numbness of the face. CSF was positive for neoplastic meningitis. The patient underwent surgery for Ommaya shunt placement. During the operation, the brain was covered with a thick yellow layer of metastatic melanoma cells. Linear, meningeal-enhanced thickening can be seen on T1-weighted, gadolinium-enhanced spinal MRI representing leptomeningeal disease (white arrow). The spinal cord appears to be infiltrated by the disease below that level.

CSF cerebrospinal fluid, MRI = magnetic resonance imaging.
(53%), cerebral (66%), and multilevel abnormalities (83%) were more likely to have findings on MRI.12

MRI tends to be less reliable than cytology because the latter has a high rate of specificity but a low rate of sensitivity. Thus, gadolinium-enhanced MRI is commonly used to support the diagnosis, rather than be used as the sole indicator.14 In 1 study, 31% of patients were diagnosed based on symptomatology and radiological findings when cytology findings were negative.14 The study also suggests that MRI-proven leptomeningeal seeding is an indicator of poor prognosis and could be used to identify response to intrathecal chemotherapy.

A small study of 68 patients with suspected neoplastic meningitis compared the diagnostic ability of gadolinium-enhanced MRI and CSF cytology and found that the overall sensitivity rate of gadolinium-enhanced MRI in neoplastic meningeal disease was significantly lower than that of CSF cytology (45.5% vs 93.2%); however, in neoplastic meningitis from solid tumors, both methods had a sensitivity rate of 84.6%.2 The authors suggest that MRI alone can be used to diagnose neoplastic meningitis in this setting. In leukemia and lymphoma, the rates significantly decreased to 20% and 37.6%, respectively.2 Furthermore, the positive predictive value of MRI in differentiating between infectious and malignant meningitis was highest in lymphoma (83.3%), high in solid tumors (72.7%), but low in leukemia (33.3%).2

Other MRI techniques, such as perfusion, may add to the potential for radiographic diagnosis.54 One group tested the value of magnetic resonance spectroscopy for diagnosing neoplastic meningitis, and they found that magnetic resonance spectroscopy fared better than CSF cytology from the first lumbar puncture in identifying neoplastic meningitis.55,56

**Other Imaging Tests**

CT myelography preceded MRI as the diagnostic imaging technique for neoplastic meningitis. Although CT myelography is not as sensitive as gadolinium-enhanced MRI, it can reveal nerve root thickening, cord enlargement, and CSF flow abnormalities better than MRI.52 In general, it is performed with a water-based, nonionic dye injected via lumbar puncture; however, if a block is suspected, then the injection is administered using a lateral cervical route. These 2 techniques are comparable, and CT can be used as an alternative to MRI when the latter is contraindicated.6

If possible, CSF pathway blockage should be evaluated (present in 31% to 61% of neoplastic meningitis cases) by performing a radionuclide cisternogram.6 Indium-diethylenetriamine penta-acetic acid or macroaggregated albumin may be used to assess the flow of CSF, which is abnormal in 30% to 40% of patients with neoplastic meningitis.6 This nuclear medicine study is performed with a lumbar injection of the radionuclide followed by serial imaging of its flow to rule out a block to the flow of CSF. The results of such a test are important as they may have therapeutic implications because blockage remediation with radiotherapy will allow for a uniform distribution of intra-CSF chemotherapy.57 Although its use is included in clinical practice guidelines, radionuclide cisternogram is not routinely used and other MRI techniques may obviate its need.6

A few isolated case reports have been published in which positron emission tomography (PET)/CT has been useful in the diagnosis of neoplastic meningitis.58-61 Fluorodeoxyglucose, thymidine, or methionine has been used when MRI and cytology failed, but the results of these reports are not enough to establish a role for PET/CT in this setting.58-61

**Response Assessment in Neuro-Oncology**

No method of quantifying neoplastic meningitis has been described, so no systematic method exists to evaluate a radiographic response to therapy. During the course of our research, we have found that many studies do not include repeat MRI after diagnosis. Chamberlain et al52 are developing criteria for the as-
The standard diagnostic test for neoplastic meningitis remains the cytological identification of malignant cells in CSF. MRI appears to be sensitive for detecting metastatic deposits along the neuraxis. However, metastases at a microscopic level are below the resolution available for MRI, which may explain why MRI is less sensitive in detecting neoplastic meningitis than CSF cytology. Malignant cells go undetected in up to one-third of patients who have clinical presentation, findings on laboratory studies, and observations on imaging.

