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Leukemia and Lymphoma Metastases

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Central nervous system (CNS) metastases can occur with any primary systemic cancer, but some primary cancers such as melanoma have a specific predilection for the CNS. Brain metastasis is the most common CNS metastasis, occurring in 15% of all cancer patients (Posner, 1995). Leptomeningeal metastasis is less common, 3% to 8%, and epidural metastasis occurs in approximately 5% of cases (Posner, 1995; Byrne and Waxman, 1990). Leukemias and lymphomas do metastasize to the nervous system but rarely involve brain parenchyma and more characteristically involve the leptomeninges. Although epidural metastases do not represent nervous system metastases because they occur outside of the CNS, they typically have a neurologic presentation and for that reason are considered here.

The overwhelming majority of CNS metastases are due to solid tumors rather than to lymphoreticular malignancies. Lymphoma accounts for only 10% of epidural metastases whereas solid tumors account for the remaining 90% (Posner, 1995; Byrne and Waxman, 1990); leukemia rarely causes epidural disease (Bower et al., 1997; Kataoka et al., 1995). In contradistinction, the lymphoreticular malignancies account for a preponderance of patients with leptomeningeal metastases. The overall incidence is difficult to ascertain because leukemias and lymphomas are often excluded from most series, but approximately 24% of patients with leptomeningeal metastasis have non-Hodgkin's lymphoma (NHL) (Olson et al., 1974). Therefore, the pattern of CNS metastases from lymphoma and leukemia is different from that of solid tumors, and the differential diagnosis of these entities is different for patients with lym-

phoreticular malignancies. For example, leptomeningeal metastasis can mimic vincristine peripheral neuropathy, which is common among patients with lymphoma or leukemia. Patients with lymphoreticular malignancies are particularly vulnerable to opportunistic infections, which can mimic metastasis. Finally, isolated CNS metastasis is far more common with lymphoma or leukemia than with solid tumors where CNS disease typically occurs in the setting of widespread systemic metastases.

Systemic therapy of leukemia and lymphoma can be highly effective and can eradicate extra-CNS disease. However, microscopic tumor within the CNS may be protected from circulating systemic chemotherapy by the blood–brain barrier. This disease can progress while the patient is in remission systemically, leading to an isolated CNS relapse. This pattern of recurrence is characteristic of the leukemias and lymphomas, making them different from the solid tumors and warranting special consideration.

EPIDURAL METASTASES

Epidural metastases are seen in 3% to 5% of patients with systemic NHL (Levitt et al., 1980; Mackintosh et al., 1982; Raz et al., 1984). Epidural lymphoma can be the presenting manifestation of disseminated NHL, or can be an isolated site of disease, which accounts for approximately 1% of patients with NHL (Lyons et al., 1992; Gilbert et al., 1978). Epidural tumor occurs primarily in those patients with intermediate- to high-grade subtypes and in those with advanced dis-

ease (i.e., stage III or IV). Occasionally, the development of a complication such as epidural metastasis heralds the transformation of a previously low-grade or indolent neoplasm into a higher grade malignancy or may be the initial manifestation of the illness. The development of epidural metastases tends to occur in those patients with bone metastases, particularly vertebral metastases, and in those who have paraspinal nodal involvement. It has also been associated with retroperitoneal adenopathy and, in some series, with bone marrow infiltration.

Epidural metastasis is a very rare complication of any type of leukemia. It can be seen as a consequence of paraspinal chloroma formation in patients with acute myeloblastic leukemia (AML). It has a presentation, diagnosis, and treatment identical to epidural metastasis from NHL, and the following discussion can be applied to these unusual patients.

Clinical Features

The clinical features of epidural metastasis from lymphoma are not substantially different from those seen in solid tumors and described in Chapter 14. The predominant clinical symptom is back or neck pain (Byrne and Waxman, 1990; Gilbert et al., 1978; Posner, 1987), which is present in 95% of patients with epidural metastasis. Usually the first symptom, it often predates the development of neurologic deficits by months. The pain is typically thoracic, an unusual site of pain due to degenerative disease, because 80% of epidural metastases are in the thoracic spine. Most patients with epidural metastasis from solid tumors present first with back pain, which may develop a radicular component as the disease progresses. This occurs because the metastasis initially originates in the bone, usually the vertebral body, and then grows outside of the bone to involve paraspinal structures and cause nerve root compression.

In contrast, NHL more commonly involves the epidural space by tumor growing from the paravertebral area directly through the intervertebral foramen, causing spinal cord compression. For this reason, there is less back pain from bone destruction. The pain more commonly has a radicular component or may even be referred within the dermatomal distribution of the compressed root, which can lead to misdiagnosis. Radicular pain down a limb or across the trunk may, in fact, be the first indication of an epidural tumor from NHL. Unlike solid tumors, NHL can occasionally metastasize

directly to the epidural space without bone or paravertebral involvement. These lesions may be asymptomatic and initially detected on body CT scans done to completely stage the patient's NHL. If suggested on CT scan, a comprehensive evaluation with magnetic resonance imaging (MRI) (see below) is essential to establish the diagnosis.

In order of frequency pain is followed by leg weakness, which occurs in approximately 50% of patients, and may be accompanied by sensory dysfunction in a comparable proportion. Sphincter dysfunction is seen in about 20% of patients. The back pain of epidural cord compression is characterized by progressive severity as well as increased severity when the patient lies down, in contrast to pain from degenerative spinal disease, which characteristically improves upon recumbency. In addition, pain that intensifies with cough, sneeze, or Valsalva strongly indicates compression of the spinal cord, which is transiently intensified with the increase in intraspinal pressure that occurs with these maneuvers. Sometimes these features can alert the physician that the back pain is due to something more serious than the common, benign causes of back pain.

Diagnosis

The best and only test necessary to establish a diagnosis of epidural metastasis is a spinal MRI (Jordan et al., 1995). This should be done without intravenous contrast material (i.e., gadolinium), which can actually obscure the diagnosis and make it more difficult to see tumor. Magnetic resonance imaging can visualize the entire spine noninvasively and identify epidural tumor at any level (Fig. 15–1). It is particularly useful for patients with lymphoma in whom tumor can enter the epidural space via the intervertebral foramen and not involve or destroy bone. This is a major limitation of plain films and bone scans, which can only identify sites of bony destruction. Even if a bone metastasis is present, these techniques do not indicate whether or not the disease has progressed to involve the epidural space. Furthermore, they can be negative in the face of significant bone involvement with epidural tumor causing spinal cord compression. Any patient with NHL who has significant, progressive back pain should be considered for spinal MRI even in the absence of neurologic deficits.

