Leptomeningeal Carcinomatosis: Cerebral spinal fluid tumours.

Megan Stone

Abstract
Leptomeningeal Carcinomatosis (LC) is the dissemination of cancer, commonly breast, lung, melanoma, acute lymphoblastic leukaemia and Non-Hodgkin lymphoma occurring through either direct extension from surrounding tumours or metastasis of a preexisting, parenchymal central nervous system tumour. A rise in the diagnosis of leptomeningeal disease has been seen with increased survival rates of cancer due to improved medical treatment, with 5-8% of patients with cancer going on to develop LC.

Leptomeningeal Carcinomatosis spreads to the meninges, the outer covering of the brain and spinal cord, directly migrating into the cerebral spinal fluid (CSF), arachnoid and pia mater. This migration of tumour cells occurs throughout the arachnoid vessels or choroid plexus into the surrounding outer layers extending into the CSF. On entry into the CSF, tumour cells are infiltrated in a diffuse or multifocal manner where the leptomeninges cover the surface of the brain and spinal cord. This covering causes the meninges to become irritated causing patients to exhibit signs of photophobia, neck stiffness, neurological decline and cranial nerve defects. LC has a significant morbidity and mortality rate with a median survival of 4-6 weeks if untreated and 2-3 months if treated. Diagnosis is based on analysis of the cerebral spinal fluid, through detection of positive cytology of LC tumour cells, elevated protein and CSF pressures. Magnetic resonance imaging findings identify areas of meningeal enhancement indicative of meningeal irritation.

The neuroscience nurse role in the patient care includes providing a supportive environment and thorough assessment of vital and neurological signs. Treatment aims to improve or maintain a patient's neurological status while prolonging survival and palliation. The literature review will highlight the diagnosis, progression and treatment for LC to further increase awareness and inform neuroscience nurses of increasing trends in management.

Key Words: *Leptomeningeal carcinomatosis, meninges, cerebral spinal fluid, tumour.*

Introduction

Leptomeningial carcimomatosis (LC) was first identified in the 1870 by Ebert in a patient with lung cancer, and was named in 1902 by Sieffert as meningitis carcinomatosa (Schiff, Kesari & Wen, 2008). Sixteen thousand patients globally will be diagnosed with LC each year (Abrey, 2002). There has been a significant rise in the incidence of LC since 1970, thought to be due to improvements in the diagnostic techniques and neuro imaging available in today's healthcare system (Schiff, Kesari & Wen, 2008). The rise in diagnosis is the direct result of patients surviving their primary cancer. Hence there is a need for health professionals to be aware of LC and the clinical presentation, in order to provide appropriate care and interventions along with the potential for future research and cure.

Questions or comments about this article should be directed to Megan Stone, Registered Nurse, St Vincent's Private Hospital, Victoria Australia.
Meganrstone@hotmail.com

Currently epidemiological studies suggest that 3-8% of patient with solid tumours will develop leptomeningeal metastasis (LM) throughout their illness (Abrey, 2002). Twenty per cent of patients are diagnosed on autopsy. These are patients undiagnosed and asymptomatic (Le Rhun, Taillibert & Chamberlain, 2013). It was determined that the rise in diagnosis is due to increased survival rates of cancer as a result of improved medical treatment. All cancers have the potential to metastasise into the meninges causing LM. The leading primary cancers associated with LM include lung cancer (10-26%), melanoma (5-25%), gastrointestinal (4-14%), cancer of unknown primary (1-7%) and breast cancer (12-35%) (Le Rhun et al 2013).

The brain and spinal cord are surrounded by three membranes referred to as the meninges, composed of the dura mater being the pachymeninges, arachnoid mater and pia mater referred to as the leptomeninges. The space between is referred to as the subarachnoid space, containing the CSF and the Circle of Willis providing arterial blood supply. Approximately 140ml of cerebral spinal fluid surround the brain and spinal cord at any one time, replenishing approximately five times a day (Hickey, 2014). CSF is produced in the choroid plexus of the third, fourth and lateral ventricles. Tumours cells gain entry into the CSF and subarachnoid space by metastatic seeding. Entry is gained by hematogenous spread to the choroid plexus onto the leptomeninges, primary hematogenous metastasis through leptomeningeal vessels, metastasis from the Batson venous plexus, retrograde dissemination, centripetal extension or direct extension from contiguous tumour deposits (Gleissner & Chamberlain, 2006; Le Rhun et al 2013). Once tumour cells have invaded the leptomeninges, the flow of CSF causes the seeding and infiltration of tumour cells in a diffuse and multifocal manner (Le Rhun et al 2013). Greatest infiltration occurs in the basal cisterns and dorsal surface of the spinal cord and cauda equina.

