Leptomeningeal metastasis (LM) is usually a late complication of cancer, often accompanying systemic relapse of tumour. LM can affect any part of the neuraxis. It may seed the leptomeninges diffusely or multi-focally. Tumour deposits may be macroscopic or microscopic. The incidence of LM at autopsy in cancer patients is 8%.1 The incidence is decreasing in acute lymphoblastic leukaemia, and increasing in breast cancer and in small cell lung cancer (SCLC). LM is common in haematological malignancies (leukaemia and non-Hodgkin’s lymphoma) and in solid tumours (breast, melanoma and lung, especially small cell). It occurs more commonly in adenocarcinoma than in squamous cell carcinoma. Occasional patients have primary leptomeningeal tumour: lymphomas, especially T-cell lymphomas, and melanoma. The central nervous system, and particularly the cerebrospinal fluid (CSF), can be a sanctuary site and therefore a site of recurrence for patients whose metastatic tumour has otherwise responded to chemotherapy.2

Pathophysiology

Neurological symptoms occur through several pathophysiological mechanisms.3 Tumour may invade the parenchyma. It can cause ischemia by direct interference with the blood supply to the brain or by competing for oxygen and metabolites. Occlusion of CSF outflow from the fourth ventricle and resistance to CSF absorption can lead to hydrocephalus.

Clinical symptoms and signs

Clinical symptoms and signs can occur at any level of the neuraxis and are often multifocal.4 Symptoms and signs can be divided into cerebral, cranial nerve, spinal, and meningeal irritation. Cerebral symptoms may include headache, gait ataxia or apraxia, cognitive difficulties, episodic loss of consciousness, seizures, dysarthria or dysphasia and dizziness. Involvement of cranial nerves is rarely a presenting complaint but cranial nerve signs are often present. Diplopia is the most common symptom, but an extraocular muscle palsy may be present without symptomatic diplopia. Other cranial nerve symptoms include hearing loss, facial numbness, facial weakness, visual loss, dysphagia and hoarse voice. Spinal leptomeningeal disease can lead to invasion of spinal nerve roots producing radicular pain, weakness, parasthesia, and bladder or bowel disturbance. Reflexes are often absent. Meningeal irritation can lead to neck or back pain and neck stiffness. LM can produce virtually any neurological symptom and sign, and so must be considered in the differential diagnosis in patients with cancer and neurological symptoms.

Diagnosis

The diagnosis is often difficult to establish, even when strongly suspected clinically. Traditionally, to establish a definitive diagnosis requires the finding of malignant cells in CSF on cytological examination, but several lumbar punctures may be required to establish the diagnosis.5 A single examination is positive in approximately 50% of cases, and this rises to 85-90% after three procedures. Cytology remains negative in some patients despite repeated testing of CSF from multiple lumbar punctures. These false-negative results may result from strong adherence of malignant cells to the leptomeninges or to the presence of focal rather than widespread leptomeningeal tumour.

Obtaining CSF from a different site than the lumbar space, such as performing a cisternal puncture, may improve the yield of positive cytology, and this may be true particularly in patients with predominantly cerebral symptoms.6 In some instances cytology of ventricular fluid obtained through an intraventricular reservoir is positive when lumbar CSF cytology is negative. Other CSF markers such as elevated protein, raised cell count, low glucose, raised opening pressure and elevated tumour markers may give an indication of the presence of LM, but they are not diagnostic since they may be abnormal in other conditions. In some clinical circumstances CSF cannot be obtained, for example in patients with raised intracranial pressure and in patients with a coagulopathy.