Another feature of MRI is that it easily images the entire spine. This is essential as multilevel epidural

Figure 15–1. Magnetic resonance image of the spine demonstrating ventral epidural lymphoma extending from T2 to T5. Note the preserved vertebral bodies and absence of bone destruction.

disease occurs in about 5% of patients with an epidural metastasis. Consequently, if MR images are obtained, an epidural metastasis identified, and only a portion of the spinal column visualized, then the patient should return to the scanner to complete imaging of the remainder of the spine.

Some patients are unable to undergo MR imaging because they have a pacemaker or other device that prohibits them from being in a high magnetic field. A computed tomography (CT) myelogram should be performed for such patients. If a complete block is identified with dye introduced into the lumbar space, then a C1–C2 puncture should be performed to introduce dye from above to define the upper limit of the epidural tumor. This is particularly important in NHL in which the disease can grow extensively in the rostral caudal direction once it has reached the epidural space. Accurate identi-

fication of the full extent of tumor is critical for treatment planning.

Initial Management

Many patients with an epidural metastasis are easily identified clinically. They have severe progressive back pain accompanied by neurologic symptoms and signs suggestive of a myelopathy. For such patients, dexamethasone is often administered even before neuroimaging is obtained. Dexamethasone rapidly relieves the pain of spinal cord compression and may facilitate neurologic recovery. Experimental data and substantial but retrospective clinical data suggest a dose–response relationship between corticosteroids and control of back pain associated with epidural tumor (Posner, 1995). The pain can be substantially ameliorated within hours of drug administration, which can facilitate the patient's ability to tolerate any diagnostic procedure, especially an MRI scan. Typically, an intravenous bolus of dexamethasone is administered. Clinical data support the use of a very high initial dose, 100 mg, to rapidly relieve back pain (Loblaw and Laperriere, 1998). With the exception of patients with NHL, for those patients with known cancer, particularly solid tumors, this is a very reasonable approach.

Corticosteroids are a well-recognized, effective chemotherapeutic agent for the treatment of NHL. Because they can cause rapid cell lysis, tumor can disappear very quickly after their administration (Posner et al., 1977). Consequently, it is essential that neuroimages be obtained before the dispensation of any corticosteroids to NHL patients suspected of having epidural tumor. Their pain should be managed with narcotic analgesics to facilitate performing the necessary neuroimaging. Once the MRI scan is complete and an epidural metastasis has been identified, administration of dexamethasone is appropriate.

This approach is very straightforward for patients with known NHL, but it becomes more complicated for patients whose malignancy presents for the first time as an epidural mass. For such patients, MR images are obtained first, and there is usually no consideration given to administering corticosteroids before identification of an epidural mass. Once such a mass is seen on an MRI scan, however, corticosteroids are usually given immediately. If the mass is a lymphoma, one can see rapid resolution of the lesion. If tissue has not yet been obtained for diagno-

sis, the opportunity to confirm the diagnosis pathologically is thus lost, and appropriate treatment is deferred, resulting in a significant delay for the patient. Despite their clinical response to the corticosteroids, patients must be tapered off the drug to allow the disease to declare itself once again so that tissue can be obtained for biopsy. Not only does this delay definitive treatment, but also puts the patient at substantial risk of progressive neurologic compromise from recurrent epidural metastasis. It is essential that these issues be considered before "standard therapy" is administered on a routine basis.

Treatment

Once the diagnosis is established, treatment of epidural metastasis should be implemented as rapidly as possible. Treatment may involve any one of the three major anticancer therapeutic modalities: radiotherapy (RT), surgery, and chemotherapy. The choice of treatment, or combination of therapies, depends on the patient's clinical and neurologic condition, his or her prior treatment for the underlying lymphoma, and any prior therapy for epidural metastasis. Rapid institution of treatment is imperative as a patient's neurologic function can deteriorate precipitously. A general rule of thumb for most patients with spinal cord compression is that if they are ambulatory at diagnosis, they remain ambulatory after treatment, but if they are nonambulatory at diagnosis, they rarely regain the ability to ambulate independently (Posner, 1995).

Radiotherapy

Radiotherapy is the most common and effective modality for the treatment of epidural spinal cord compression (Maranzano et al., 1991; Bilsky et al., 1999). It is easily administered and highly effective, particularly for a radiosensitive primary tumor such as lymphoma. A complete spinal MRI will define the rostral caudal extent of the epidural metastasis. Typically, we administer radiotherapy to a port encompassing the area of tumor plus two vertebral bodies superior and inferior to the tumor margin. The usual course of treatment is 300 cGy for 10 fractions, for a total of 30 Gy. Patients should receive corticosteroids before and during RT to minimize exacerbation of neurologic problems from edema engendered by the treatment, but for select patients steroids are not required during RT (Maranzano et al., 1996).

Radiotherapy is particularly effective for NHL for two reasons: *(1)* Lymphoma is a highly radiosensitive neoplasm so that focal RT can be very effective in relieving a spinal cord compression from epidural metastasis; and *(2)* because lymphoma frequently involves the epidural space by growing through the intervertebral foramen, or metastasizing directly to the epidural compartment, bone destruction is a less prominent feature of epidural metastases from NHL. Epidural spinal cord compression is typically caused by the tumor itself and is a consequence of soft tissue compression rather than bone compression so that RT is more likely to relieve spinal cord compression in this circumstance.

Side effects from RT can include myelosuppression, particularly if the patient is heavily pretreated with chemotherapy or a long expanse of spine must be included in the port of RT. Patients can also develop gastrointestinal irritation from RT to the lower spine or mucositis from cervical RT.

Surgery

Surgery is rarely the first line of treatment for patients with spinal cord compression from lymphoma (Byrne and Waxman, 1990). It is used initially when a tissue diagnosis has not been made. Surgery can establish the diagnosis and also decompress the spinal cord. Even if gross total excision of the disease seems to have been accomplished in such patients, postoperative RT is appropriate to avoid local recurrence and subsequent recompression of the spinal cord.

Surgery may be appropriate for patients who are experiencing spinal cord compression in a previously irradiated location. For those patients who are not candidates for a second course of RT (Schiff et al.,1995), surgery may improve or at least maintain neurologic function (Bilsky et al.,1999; Sioutos et al., 1995; Klekamp and Samii, 1998). The surgical approach depends on the location of the tumor mass. If the tumor has arisen from a vertebral body metastasis and is compressing the cord anteriorly, a vertebrectomy from an anterior approach may be most appropriate. Data suggest that such patients who have severe neurologic impairment may regain sphincter control and leg strength when a complete decompression is achieved by anterior resection. However, disease that has arisen in the paravertebral location or more posteriorly may be more amenable to laminectomy, which would allow for tumor removal

and direct decompression of the spinal cord. Laminectomy for patients with disease located anteriorly probably does not improve neurologic outcome and does not effectively treat the tumor.