Cytology: The standard diagnostic test for neoplastic meningitis remains the cytological identification of malignant cells in CSF. MRI appears to be sensitive for detecting metastatic deposits along the neuraxis. However, metastases at a microscopic level are below the resolution available for MRI, which may explain why MRI is less sensitive in detecting neoplastic meningitis than CSF cytology. Malignant cells go undetected in up to one-third of patients who have clinical presentation, findings on laboratory studies, and observations on imaging.

Lumbar Puncture

Positive findings on CSF cytology require optimal sampling and processing. Malignant cells can be found in the initial lumbar puncture sample in 50% to 70% of patients and in nearly all cases after 3 attempts. Performing lumbar puncture to obtain CSF can — and likely should — be repeated until findings are positive if the patient has no evidence of obstructive hydrocephalus. In the setting of communicating hydrocephalus, lumbar puncture can be performed and CSF diversion through lumbar puncture or ventriculostomy would be indicated. Contradictions to lumbar puncture include bleeding diathesis, skin infections at the puncture site, and vertebral or other skeletal deformities (scoliosis or kyphosis). The procedure should only be performed by experienced clinicians.

Gadolinium-enhanced MRI of the area of maximal symptomatology should precede lumbar puncture, because the latter may lead to false-positive results on MRIs. Cytology of the CSF obtained by lumbar puncture is more likely to be positive than CSF obtained using a ventricular catheter if spinal cord–related symptoms are present and vice versa if cranial-related symptoms are present. Periodic lumbar puncture is recommended in the follow-up of patients with neoplastic meningitis, even in those with ventricular catheters, because cytology results have high rates of false-negative results when using samples taken from ventricular catheters.

Essential elements of the CSF laboratory evaluation include cell count and differential, cytology, protein, and glucose concentrations (Table 2). In patients who have primary solid tumors, a finding of malignant cells in the CSF is evidence of leptomeningeal metastases. In approximately 50% of patients with leptomeningeal metastases, the CSF opening pressure will be elevated. Similarly, most patients with leptomeningeal metastases have elevated protein levels and increased CSF cell counts. A low CSF glucose level (hypoglycorrhachia) is seen in 30% of patients with leptomeningeal metastases. However, these abnormal CSF findings alone are nonspecific and may be present in various disorders.

Carcinoma cells in the CSF are diagnostic, with the exception of certain false-positive results in patients who have reactive lymphocytes (which are difficult to distinguish from malignant lymphomatous cells) because of an infectious or inflammatory process in the CSF. However, negative findings on cytology do not rule out the diagnosis, because 30% of patients with leptomeningeal disease have a negative cytological result on the first sample obtained via lumbar puncture. This percentage decreases to 15% after 2 high-volume lumbar punctures and then 10% after 3 lumbar punctures.

Cytological findings are more likely to be positive in patients with extensive leptomeningeal involvement than in patients with focal involvement because CSF obtained from a site distant to the lesion is less likely to yield a positive finding on cytology. Other causes of false-negative results can include an inadequate sample (< 10.5 mL CSF) and delayed processing of samples. CSF pleocytosis and modest protein elevations are consistent with but not indicative of the diagnosis, whereas reduced glucose levels usually are seen with neoplastic meningitis (ie, abnormal glucose transport) or infection (ie, increased glucose utilization).