Case Study

Patient X presented to hospital with increased confusion, ataxia and lower limb mild weakness. Histology included breast cancer where a left mastectomy and lymph node clearance was completed in the 14 months prior to diagnosis. Symptoms of leptomeningeal metastases are caused by pressure from the metastases placed on the nerves that run across the meninges in both the head and the spine. This includes those running from the spinal cord out to the body, and is dependent on the location of the metastases. Symptoms that occur simultaneously in both the head and the spine suggest a diagnosis of leptomeningeal metastases (LM). Leptomeningeal metastases can also cause hydrocephalus, a condition that occurs when the metastatic cancer interferes with the flow of cerebrospinal fluid around the brain. As the spinal fluid continues to be produced, an increase in the intracranial pressure is then seen as the arachnoid villi are no longer able to effectively reabsorb the CSF.

Clinical presentation occurs in a pleomorphic and multifocal manner with neurological signs and symptoms emerging over days to weeks. Symptoms correlate to the region of malignant cell infiltration in the central nervous system (CNS). The clinical manifestation of LM can be caused by several different pathophysiological mechanisms and can be characterised into the following main categories:

- cerebral hemisphere dysfunction causing a mass effect due to the invasion of the leptomeninges and associated inflammation thus a raised intracranial pressure (ICP) and occlusion of CSF flow occurs.
- cranial nerve and spinal cord symptoms: Through direct involvement of the tumour.
- exiting nerve roots (Demopoulos & Brown, 2014; Drappatz & Batchelor, 2007; Hickey, 2014).

A recent study described the signs and symptoms of 150 patients with solid tumour LM (Clarke, Perez, Jacks, Panageas & DeAngelis, 2010; Clarke 2012; Demopoulos & Brown, 2014). Between 30-50% of patients describe headache as their initial symptoms (see Table 1). Headaches can be associated with raised ICP or meningeal irritation resulting in neck stiffness and pain, along with signs of nuchal rigidity. Headaches occurring due to a raised ICP are known to be associated with nausea, vomiting and dizziness.

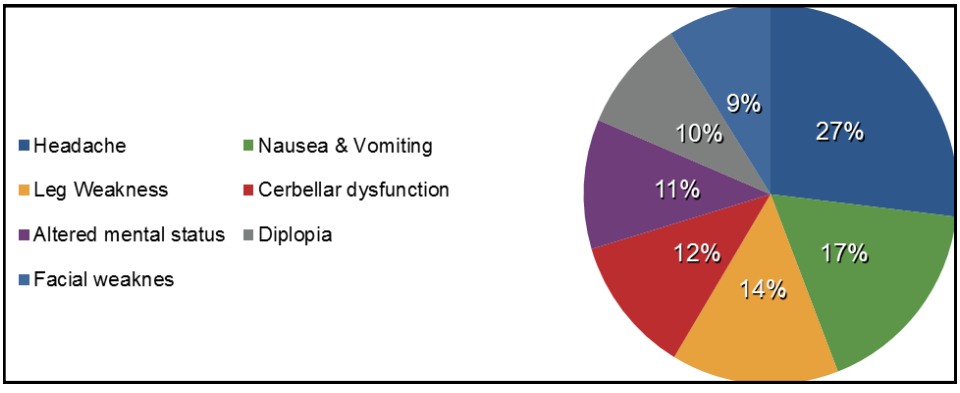

Table 1 *(Above): Initial symptoms of LM as reported by patients.*

These symptoms commonly occur in wave patterns caused by changes in position due to arachnoid villi failing to reabsorb CSF thus resulting in hydrocephalus. Altered mental status accounts for 11% of presenting symptoms with confusion, forgetfulness, disorientation, lethargy or personality changes the most common. These changes in mental state are referred to as an encephalopathy, the result of hydrocephalus, seizure activity, cerebral dysfunction or a combination of those. When cranial nerves are directly invaded by malignant cells within the subarachnoid space, cranial neuropathy occurs.