Surgery should be reserved for patients in good preoperative condition who have systemic disease that is controlled or controllable and who do not have multilevel epidural tumor (Sioutos et al., 1995; Klekamp and Samii, 1998). Surgical complications include worsening neurologic deficit, wound dehiscence or infection (particularly in those who require sustained doses of corticosteroids), and delayed hardware disruption, which often heralds tumor regrowth.

Chemotherapy

Chemotherapy is rarely the first line of treatment for epidural metastasis. However, it has been shown to be effective for those patients whose epidural tumors were identified during their extent of disease evaluation at initial presentation (Lyons et al., 1992; Oviatt et al., 1982; Wong et al., 1996). These patients typically have an epidural site of disease identified on the initial body CT scan done to evaluate intrathoracic and intra-abdominal disease. Epidural tumor is then confirmed by spinal MRI; however, patients may be asymptomatic or have minimal neurologic symptomatology. These patients usually require combination chemotherapy as an initial treatment for systemic lymphoma. For such patients, chemotherapy can be administered and the epidural disease monitored closely. Typically, the epidural tumor responds in the same fashion as the rest of the systemic disease. For those patients whose epidural disease does not respond, focal RT can be administered.

Although epidural tumor presents with neurologic symptoms and signs referable to the spinal cord, it is important to remember that epidural disease exists outside of the CNS and is not behind the blood–brain barrier. Systemically administered chemotherapy is as effective against disease in this location as in any systemic location. The choice of drugs should be based on the optimal regimen likely to be effective against the systemic lymphoma.

Chemotherapy can also be used for patients whose disease has developed in a previously irradiated site or for whom surgery is not an option or has already failed. However, for such patients who have heavily pretreated disease and for whom prior chemother-

apy has often been administered, the probability of an excellent response from such treatment is substantially less than at initial therapy.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases develop as a complication in 4% to 11% of patients with systemic NHL and in approximately 10% of patients with leukemia (Table 15–1) (Posner, 1995; Olson et al., 1974). In patients with NHL, the incidence is higher among those with high-grade and widespread disease. In leukemia patients, the incidence varies widely with type of leukemia, reaching a peak incidence of 56% at autopsy in those with acute lymphocytic leukemia (ALL). This was particularly true before the availability of prophylactic intrathecal chemotherapy (Price and Johnson, 1973). The development of vigorous systemic and CNS therapies has markedly decreased the incidence of meningeal leukemia in both ALL and acute myelocytic leukemia (AML) (Barcos et al., 1987). Currently, the incidence of CNS relapse is 2.2% in AML and 4.3% in ALL (Castagnola et al., 1997; Stark et al., 2000).

Clinical Features

The hallmark of leptomeningeal metastasis is multifocal involvement of the CNS (Wasserstrom et al., 1982; Balm and Hammack, 1996). The disease primarily involves three main regions of the CNS: cranial nerves, the cerebrum, and spinal compartment (Table 15–2). Patients may present with symptoms and signs involving one or all of these locations and

Table 15–1. Frequency of Leptomeningeal Metastasis

	No. of *Autopsies*	No. of *Metastases* (%)
Leukemia	287	28 (10)
ALL	87	21 (24)
AML	104	5 (5)
Lymphoma	309	15 (4)
Hodgkin's	119	2 (2)
Non-Hodgkin's	190	13 (7)

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia.
Source: Adapted from Posner (1995).

Table 15–2. Symptoms and Signs of Leptomeningeal Metastases in Lymphoma

Radiculopathy	44%
Impaired mental function	42%
Cranial neuropathy	36%
Headaches	23%
Seizures	3%
None (positive CSF cytology only)	11%

Source: Adapted from Recht et al. (1998).

generally have more neurologic signs on examination than symptoms. This discrepancy is often the first clue that meningeal tumor is present.

Common symptoms are facial weakness, facial numbness and diplopia (Posner, 1995; Levitt et al., 1980). Radicular symptoms are most commonly observed in the legs, and numbness or weakness may be bilateral but is often asymmetric. Bowel and bladder disturbances are frequent. Cerebral symptoms are usually due to raised intracranial pressure and communicating hydrocephalus caused by tumor impairing absorption of cerebrospinal fluid (CSF) over the cerebral convexities. Headache and mental status changes are the most common cerebral symptoms. Seizures and ataxia are infrequent, occurring in fewer than 10% of patients. Lateralizing symptoms and signs, including hemiparesis, aphasia, or a visual field deficit, are not seen with leptomeningeal metastasis unless there is an accompanying parenchymal lesion, such as a brain metastasis; or leptomeningeal tumor has caused vascular occlusion leading to a stroke.

Pain is a variable accompaniment to leptomeningeal tumor. The cranial neuropathies are typically painless, except facial pain is reported occasionally. The radicular symptoms and signs may be painless, which is often a clue that the cause is leptomeningeal tumor rather than epidural tumor, which is almost always painful. However, radicular pain can be a prominent symptom of leptomeningeal metastasis and can be difficult to treat. When there is significant radicular, back, or neck pain, epidural tumor is the most important differential diagnostic consideration.

Diagnosis

The diagnosis of leptomeningeal lymphoma or leukemia has usually required the demonstration of tu-

mor cells in the CSF, which are almost always abnormal in the presence of leptomeningeal metastasis. Positive cytology is, however, observed in only 50% of patients with documented leptomeningeal metastasis from solid tumors on the first lumbar puncture (Wasserstrom et al., 1982). Repeated spinal taps are frequently needed to demonstrate the presence of tumor cells, and positive cytology results can be obtained in 90% of patients with three lumbar punctures. However, with NHL leptomeningeal metastasis, the CSF yields a positive cytologic examination in 88% of patients with two lumbar punctures (Recht et al., 1988).

Routine studies of CSF are less helpful in patients with leukemia and NHL than in those with solid tumors (Posner, 1995; Wasserstrom et al., 1982; Recht et al., 1988). Cerebrospinal fluid protein concentration is elevated in approximately 60%, but rarely above 200 mg/dL. The CSF glucose level may be depressed, but only in a minority of patients. The CSF cell count is usually elevated and may be composed of tumor cells and reactive lymphocytes, making a cytologic distinction between the two very difficult in some patients. These abnormalities are seen in many patients with leptomeningeal lymphoma and leukemia, as they are in patients who have this complication from solid tumors. The exception is leptomeningeal leukemia, which can be present in otherwise completely normal CSF (Tubergen et al., 1994; Mahmoud et al., 1993). In particular, the cell count may be normal if patients are pancytopenic from either their disease or its treatment. Therefore, vigilance in the cytologic examination is essential for patients suspected of this process. Sending large volumes of CSF to the cytopathologist with rapid fixation of the specimen can increase the yield. In addition, sampling CSF from a location close to the area of clinical symptoms also improves yield. For example, patients with lumbar radicular symptoms have the highest incidence of positive cytology when CSF samples from a lumbar puncture are used (Rogers et al., 1992). However, those with cerebral symptoms or cranial neuropathies have a higher yield when CSF is obtained from a C1–C2 puncture or a ventricular sample when a ventricular reservoir is already in place.