Table 2. — Findings on Examination of the Cerebrospinal Fluid

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<th>Laboratory Study</th>
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<td>Pressure</td>
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<td>White blood count</td>
<td>&gt; 4 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Solid tumors: Most frequently neutrophils, mononuclear cells, or both</td>
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<td>Lymphomas: Mostly lymphocytes</td>
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<td>Protein</td>
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<td>Chromosomal abnormalities</td>
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<td>Solid tumors not useful</td>
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aIndicative of frequently used cut-offs values.
The lymphocyte count is elevated in more than 50% of patients with neoplastic meningitis, and the presence of eosinophils in a patient with clinical evidence of neoplastic meningitis is suspicious for lymphomatous infiltration, although eosinophilia can also herald a number of other conditions that should be entertained in the differential diagnosis.69 Xanthochromia can occur from leptomeningeal bleeding and is seen more frequently in neoplastic meningitis from melanoma.65 Several series have demonstrated that, in some cases, serial CSF sampling via lumbar puncture or sampling from alternate sites (eg, cisternal, ventricular) is required to detect malignant cells.11,67,70,71 LDH concentrations are elevated in cases of stroke, bacterial meningitis, CSF pleocytosis, head injury, primary CNS tumors, and some metastases,84,72 Levels of LDH are also elevated in 80% of neoplastic meningitis; therefore, they can be useful in confirming the diagnosis.72 LDH isoenzyme 5 levels are elevated in neoplastic meningitis from breast or lung primary tumors and melanoma, as well as bacterial meningitis, although they can be normal even when cytological findings are positive.73 Ferritin levels are sensitive to inflammatory changes in the CSF, but they are nonspecific for early neoplastic meningitis, whereas CSF alkaline phosphatase levels may be elevated in neoplastic meningitis due to lung primary tumors.70,74,75

**Tumor Markers and Metabolomics**

Most tumor markers in CSF have poor rates of sensitivity and specificity; however, if they are present, then their levels should decline with successful therapy. Their re-elevation can cause disease relapse before any other findings become apparent. Useful markers include carcinoembryonic antigen in adenocarcinomas, α-fetoprotein and β-human chorionic gonadotropin in germ cell tumors, 5-hydroxyindoleacetic acid in carcinoid tumors, and immunoglobulins in multiple myeloma; their presence in CSF is diagnostic.77,78 Levels of CSF β-2-microglobulin may be useful in detecting neoplastic meningitis caused by hematological spread but not in neoplastic meningitis from solid tumors.79 Levels may also be elevated after treatment with intra-thecal methotrexate.80 Prostate-specific antigen may be elevated in neoplastic meningitis from a prostate primary tumor.81,82

Nonspecific markers can be strong, indirect indicators of neoplastic meningitis, but none are sensitive enough to improve on the cytological diagnosis.5 Epithelial-associated glycoprotein is present in up to 90% of neoplastic meningitis cases.83 Cytokeratins measured by tissue polypeptide antigen and tissue polypeptide-specific antigen have a sensitivity rate of 80% to neoplastic meningitis from breast cancer.84 Neither carcinoembryonic antigen nor β-glucuronidase is helpful in detecting solid tumors or metastases, nor are these values useful in detecting leptomeningeal lymphomatosis. However, if their levels are elevated when neoplastic meningitis is diagnosed, then a return to normal levels of both markers signifies successful treatment.85,86

CSF β-glucuronidase values are frequently elevated, but wide fluctuations make it unreliable as a marker, and elevations can also occur with bacterial, viral, fungal, or tubercular meningitis. However, in association with an elevated LDH level, high CSF β-glucuronidase levels can indicate neoplastic meningitis from a breast primary tumor with high sensitivity and specificity rates. CSF fibronectin and myelin basic protein values can be elevated in neoplastic meningitis, bacterial meningitis, tick-borne encephalitis, multiple sclerosis, trauma, and a number of other conditions.87,88 Epidermal growth factor, vascular endothelial growth factor, and antithrombin 3 have been suggested as useful biomarkers, although antithrombin 3 has been evaluated in primary CNS lymphoma but not neoplastic meningitis.89-91 Other markers such as creatinine kinase BB, tissue polypeptide antigen, and β-2 microglobulin are all indirect indicators of neoplastic meningitis and are still not sensitive enough to improve on findings seen on cytology.91-93

The metabolome of CSF could be of use in detecting neoplastic meningitis. Use of nuclear magnetic resonance spectroscopy based on variation seen in CSF metabolites is encouraging for the early detection of neoplastic meningitis in an animal model and now in humans.55,56 The proteomics in CSF samples of children with acute lymphoblastic leukemia were used to predict CNS clot formation, and mass spectrometry of CSF in the setting of glialoma was associated with glioma grade and prognosis.94,95 However, the diagnostic path of proteomics in CSF must be further explored.