The first intervention in diagnosis is a lumbar puncture to obtain a CSF specimen. Malignant cells are detected in 70-89% of CSF specimens (Le Rhun et al, 2013). Repeated samples are often necessary as only 50% of patients with LM on initial lumbar puncture exhibit positive cytology. Patients are 25% more likely to have positive cytology on second lumbar puncture. Multiple lumbar punctures are often required due to the meningeal dissemination, where tumour cells are localised in the brain rather than the spinal cord hence movement of CSF must occur in order to obtain a positive sample. Therefore negative CSF cytology is directly related to the flow of malignant cells within the spinal cord CSF when lumbar punctures are taken.

Clinical finding on CSF analysis includes, an elevated opening pressure of > 200mm Hg in 57% of patients, decreased glucose concentration, high protein concentration, lymphocytic pleocytosis and a positive cytology for malignant cells (Chamberlain, 2008; Drappatz & Batchelor, 2007; Palma, Fernandez-Torron, Esteve-Belloch, Fontes-Villalba, Hernandez, Fernandez-Hidalgo, Gallego Perez-Larraya & Martinez-Vila, 2013).

A positive MRI assessment of an undiagnosed patient includes a whole CNS scan where a complete neuraxis and A T1 C+ gadolinium enhancement is completed in order to obtain the primary diagnosis (Drappatz & Batchelor, 2007).

Typical findings include a thin diffused enhancement along the contours of the gyri and sulci with multiple nodular deposits in the subarachnoid space in 30-50% of cases (Le Rhun et al, 2013). LM enhancement can be found in cerebellar folia, cortical surface, basal cisterns and ventral surface along the brainstem, indicating abnormal thickening and enhancement. However these are not the most common sites of LM. Between 15-25% of patients present with spinal enhancement, showing linear or nodular enhancement along the spinal cord or cauda equina where clumping of nerve roots can be seen (Le Rhun et al, 2013). CT is an uncommon practice due to poor diagnostic value, with significantly reduced sensitivities of 23-38% when compared with the MRI.

Prognosis

The overall prognosis for a patient with LM is poor; patients have an expected survival rate of 4-6 weeks if untreated and 4-6 months if treated. Research indicated that 14% of LM cases occur as a result of an advanced primary breast cancer with no well-established prognostic makers for patients with LM other than the presence of malignant cells within the CSF and low performance in Karnofsky performance status scale (Palma, et al 2013).

Treatment

Due to current poor prognostic outcomes, treatment aims to reduce mortality through improving and stabilising the patient's neurological status, while maintaining neurological quality of life (Gleissner & Chamberlain, 2006). Current treatment plans are comprised of intrathecal or systemic chemotherapy and focal radiation therapy with the goal to reduce size of tumours and growth. Statistically 20% of patients who receive treatment will respond (Demopoulos & Brown, 2014; Palma et al, 2013). Suitable patients will undergo insertion of a ventriculo-peritoneal shunt to alleviate hydrocephalus symptoms.

Chemotherapy is the only treatment which allows for simultaneous treatment of the brain and spinal cord. Intrathecal administration is defined as injecting chemotherapy into a cerebral- access device inserted surgically or via repeated lumbar punctures (Demopoulos & Brown, 2014). Intrathecal administration allows for an even distribution throughout the subarachnoid space and is not required to cross the blood brain barrier (Drappatz & Batchelor, 2007). Access devices avoid the risk of epidural or subdural hematomas. Methotrexate and thiotepa are the most effective chemotherapies in the treatment of LM patients with metastasis from primary breast cancer (Demopoulos & Brown, 2014; Drappatz & Batchelor, 2007). Chemotherapy is administered initially twice weekly for three weeks then weekly for four week followed by monthly (Demopoulos & Brown 2014).

Radiation therapy involves field radiotherapy

to symptomatic sites of the disease, bulky disease and sites where CSF flow is obstructed. The aim is to shrink tumour cells, stabilise neurological symptoms, establish CSF flow and relieve pain caused by radiculopathies (Demopoulos, 2014).

Nurses must consider the adverse effects of chemotherapy and radiation therapy. Administration of chemotherapy may result in raised ICP and impaired CSF flow. Nurses must observe for acute signs of fever, headache, nuchal rigidity, seizures, dizziness or blurred vision. Subacute signs include transverse myelitis, cranial nerve palsies, seizures or coma (Demopoulos, 2014). When administering radiation therapy the nurse should be aware of increased patient fatigue, changes in skin colour and flushing of skin along with skin tension and Lhermitte's sign - an electrical signal running from the back of the cervical spine to the tips of the feet, when the neck is bent forwards (Demopoulos, 2014).