Cerebrospinal fluid tumor markers can occasionally be helpful in identifying tumors (Schold et al., 1980; Oschmann et al., 1994; DeAngelis, 1998), but because there are no specific tumor markers for leu-

kemia and lymphoma, they are more effective for identifying solid tumors. β_2 Microglobulin is often elevated in CSF in lymphoma and occasionally in leukemia, but is nonspecific and can be elevated in any inflammatory condition associated with a CSF pleocytosis. While this is also true of the nonspecific markers β-glucuronidase and LDH isoenzymes, these markers can nevertheless be useful in some patients (Lossos et al., 2000). Vascular endothelial growth factor has recently been shown to be predictive in patients with leptomeningeal metastasis from solid tumors; it may also prove valuable in hematologic malignancies (Stockhammer et al., 2000). Flow cytometry and molecular markers are helpful if adequate cells are available and the molecular phenotype is known (van Oostenbrugge et al., 1998; Cibas et al., 1987; Rhodes et al., 1996).

Demonstration of tumor cells in the CSF is not the only way to establish a diagnosis of leptomeningeal metastasis. Gadolinium-enhanced MRI of the neuraxis sometimes reveals findings that are so characteristic of leptomeningeal tumor as to be diagnostic (Rodesch et al., 1990; Freilich et al., 1995). Prominent enhancement and enlargement of cranial nerves due to tumor infiltration, nodules adherent to the cauda equina, large subarachnoid masses compressing the spinal cord, and prominent enhancement coating the surface of the brain extending deep into sulci are all definitive neuroradiologic features of tumor in the subarachnoid space in patients known to have cancer (Fig. 15–2). The presence of such findings, even in the absence of a positive CSF cytologic examination, can establish the diagnosis and be sufficient to initiate treatment.

These findings are not manifest in every patient who has leptomeningeal tumor. Normal neuroradiologic studies do not exclude leptomeningeal tumor, which is particularly problematic for patients with leukemia and lymphoma who have a lower incidence of neuroradiologic abnormalities than those with solid tumors. Furthermore, cranial imaging that reveals a pattern of miliary brain metastases with small lesions evident in the sulci of the brain, or superficially on the cortex, may suggest the presence of leptomeningeal tumor. These findings are exceedingly rare in lymphoma and leukemia. All patients suspected of having leptomeningeal tumor, and those in whom tumor has been confirmed on CSF cytologic examination, should undergo complete imaging of the neuraxis with gadolinium to delineate areas of focal or bulky disease, which may require focal RT as part of the treatment plan.

While the diagnosis of leptomeningeal tumor can be extremely difficult to make in any circumstance, the situation is particularly challenging for patients with leukemia and lymphoma. The tendency of these tumors to grow in sheets and not to form nodules makes diagnosis difficult because the incidence of
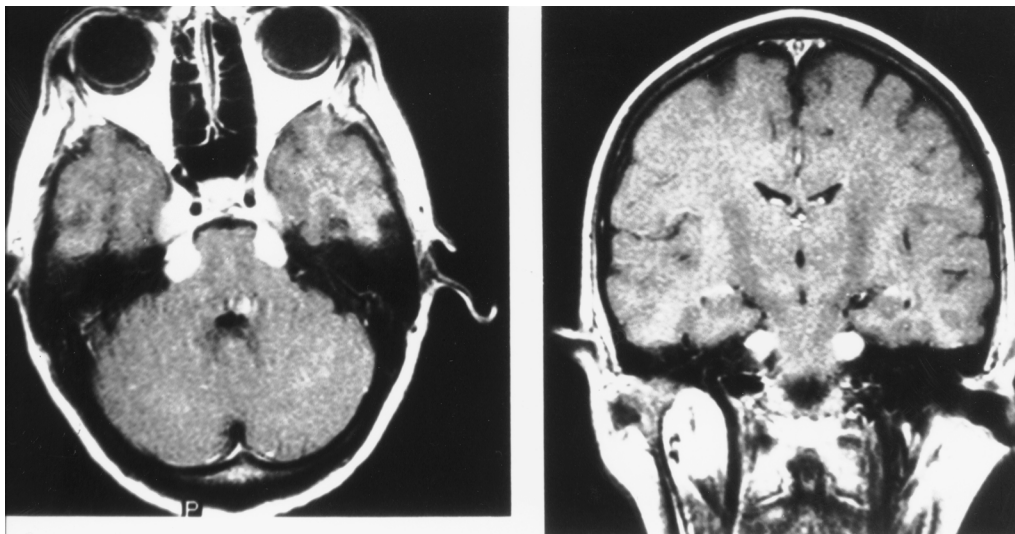
Figure 15–2. Gadolinium-enhanced MRI demonstrating bilateral enhancement and infiltration of the trigeminal nerves by lymphoma.

bulky disease, and, therefore, detectable disease on neuroimaging, is much lower. Furthermore, the incidence of leptomeningeal metastases is higher in these tumor types than in any other, making the need for recognition and aggressive treatment a common concern. Most importantly, vigorous treatment of leptomeningeal metastases in patients with leukemia and lymphoma can lead to prolonged remission and, sometimes, even cure. Consequently, it is imperative to diagnose these tumor types early.

When the diagnosis is not established on CSF analysis or neuroimaging, the clinician may deduce it by process of elimination. Imaging helps to exclude alternatives such as epidural or vertebral bone metastases, brachial or lumbosacral plexopathy, and parenchymal brain pathology. Laboratory work can exclude metabolic causes of lethargy or seizure. The medical history can usually indicate whether cranial neuropathies can be attributed to drugs such as vincristine. When all alternative diagnoses have been excluded and the patient has a characteristic presentation such as cranial neuropathy, some experienced clinicians will treat leukemia or lymphoma patients for leptomeningeal metastasis even in the absence of diagnostic confirmation.