**Flow Cytometry**

Other useful adjuncts to CSF cytology include flow cytometry, measuring of immunophenotype, fluorescence in situ hybridization, chromosomal analysis, and immunohistochemical studies of tumor cells. The underlying diagnostic utility of such studies depends on the underlying systemic malignancy. For example, lymphocytes in the CSF may not be identifiable as malignant by the cytopathologist, but a demonstration of monoclonality (α- or κ-light chain–directed monoclonal antibody analysis), B-cell lineage, or a specific chromosomal abnormality may differentiate leukemic or lymphomatous meningitis from a normal or reactive T-cell population56; however, additional research is necessary. Glial fibrillary acidic protein assessed by immunohistochemistry in CSF may facilitate the identification of malignant glial cells.1,63-65,97

Several studies have demonstrated that the sensitivity of flow cytometry is several-fold higher than that of cytology for detecting CSF leukemia or lym-
Flow cytometry allows for the early detection of neoplastic meningitis before the onset of clinical symptoms and CSF pleocytosis; therefore, its use may enable more effective treatment. Patients with negative findings on cytology but positive findings on flow cytometry are often asymptomatic and have lower CSF cell counts and fewer neoplastic B cells when compared with patients whose cytology findings are positive.\(^\text{103,104}\) Future consensus regarding standardized antibody panels for flow cytometry that uniformly define positivity is likely to advance the early detection of neoplastic meningitis and will help permit its broader clinical applicability.\(^\text{1,63-65}\)

Another group of researchers studied patients with epithelial cell cancers to explore how flow cytometry immunophenotyping contributed to the diagnosis and prognosis of neoplastic meningitis.\(^\text{101}\) CSF samples from patients diagnosed with neoplastic meningitis were studied using flow cytometry immunophenotyping. Expression of EpCAM was used to identify the epithelial cells. The prognostic value of flow cytometry immunophenotyping was evaluated in 72 patients diagnosed with neoplastic meningitis and eligible for therapy.\(^\text{101}\) Compared with cytology, flow cytometry immunophenotyping had greater sensitivity and negative predictive value (80% vs 50% and 69% vs 52%, respectively), but lower specificity and positive predictive value (84% vs 100% and 90% vs 100%, respectively).\(^\text{101}\) The multivariate analysis revealed that the percentage of CSF EpCAM-positive cells predicted an increased risk of death.\(^\text{101}\) A cut-off value of 8% EpCAM-positive cells in the CSF distinguished 2 groups of patients with statistically significant differences in overall survival (\(P = .018\)).\(^\text{101}\) This cut-off value kept its statistical significance regardless of the absolute CSF cell count.

In another study, EpCAM-based flow cytometry showed 100% sensitivity and 100% specificity rates in detecting neoplastic meningitis compared with a sensitivity rate of 61.5% for cytology.\(^\text{102}\) Although this study was limited by a small number of participants (\(n = 29\)), its results suggest that flow cytometry warrants further study for diagnosing neoplastic meningitis.\(^\text{102}\)

However, a caveat to the use of flow cytometry on CSF samples is its low cell number and suboptimal cell environment, meaning that cancer cells degenerate following their in situ removal and even more so when repeatedly centrifuged. Other potentially significant limitations of flow cytometry include a high rate of false-positive results at low cell counts (<25 cells/μL) and an inability to provide differential data (poor differentiation between monocytes and eosinophils and an inability to detect mitoses and neoplastic cells).\(^\text{103,104}\) Thus, the clinical use of flow cytometry for the detection of neoplastic cells in the CSF is limited by variations in the equipment and methods.