Neuroimaging is an additional tool to assess for LM. Neuroimaging is useful both to help confirm a clinical suspicion of LM and to exclude other causes of neurological symptoms and signs. Magnetic resonance imaging (MRI) may be abnormal in patients with LM, but these abnormalities are often not specifically diagnostic of LM. The use of neuroimaging in the clinical decision-making process in the cancer patient suspected to have LM has been examined.7 In this study MRIs were classified as either positive, suggestive, or negative for LM. Positive scans were those that showed clear leptomeningeal enhancement in the brain, spinal cord or cauda equina, or subependymal enhancement. Suggestive scans included those with dural enhancement (focal or diffuse enhancement over the convexity of the brain surface but not extending into sulci), superficial cerebral lesions that were in close proximity to the subarachnoid space or appeared to sit within sulci, enhancement of cranial nerves, communicating hydrocephalus, and slight leptomeningeal enhancement in the brain, spinal cord or cauda equina. Neuroimaging was abnormal in 79% of patients with positive cytology, and this figure is similar to those quoted in the literature.8,9 Neuroimaging, however, was more likely to be abnormal in patients with solid tumours (90%) than those with hematological tumours (55%). The higher incidence of neuroimaging abnormalities in patients with solid tumours is likely related to the surface adhesion properties of these neoplasms. This property not only leads to the formation of bulky leptomeningeal masses which enhance on neuroimaging, but is likely an important factor in the formation of superficial cerebral lesions and communicating hydrocephalus as well.

In this series a diagnosis of LM was made in 77 of the 137 patients in whom it was clinically suspected. In 24/77 (31%), this diagnosis was made on the basis of neuroimaging and clinical picture without a positive CSF cytology; the majority of these patients (19/24) had positive neuroimaging. Most of these patients did not have a lumbar puncture or had at most one CSF examination. CSF cytology and neuroimaging were complementary in the diagnosis of LM in this series. In cancer patients with a clear clinical picture consistent with LM and appropriate neuroimaging findings, it is prudent to treat the patient on the basis of this evidence rather than pursuing a positive cytology with repeated lumbar puncture. It must be emphasised, however, that the diagnosis of LM cannot be based solely on the presence of an abnormal scan, but must be considered in the context of the clinical picture. For example,
in a patient with breast cancer who has headache, multiple cranial nerve palsies and radicular symptoms and signs, the presence of leptomeningeal enhancement on brain and spine MRI is adequate to confirm the presence of LM even if CSF cytology is negative. Conversely, the presence of leptomeningeal enhancement in a patient with prostate cancer must be interpreted with caution, as this tumour rarely metastasises to the leptomeninges.

**Treatment**

Treatment of LM must be delivered to the entire neuraxis. Treatment options include radiotherapy and chemotherapy. Radiotherapy is used to treat symptomatic sites, such as a painful cauda equina lesion or the base of skull to treat cranial neuropathies, or to treat asymptomatic mass lesions. Chemotherapy is used to treat the rest of the neuraxis. Intrathecal chemotherapy delivered via an intra-ventricular reservoir is the preferred route of administration. It is more convenient than repeated lumbar punctures, and ensures more complete delivery of drugs to the neuraxis than chemotherapy delivered via the lumbar route. In patients with impaired CSF flow, however, the drug may not be adequately delivered to the entire neuraxis.

Only certain drugs can be delivered intrathecally. Some drugs, such as vincristine, are highly neurotoxic when delivered into the CSF. The most commonly used drug is methotrexate; ara-C and thiopeta also can be used. A slow-release formulation of cytarabine also has been developed. A typical regimen of methotrexate would be 12mg given twice weekly for five doses, after which the frequency of treatment is reduced, until it is eventually administered monthly. Duration of treatment is empirical. Patients are monitored clinically and by checking cytology on CSF aspirated from the intraventricular reservoir prior to each administration of chemotherapy. Side effects of intrathecal methotrexate include aseptic meningitis, which occurs within hours of administration of the drug (far sooner than bacterial meningitis introduced by this technique), acute encephalopathy, transverse myelopathy, and chronic leukoencephalopathy which can lead to dementia, hemiparesis or quadriplepsis. Patients being treated with intrathecal methotrexate should receive oral leucovorin to prevent systemic toxicity.

A ventriculo-peritoneal shunt is sometimes required if patients have raised intracranial pressure, for example if they have intractable headache, papilledema with visual loss or obtundation.

**Prognosis**

The prognosis of LM is generally poor. Untreated, most patients with symptomatic LM die within six weeks to two months. With treatment, patients with leukaemia achieve excellent results, but patients with solid tumours fare less well; 75% stabilise or improve over several months, but 25% do not respond and have progressive disease. Despite initial improvement, most patients survive only a few months. The median survival of patients with solid tumours treated for LM is of the order of six months. Breast cancer and small cell lung cancer are the two solid tumours that respond best to treatment of LM. Some patients with breast cancer and LM run a more indolent course; 15% of patients with breast cancer survive more than one year.

**References**