Initial Management

Neurologic metastatic complications frequently lead the physician to initiate corticosteroid treatment immediately. Leptomeningeal metastasis from solid tumors rarely responds to corticosteroids unless the patient has markedly increased intracranial pressure. However, in lymphoma and to a lesser extent leukemia, corticosteroids can provide symptomatic relief, particularly from pain. This is because corticosteroids can function as a chemotherapeutic agent in lymphoma and cause tumor lysis, an important issue when the diagnosis is suspected but not yet confirmed. Premature administration of corticosteroids can give false-negative CSF cytologic examination and neuroimaging results. Corticosteroids should be reserved until the diagnosis has been established, at which time they may provide symptomatic relief. In the absence of clinical improvement, steroids should be rapidly tapered and then discontinued. Unlike brain or epidural metastases, corticosteroids are not required for irradiation of leptomeningeal tumor because there is no focal involvement or compression of the nervous system, inciting significant local edema or mass effect.

Treatment

Therapy should begin immediately after confirmation of the diagnosis of leptomeningeal metastasis. The goals of treatment are not only to prolong life but also to minimize neurologic disability. Rapid institution of therapy can halt the progression of neurologic dysfunction and, if the disease has not been long–standing, can often reverse some neurologic disability. Therapeutic choices include RT, systemic chemotherapy, and intrathecal chemotherapy. Which treatment is selected depends on the location and extent of leptomeningeal involvement as well as the patient's symptoms.

Radiotherapy

Radiotherapy can be a highly effective treatment, frequently causing rapid relief of pain and occasionally reversal of neurologic symptoms (Hanssens et al., 1998). It is usually delivered to focal areas of bulky disease seen on MRI and to symptomatic areas. For example, patients with lumbosacral radiculopathy would receive RT to the cauda equina, whereas those with cranial neuropathies would receive either whole brain or skull base RT. Radiotherapy is usually delivered in 300 cGy fractions for a total of 3000 cGy. Often, its effect can be substantial and durable, but it is not curative (Mackintosh et al., 1982; Hanssens et al., 1998; Gray and Wallner, 1990).

The major limitation of RT is that it is administered focally, leaving large areas of the subarachnoid space untreated. Because the CSF circulates along the neuraxis, tumor cells can be carried by bulk flow from one region to the other. Tumor cells can thus float in and out of the port of RT, never receiving a sufficient dose. Also, large areas of the neuraxis are untreated by focal RT. Neuraxis RT can treat the entire CSF compartment, but craniospinal RT is quite morbid, resulting in esophagitis and enteritis in many patients. In addition, treatment of the entire spinal axis often results in significant myelosuppression, particularly in heavily pretreated patients who previously received substantial chemotherapy. This sequela often causes interruption of treatment and, if severe, can necessitate transfusion or result in neutropenic infection or thrombocytopenic bleeding. Even focal spinal RT can occasionally result in depressed blood counts in some patients, although the condition is usually easily managed.

Intrathecal Chemotherapy

Intrathecal chemotherapy delivers drug into the subarachnoid space to treat the entire CSF compartment. Most systemically administered chemotherapeutic agents do not achieve sufficient concentration in the CSF to treat tumor cells, so drug must be instilled directly into the CSF. This is a safer method of treating the entire CSF than neuraxis RT. However, the number of drugs that can be safely administered directly into the CSF is limited, and the most commonly used agents are methotrexate, cytarabine, and thiotepa. These agents have a relatively narrow antitumor spectrum but can be effective in treating both lymphoma and leukemia. Other agents such as etoposide have been used experimentally with some efficacy but have not been adopted for routine use (van der Gaast et al., 1992; Champagne and Silver, 1992; Berg et al., 1992).

Intrathecal chemotherapy can be administered either by repeated lumbar punctures or by placement of a ventricular catheter with an Ommaya reservoir (Berweiler et al., 1998), which allows easy accessibility to the subarachnoid compartment and results in better disease control (Shapiro et al., 1975; Bleyer and Poplack, 1979). Use of a reservoir has three major advantages over repeated lumbar punctures. Drug delivered into a reservoir has better distribution throughout the CSF than drug introduced into the lumbar space (Shapiro et al., 1975). Even when a lumbar puncture is successful and the CSF is reached, injection of drug via a spinal needle results in instillation of the drug into the epidural space in approximately 10% of patients (Larson et al., 1971). Finally, the reservoir is much easier on the patient, and drug administration is less time consuming for staff.

However, the reservoirs can pose occasional difficulties and complications. They have a low incidence of infection, but, when infected, may require removal to clear infection, which is most commonly due to skin organisms such as coagulase-negative *Staphylococcus* or *Proprionibacterium* species. The reservoirs may become obstructed. If this develops, the reservoir should not be used as the drug may leak out of the reservoir catheter and into the surrounding brain, causing an area of focal encephalomalacia or a sterile abscess that can result in focal neurologic deficits. Patients with raised intracranial pressure are particularly vulnerable to this complication. In addition, patients with hydrocephalus or any impairment of CSF flow should not have a reservoir placed.

Drug is distributed along with the bulk flow of CSF. If there is obstruction to CSF flow, the drug will be trapped in one area of the neuraxis, leaving other regions untreated and causing neurotoxicity where the concentration is high for prolonged periods of time (Glantz et al., 1995; Mason et al., 1998). [111]Indium flow studies can ascertain with a high degree of accuracy whether the CSF flow is normal or not (Chamberlain, 1998). The [111]Indium should be administered by the same route as the drug, either via an Ommaya reservoir or by lumbar puncture. The patient is scanned for distribution of the [111]Indium throughout the neuraxis and for reabsorption over the cerebral convexities. Areas of bulky disease seen on MRI, such as large subarachnoid nodules in the spine, usually impair CSF flow at that level. The flow can occasionally be restored after focal RT has been administered to the area. There is controversy regarding obstructions, so-called physiologic obstruction, seen on [111]Indium studies where neuroimaging is negative (Glantz et al., 1995; Mason et al., 1998; Chamberlain, 1998). Some authors recommend radiating areas of reduced CSF flow; restoration of flow occasionally occurs. Others, however, remain unconvinced that this is a significant phenomenon and are concerned that RT can cause toxicity.

For drugs administered into the CSF, the doses are fixed and should not be calculated on a meter square basis. The volume of CSF is the same in all individuals over the age of 4 years, and it does not fluctuate with body size (Pfefferbaum et al., 1994). Doses of the commonly used agents are indicated in Table 15–3. When delivered into a reservoir, drug should be infused slowly because rapid administration can produce raised intracranial pressure and hypotension. If there is difficulty in removing CSF from the reservoir, placing the patient in the Trendelenburg position may facilitate CSF withdrawal.

When intrathecal methotrexate is used, oral leucovorin should be given for the following 4 days at a dose of 10 mg po b.i.d. This is to protect the gastrointestinal tract and the bone marrow from the chronic low-dose systemic exposure that results from

Table 15–3. Doses of Intrathecal Chemotherapy

Methotrexate	12 mg
Cytarabine	40–60 mg
Thiotepa	10 mg

reabsorption of drug from the subarachnoid space into the bloodstream.