When selecting patient treatment options, chemotherapy or radiation therapy is considered and each play a significant role in the treatment of LM. Research indicates that intra CSF chemotherapy is better on smaller LC tumours due to the thickness of cells and diffusion capacity (Demopoulos, 2014). Radiation therapy is better at treating large bulky tumours and assisting in the restoration of CSF flow (Demopoulos, 2014). Combination therapy is currently the choice of treatment.

Nurse's Role

When nursing a patient with LM the holistic approach is essential due to the array of symptoms a patient can display. Leg weakness and difficulty walking are common symptoms, thus ongoing assessment of mobility status including the need for walking aids, wheelchairs or hoisting devices. Referral to an occupational therapist before discharge is also important. Regular speech and swallowing assessments should be performed, as LM can increase the risk of aspiration as cranial nerve deficits impair the ability to chew and swallow. Constipation is a significant issue for LM patients as decreased mobility, pain medications and chemotheraphy contribute to constipation (Drappatz & Batchelor, 2007). Nursing staff should commence a bowel regime including a high fibre diet, adequate oral intake and aperients.

Conclusion

As health professionals, it is important to note that in 3-8 % of patients with solid tumours, the chance of developing LM is a real consideration. In Patient X's case, due to a delayed diagnosis and intervention, prognosis and outcome was poor.

MRI and lumbar puncture allows for earlier diagnosis and intervention, while chemotherapy and radiation therapy improve longevity and quality of life. Nurses are critical to the care of the LM patient. An understanding of the disease process and care required will ensure quality of life during the progression of the disease. With cancers increasing in today's society and certain treatments readily available, health professionals will have an increased awareness of LM, therefore with the ability to identify and treat earlier.

Reference List

Abrey, L. (2002). Leptomeningeal neoplasms. *Curr Treat Options Neurol*, 4(2), pp.147-156.

Clarke, J. (2012). Leptomeningeal Metastasis From Systemic Cancer. *CONTINUUM: Lifelong Learning In Neurology*, *18*, 328-342. http://dx.doi.org/10.1212/01.con.0000413661.58045.e7

Clarke, J., Perez, H., Jacks, L., Panageas, K., & DeAngelis, L. (2010). Leptomeningeal metastases in the MRI era. *Neurology*, *74*(18), 1449-1454. http://dx.doi.org/10.1212/wnl.0b013e3181dc1a69

Chamberlain, M. (2008). Neoplastic Meningitis. *The Oncologist*, 13(9), pp.967-977.

Demopoulos, A. (2014). *Clinical features and diagnosis of leptomeningeal metastases from solid tumors*. Retrieved from http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-leptomeningeal-metastases-from-solid-tumors [Accessed 7 Sep. 2015].

Demopoulos, A., Brown, P. (2012).Treatment of leptomeningeal metastases (carcinomatous meningitis). *UpToDate*. Retrieved from http://www.uptodate.com/contents/treatment-of-leptomeningeal-metastases-carcinomatous-meningitis

Drappatz, J. and Batchelor, T. (2007). Leptomeningeal neoplasms. *Curr Treat Options Neurol*, 9(4), pp.283-293.

Gleissner, B., & Chamberlain, M. (2006). Neoplastic meningitis. *The Lancet Neurology*, 5 (5), pp 442-452

Hickey, J. (2014). The clinical practice of neurological and neurosurgical nursing. (7th ed.). Philadelphia: Lippincott Williams & Wilkins.

Le Rhun, E., Taillibert, S., & Chamberlain, M. C. (2013). Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. *Surgical neurology international*, *4*(Suppl 4), S265.

Palma, J., Fernandez-Torron, R., Esteve-Belloch, P., Fontes-Villalba, A., Hernandez, A., Fernandez-Hidalgo, O., Gallego Perez-Larraya, J. and Martinez-Vila, E. (2013). Leptomeningeal carcinomatosis: Prognostic value of clinical, cerebrospinal fluid and neuroimaging features. *Clinical Neurology and Neurosurgery*, 115(1), pp.19-25.

Schiff, D., Kesari, S., & Wen, P. (2008). *Cancer neurology in clinical practice*. Totowa, NJ: Humana Press.