The implementation of standardized protocols across clinical laboratories will be necessary before flow cytometry can be routinely implemented in clinical practice over conventional cytology.\(^\text{101}\)

**Fluorescence In Situ Hybridization**

Fluorescence in situ hybridization can potentially aid in the diagnosis of leptomeningeal disease in patients with cancer.\(^\text{105,106}\) It has been used to identify genetic changes in cancer cells from the CSF. For example, cells from 13 of 15 neoplastic meningitis CSF samples in 1 study showed numerical chromosomal abnormalities compared with no chromosomal abnormalities observed in the 10 control samples.\(^\text{107}\) The study was limited by the use of patients who had already been diagnosed with cytology, thus suggesting that fluorescence in situ hybridization was less sensitive than cytology.\(^\text{107}\)

**Circulating Tumor Cells and Tumor DNA in Cerebrospinal Fluid**

An analysis of CSF circulating melanoma cells was performed using immunomagnetic enrichment of cells expressing CD146 to diagnose neoplastic meningitis.\(^\text{108}\) Enumeration of circulating melanoma cells in the CSF was correlated with CSF cytology obtained during the same lumbar puncture and with results on MRI. Among the negative CSF circulating melanoma cells, no study patient had neoplastic meningitis and 3 had brain metastasis.\(^\text{108}\) It is worth mentioning that new technologies to collect CSF circulating cancer cells are being evaluated because they have been shown to perform better than cytology in detecting neoplastic meningitis in patients with lung cancer.\(^\text{109}\)

Lin et al\(^\text{110}\) presented the validation of CSF circulating tumor cells (CTCs) to diagnose neoplastic meningitis from epithelial tumors in patients suspected of having the disease. MRI and CSF analyses were performed using conventional cytology and enumeration of CSF CTCs for all study participants. Samples were considered positive for CSF CTCs when at least 1 CSF CTC was detected in a 3-mL sample (≥0.33 CSF CTCs/mL). The diagnostic performance of CSF CTCs was evaluated, and the gold standard was either a positive finding on CSF cytology or unequivocal findings on MRI. The rates of sensitivity were 95% for CSF CTCs compared with 81% for CSF cytology alone and 62% for MRI alone.\(^\text{110}\) The rate of specificity was 83%.\(^\text{110}\) Thus, this method had superior diagnostic performance when compared with CSF cytology or MRI.

A study of circulating tumor DNA in CSF was also published in patients with leptomeningeal disease.\(^\text{111}\) Detecting tumor-derived, cell-free DNA in the blood of patients with brain tumors is challenging, presumably owing to the blood–brain barrier. The CSF may serve as an alternative “liquid biopsy” of brain tu-
mors by allowing circulating DNA within the CSF to be measured so that tumor-specific mutations can be characterized. Many aspects of the characteristics and detectability of tumor mutations in CSF remain undetermined. Because CSF circulates through the CNS and interfaces with the brain as well as malignant tissues, CSF can potentially carry cell-free DNA and CTCs. Although cytology requires morphologically intact tumor cells for positive findings, cell-free DNA can presumably originate from dying but not CTCs anatomically distant from the site of CSF collection. Some studies have examined the nucleic acids in the CSF of individuals with brain tumors by using methods based on polymerase chain reaction, but the characteristics of CSF tumor cell-free DNA have not been comprehensively investigated using high-throughput sequencing.\(^\text{11,12}\)

Methylation of promoter 2 of \textit{SHPI} in CSF was used as a detector of neoplastic meningitis related to epithelial-derived malignancy with a much higher rate of sensitivity than cytology.\(^\text{13}\)

Conclusions

In many cases, neoplastic meningitis presents with various neurological symptoms that are not always attributable to a single area of the central nervous system. Although the disease must be differentiated from paraneoplastic and infectious syndromes, the diagnosis is not difficult to identify in a patient with advanced malignancy. However, a definitive diagnosis is more elusive, because both radiology and cytology findings of the cerebrospinal fluid may not yield adequate proof of neoplastic meningitis. Persistence on the part of the clinician is required so that the diagnosis can be established and therapy can be initiated. The complexity of establishing the diagnosis cannot be understated, as multiple false-negative results on cytology and imaging may not necessarily exclude neoplastic meningitis. Thus, the diagnosis may depend on clinical judgment and experience.\(^\text{6}\) To help aid in the diagnosis, newer techniques are being investigated to facilitate the diagnostic process.

Acknowledgment: We thank Theodoros Poufos for his help in the editing and formatting of this article.

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January 2017, Vol. 24, No. 1  Cancer Control 19


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