The optimal duration and schedule of intrathecal treatments for leptomeningeal metastasis is unknown. The schedule has been derived largely from empiric information and from what is known about the pharmacokinetics of drug in the CSF (Mackintosh et al., 1982). Methotrexate is the best-studied agent. It rapidly achieves high concentrations after an intrathecal dose and maintains therapeutic concentrations in the CSF for at least 24 hours (Shapiro et al., 1975), which has led to initial treatment on a twice-a-week schedule so that the tumor receives therapeutic concentrations for a substantial period of time. If the patient appears to be responding to intrathecal drug, as assessed by improvement in the CSF and the absence of clinical deterioration, then after several weeks of giving the drug twice a week the frequency is reduced to once a week for an additional 3 to 4 weeks. This is followed by a further reduction to every other week and then a few months of monthly maintenance therapy, which is then discontinued.

An alternative approach is to use the concentration $\times$ time approach where small doses are given daily for 3 to 5 days (Moser et al., 1999), which produces sustained therapeutic concentrations in the CSF with a reduced total dose, possibly diminishing the risk of neurotoxicity. This is a superior approach but can be difficult to administer because of the requirement for daily injections. A new preparation of cytarabine addresses some of these issues. This liposomal preparation can be administered intrathecally once every 2 weeks (Glantz et al., 1999). This method releases drug slowly and can produce therapeutic concentrations of cytarabine in the CSF for more than 1 week in most patients. The consequent need for less frequent administration is an improvement in the patient's quality of life. This preparation may or may not represent a substantial therapeutic advantage over standard cytarabine or methotrexate but that remains to be ascertained.

Systemic Chemotherapy

Most systemic agents do not penetrate sufficiently into the subarachnoid space to treat leptomeningeal metastases. However, agents such as methotrexate and cytarabine when given in high doses can achieve therapeutic concentrations in the CSF (Glantz et al., 1998). This is particularly true when tumor involves the leptomeninges, which enhances drug penetration.

The advantage of delivering chemotherapy systemically is that sufficient drug concentration can be achieved throughout the subarachnoid space because the drug does not have to circulate with the CSF to reach all areas of the subarachnoid compartment. In addition, systemically administered drug can reach and penetrate into nodules of tumor in the subarachnoid space and into neural structures infiltrated by tumor. Intrathecally administered drug can penetrate only 5 mm into the tumor and therefore cannot reach these areas of disease.

Other important agents in the treatment of lymphoma and leukemia such as anthracyclines, vincristine, and cyclophosphamide do not achieve sufficient penetration into the CSF to effectively treat leptomeningeal metastasis. Consequently, the options available for systemic chemotherapy are virtually the same drugs that can be administered directly into the CSF. Nevertheless, data suggest that patients do better when systemic chemotherapy is included in the therapeutic regimen of leptomeningeal metastasis (Siegal et al., 1994; Siegal, 1998).

OUTCOME

The prognosis for most patients with leptomeningeal metastasis is poor, with a median survival of 6 to 8 months for patients with NHL and 10 months for those with AML (Posner, 1995; Castagnola et al., 1997; Recht et al., 1988). It is difficult to control tumor in the CNS, and also, because leptomeningeal metastasis is usually a late complication of either lymphoma or leukemia, the systemic disease is often aggressive and refractory to treatment by the time metastasis is diagnosed, and death is related to progressive systemic tumor in most patients (Recht et al., 1988). Nevertheless, some patients do respond well to treatment and have prolonged survival (Siegal et al., 1994). Furthermore, for patients with isolated CNS relapse, control or remission of CNS disease can result in a sustained second remission so that vigorous treatment is warranted. Aggressive therapy can prevent neurologic dysfunction even if survival is not prolonged, which provides a substantial contribution to a patient's quality of life. Patients who do survive for 1 year or longer are, however, vulnerable to late neurotoxic effects of treatment (Siegal et al., 1994). Primarily restricted to the brain, this is a particular problem for patients who have received whole-brain RT in addition to chemotherapy.

NEUROTOXICITY

Combining cranial irradiation with systemic and/or intrathecal chemotherapy amplifies the potential of each modality to cause neurologic dysfunction. The risk rises with increasing doses of RT, a rising cumulative dose of systemic and/or intrathecal chemotherapy, and older age. The primary manifestation of neurotoxicity is memory impairment, which can progress to a severe dementia in adults or be a static learning deficit in children. Radiographically, a diffuse leukoencephalopathy is seen on MRI with increased signal throughout the periventricular white matter on T_2 or FLAIR images. Atrophy and ventricular dilatation are also common features. Occasionally, some patients may have amelioration of their symptoms with placement of a ventriculoperitoneal shunt, but improvement is usually incomplete and can be temporary. Once neurotoxicity develops, it is a permanent and irreversible condition. Considerable effort has been devoted to the development of efficacious, less toxic regimens for CNS prophylaxis, particularly for childhood ALL. Data show that vigorous systemic chemotherapy combined with extended triple intrathecal chemotherapy can produce control of CNS disease comparable to cranial RT plus drug (Stark et al., 2000). This type of regimen carries less risk of subsequent cognitive impairment.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Clinical Features

Primary CNS lymphomas (PCNSL) represent 3.5% of primary brain tumors (Davis and Preston-Martin, 1999) and are usually large cell or immunoblastic lymphomas. There is a higher incidence of PCNSL in transplant recipients and patients with acquired immunodeficiency syndrome (AIDS), but these tumors are stimulated by latent Epstein-Barr virus infection whereas those in the immunocompetent population are not.

Diagnosis

PCNSL usually occurs in the fifth and sixth decades of life. Neurologic symptoms and signs depend on the site(s) of disease in the brain, but cognitive changes and lateralizing signs are common. PCNSL arises in the basal ganglia, corpus callosum, and periventricular regions. Following gadolinium administration, these tumors show intense and distinctive homogeneous enhancement on MR scans. Because glucocorticoids alone are sufficient to reverse vascular permeability of the tumor and lyse tumor cells, they must be withheld until tissue has been obtained to make a definitive diagnosis. An open or stereotactic biopsy is required to establish the diagnosis of PCNSL, but resection has no therapeutic role in this disease.

Initial Management

Radiation therapy alone is palliative with local control rates of 39% and a median survival of less than 1 year after 60 Gy (Nelson, 1999). Conventional systemic lymphoma drug combinations such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) are ineffective (Mead et al., 2000). At present, high-dose methotrexate (HD-MTX) is the single most active agent for the treatment of PCNSL. HD-MTX combined with cranial irradiation yields a median survival of 60 months (Abrey, 2000), but has been associated with neurotoxicity in a significant proportion of patients, particularly those over the age of 60 at the time of treatment. Almost 100% of such patients develop severe dementia (Abrey, 1998).

Efforts to overcome CNS toxicity from irradiation has led to the use of chemotherapy alone, particularly in older patients. Using an HD-MTX based regimen, patients older than 60 years have the same median survival (32 months) as those treated with the same regimen plus cranial radiotherapy. However, no neurotoxicity was observed in those who only received chemotherapy. Intrathecal chemotherapy has not attained a defined role in PCNSL management as data indicate that treatment with HD-MTX alone produces comparable results in patients with a negative CSF cytologic examination at diagnosis. Those with a positive CSF cytology should receive concurrent intrathecal and systemic chemotherapy. Chemotherapy combined with blood-brain barrier disruption has been another approach; in one study, 74 patients had an estimated median survival of 40.7 months. Of 36 patients with a complete response lasting more than 1 year and available for study, none demonstrated evidence of cognitive loss in neuropsychologic tests and/or clinical examinations (McAllister et al., 2000).

Most neuro-oncologists agree that the optimal treatment for PCNSL has not yet been identified. In a recent review of published clinical trials, Ferreri and

colleagues (Ferreri et al., 2000) found that chemotherapy followed by radiotherapy yielded a 5-year survival of 22%–40% compared with 3%–26% for irradiation only. In their review, HD-MTX was the most effective chemotherapy, producing response rates of 80%–90% and a 2-year survival rate of 60%–65%. To date, the addition of other drugs at conventional doses for treatment has not consistently improved outcome. With a few exceptions, any regimen without HD-MTX performed no better than RT alone.

REFERENCES

Abrey LE, DeAngelis LM, Yahalom J. 1998. Long-term survival in primary CNS lymphoma. J Clin Oncol 16:859–863.

Abrey LE, Yahalom J, DeAngelis LM. 2000. Treatment for primary CNS lymphoma: the next step. J Clin Oncol 18:3144–3150.

Balm M, Hammack J. 1996. Leptomeningeal carcinomatosis. Presenting features and prognostic factors. Arch Neurol 53:626–632.

Barcos M, Lane W, Gomez GA, et al. 1987. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982).Cancer 60:827–837.

Berg SL, Balis FM, Zimm S, et al. 1992. Phase I/II trial and pharmacokinetics of intrathecal diaziquone in refractory meningeal malignancies. J Clin Oncol 10:143–148.

Berweiler U, Krone A, Tonn JC. 1998. Reservoir systems for intraventricular chemotherapy. J Neurooncol 38:141–143.

Bilsky MH, Lis E, Raizer J, Lee H, Boland P. 1999. The diagnosis and treatment of metastatic spinal tumor. Oncologist 4:459–469.

Bleyer WA, Poplack DG. 1979. Intraventricular versus intra-lumbar methotrexate for central-nervous-system leukemia: prolonged remission with the Ommaya reservoir. Med Pediatr Oncol 6:207–213.

Bower JH, Hammack JE, McDonnell SK, Tefferi A. 1997. The neurologic complications of B-cell chronic lymphocytic leukemia. Neurology 48:407–412.

Byrne TN, Waxman SG. 1990. Spinal Cord Compression: Diagnosis and Principles of Management. Philadelphia: FA Davis, 278 pp.

Castagnola C, Nozza A, Corso A, Bernasconi C. 1997. The value of combination therapy in adult acute myeloid leukemia with central nervous system involvement. Haematologica 82:577–580.

Chamberlain MC. 1998. Radioisotope CSF flow studies in leptomeningeal metastases. J Neurooncol 38:135–140.

Champagne MA, Silver HK. 1992. Intrathecal dacarbazine treatment of leptomeningeal malignant melanoma. J Natl Cancer Inst 84:1203–1204.

Cibas ES, Malkin MG, Posner JB, Melamed MR. 1987. Detection of DNA abnormalities by flow cytometry in cells from cerebrospinal fluid. Am J Clin Pathol 88:570–577.

Davis FG, Preston-Martin S. 1999. Epidemiology. Incidence and survival. In: Bigner DD, McLendon RE, Bruner JM (eds), Russell and Rubinstein's Pathology of Tumors of the Nervous System, London: Arnold, pp. 5–46.

DeAngelis LM. 1998. Current diagnosis and treatment of leptomeningeal metastasis. J Neurooncol 38:245–252.

Ferreri AJ, Reni M, and Villa E. 2000. Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. Ann Oncol 11:927–937.

Freilich RJ, Krol G, DeAngelis LM. 1995. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. Ann Neurol 38:51–57.

Gilbert RW, Kim JH, Posner JB. 1978. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. Ann Neurol 3:40–51.

Glantz MJ, Cole BF, Recht L, et al. 1998. High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: is intrathecal chemotherapy necessary? J Clin Oncol 16:1561–1567.

Glantz MJ, Hall WA, Cole BF, et al. 1995. Diagnosis, management, and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. Cancer 75:2919–2931.

Glantz MJ, LaFollette S, Jaeckle KA, et al. 1999. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol 17:3110–3116.

Gray JR, Wallner KE. 1990. Reversal of cranial nerve dysfunction with radiation therapy in adults with lymphoma and leukemia. Int J Radiat Oncol Biol Phys 19:439–444.

Hanssens PE, Lagerwaard FJ, Levendag PC. 1998. Principles of radiotherapy of neoplastic meningosis. J Neurooncol 38:145–150.

Jordan JE, Donaldson SS, Enzmann DR. 1995. Cost effectiveness and outcome assessment of magnetic resonance imaging in diagnosing cord compression. Cancer 75:2579–2586.

Kataoka A, Shimizu K, Matsumoto T, et al. 1995. Epidural spinal cord compression as an initial symptom in childhood acute lymphoblastic leukemia: rapid decompression by local irradiation and systemic chemotherapy. Pediatr Hematol Oncol 12:179–184.

Klekamp J, Samii H. 1998. Surgical results for spinal metastases. Acta Neurochir (Wien) 140:957–967.

Larson SM, Schall GL, DiChiro G. 1971. The influence of previous lumbar puncture and pneumoencephalography on the incidence of unsuccessful radioisotope cisternography. J Nucl Med 12:555–557.

Levitt LJ, Dawson DM, Rosenthal DS, Moloney WC. 1980. CNS involvement in the non-Hodgkin's lymphomas. Cancer 45:545–552.

Loblaw DA, Laperriere NJ. 1998. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J Clin Oncol 16:1613–1624.

Lossos IS, Breuer R, Intrator O, Lossos A. 2000. Cerebrospinal fluid lactate dehydrogenase isoenzyme analysis for the diagnosis of central nervous system involvement in hematooncologic patients. Cancer 88:1599–1604.

Lyons MK, O'Neill BP, Marsh WR, Kurtin PJ. 1992. Primary spinal epidural non-Hodgkin's lymphoma: report of eight patients and review of the literature. Neurosurgery 30:675–680.

Mackintosh FR, Colby TV, Podolsky WJ, et al. 1982. Central nervous system involvement in non-Hodgkin's lymphoma: an analysis of 105 cases. Cancer 49:586–595.

Mahmoud HH, Rivera GK, Hancock ML, et al. 1993. Low leuko-cyte counts with blast cells in cerebrospinal fluid of children with newly diagnosed acute lymphoblastic leukemia. N Engl J Med 329:314–319.

Maranzano E, Latini P, Beneventi S, et al. 1996. Radiotherapy without steroids in selected metastatic spinal cord compression patients. A phase II trial. Am J Clin Oncol 19:179–183.

Maranzano E, Latini P, Checcaglini F, et al. 1991. Radiation therapy in metastatic spinal cord compression. Cancer 67:1311–1317.

Mason WP, Yeh SDJ, DeAngelis LM. 1998. [111]Indium-diethyl-enetriamine pentaacetic acid cerebrospinal fluid flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. Neurology 50:438–444.

McAllister LD, Doolittle ND, Guastadisegni PE, et al. 2000. Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. Neurosurgery 46:51–60.

Mead GM, Bleehen NM, Gregor A, et al. 2000. A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer 89:1359–1370.

Moser AM, Adamson PC, Gillespie AJ, Poplack DG, Balis FM. 1999. Intraventricular concentration times time ($C \times T$) methotrexate and cytarabine for patients with recurrent meningeal leukemia and lymphoma. Cancer 85:511–516.

Nelson DF. 1999. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). J Neurooncol 43:241–247.

Olson ME, Chernik NL, Posner JB. 1974. Infiltration of the leptomeninges by systemic cancer. Arch Neurol 30:122–137.

Oschmann P, Kaps M, Volker J, Dorndorf W. 1994. Meningeal carcinomatosis: CSF cytology, immunocytochemistry and biochemical tumor markers. Acta Neurol Scand 89:395–399.

Oviatt DL, Kirshner HS, Stein RS. 1982. Successful chemotherapeutic treatment of epidural compression of non-Hodgkin's lymphoma. Cancer 49:2446–2448.

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol 51:874–887.

Posner JB. 1987. Back pain and epidural spinal cord compression. Med Clin North Am 71:185–205.

Posner JB. 1995. Neurologic Complications of Cancer. Philadelphia: FA Davis, 482 pp.

Posner JB, Howieson J, Cvitkovic E. 1977. "Disappearing" spinal cord compression: oncolytic effect of glucocorticosteroids (and other chemotherapeutic agents) on epidural metastases. Ann Neurol 2:409–413.

Price RA, Johnson WW. 1973. The central nervous system in childhood leukemia: I. The arachnoid. Cancer 31:520–533.

Raz I, Siegal T, Siegal T, Polliack A. 1984. CNS involvement by non-Hodgkin's lymphoma. Response to a standard therapeutic protocol. Arch Neurol 41:1167–1171.

Recht L, Straus DJ, Cirrincione C, Thaler HT, Posner JB. 1988. Central nervous system metastases from non-Hodgkin's lymphoma: treatment and prophylaxis. Am J Med 84:425–435.

Rhodes CH, Glantz MJ, Glantz L, et al. 1996. A comparison of polymerase chain reaction examination of cerebrospinal fluid and conventional cytology in the diagnosis of lymphomatous meningitis. Cancer 77:543–548.

Rodesch G. Van Bogaert P, Mavroudakis N, et al. 1990. Neuroradiologic findings in leptomeningeal carcinomatosis: the value interest of gadolinium-enhanced MRI. Neuroradiology 32:26–32.

Rogers LR, Duchesneau PM, Nunez C, et al. 1992. Comparison of cisternal and lumbar CSF examination in leptomeningeal metastasis. Neurology 42:1239–1241.

Schiff D, Shaw EG, Cascino TL. 1995. Outcome after spinal reirradiation for malignant epidural spinal cord compression. Ann Neurol 37:583–589.

Schold SC, Wasserstrom WR, Fleisher M, Schwartz MK, Posner JB. 1980. Cerebrospinal fluid biochemical markers of central nervous system metastases. Ann Neurol 8:597–604.

Shapiro WR, Young DF, Mehta BM. 1975. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med 293:161–166.

Siegal T. 1998. Leptomeningeal metastases: rationale for systemic chemotherapy or what is the role of intra-CSF-chemotherapy? J Neurooncol 38:151–157.

Siegal T, Lossos A, Pfeffer MR. 1994. Leptomeningeal metastases: analysis of 31 patients with sustained off-therapy response following combined-modality therapy. Neurology 44:1463–1469.

Sioutos PJ, Arbit E, Meshulam CF, Galicich JH. 1995. Spinal metastases from solid tumors. Analysis of factors affecting survival. Cancer 76:1453–1459.

Stark B, Sharon R, Rechavi G, et al. 2000. Effective preventive central nervous system therapy with extended triple intrathecal therapy and the modified ALL-BFM 86 chemotherapy program in an enlarged non-high risk group of children and adolescents with non-B-cell acute lymphoblastic leukemia: the Israel National Study report. Cancer 88:205–216.

Stockhammer G, Poewe W, Burgstaller S, et al. 2000. Vascular endothelial growth factor in CSF. A biological marker for carcinomatous meningitis. Neurology 54:1670–1676.

Tubergen DG, Cullen JW, Boyett JM, et al. 1994. Blasts in CSF with a normal cell count do not justify alteration of therapy for acute lymphoblastic leukemia in remission: a Childrens Cancer Group Study. J Clin Oncol 12:273–278.

van der Gaast A, Sonneveld P, Mans DR, Splinter TAW. 1992. Intrathecal administration of etoposide in the treatment of malignant meningitis: feasibility and pharmacokinetic data. Cancer Chemother Pharmacol 29:335–337.

Van Oostenbrugge RJ, Hopman AH, Ramaekers FC, Twijnstra A. 1998. In situ hybridization: a possible diagnostic aid in leptomeningeal metastasis. J Neurooncol 38:127–133.

Wasserstrom WR, Glass JP, Posner JB. 1982. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. Cancer 49:759–772.

Wong ET, Portlock CS, O'Brien JP, DeAngelis LM. 1996. Chemosensitive epidural spinal cord disease in non-Hodgkin's lymphoma. Neurology 46:1543–1547.