Hong Kong J Radiol. 2013;16:50-4 | DOI: 10.12809/hkjr1312111

CASE REPORT

Leptomeningeal Carcinomatosis of the Spinal Cord Originating from Nasopharyngeal Carcinoma

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ABSTRACT

We report on a 44-year-old man with nasopharyngeal carcinoma with intracranial extension and leptomeningeal metastases in the spinal cord. Marked resolution of the nasopharyngeal carcinoma and leptomeningeal metastases was achieved by using cisplatin-based chemotherapy for six cycles. He was then treated by radiotherapy to residual leptomeningeal metastases at a dose of 30 Gy over 10 fractions, followed by high-dose palliative radiotherapy of 60 Gy over 30 fractions to the nasopharynx and regional lymph nodes. Excellent tumour shrinkage with prolonged survival of more than 1 year was achieved. To the authors' knowledge, this is the first published report of nasopharyngeal carcinoma resulting in leptomeningeal disease of the spinal cord.

Key Words: *Meningeal carcinomatosis; Nasopharyngeal carcinoma*

中文摘要

一宗鼻咽癌轉移到脊髓軟腦膜的罕見病例

岑翠瑜、吳偉棠

本文報告一名患有鼻咽癌並有顱內及脊髓軟腦膜轉移的44歲男子，病人接受六個療程的順鉑化療後，鼻咽及軟腦膜腫瘤顯著縮小。其後他繼續接受總劑量為30 Gy分10次針對殘留的軟腦膜轉移灶的放射治療，然後接受總劑量為60 Gy分30次針對鼻咽部及局部淋巴結的高劑量的姑息性放療。病人腫瘤灶明顯縮小，生存期延長了一年多。這是文獻中首宗有關鼻咽癌轉移至脊髓軟腦膜的病例報告。

INTRODUCTION

Leptomeningeal carcinomatosis is the invasion of neoplastic cells into the leptomeninges of the brain, cranial nerves, and spinal cord. This process occurs by three possible mechanisms: haematogenous spread, perineural spread along the spinal or cranial nerves, and direct invasion from an adjacent primary source. Once cancer cells enter the subarachnoid space, they are transported by the cerebrospinal fluid (CSF) resulting in disseminated and multifocal seeding of the leptomeninges. Tumour infiltration is most prominent at the base of the brain, the dorsal surface of the spinal cord, and the cauda equina.[1] Leptomeningeal carcinomatosis occurs in 4 to 15%

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Submitted: 4 Jun 2012; Accepted: 9 Nov 2012.

of patients with solid tumours. Adenocarcinoma is the most common histology. Primary cancers of the breast, lung, and skin (melanoma) are the most common sources of leptomeningeal carcinomatosis.[2] In contrast, leptomeningeal carcinomatosis occurs rarely in head and neck cancers. A few reports of leptomeningeal carcinomatosis occurring from cancers of the larynx,[3] lip,[4] and nasopharyngeal carcinoma have been published.[5-7] However, to the authors' knowledge, leptomeningeal carcinomatosis in the lower spinal cord arising from nasopharyngeal carcinoma, as in this patient, has not been reported in literature.

It is believed that cytotoxic chemotherapy is ineffective against leptomeningeal metastases as these tumours are associated with poor prognoses. This report is of a man, with nasopharyngeal carcinoma and leptomeningeal carcinomatosis, having dramatic response to systemic chemotherapy and a long survival time after treatment.

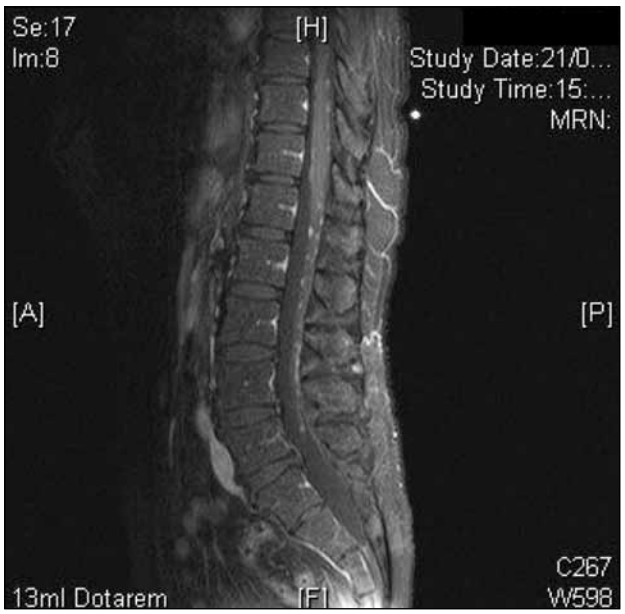

Figure 1. Prechemotherapy magnetic resonance imaging (gadolinium-enhanced T1-weighted sequences) showing leptomeningeal nodular enhancement in the lower spinal cord from T9 to the conus.

CASE REPORT

A 44-year-old Chinese man with a history of good past health presented with left proptosis for 10 days in June 2010. He also had hearing loss in his left ear for 2 months and subjective bilateral lower limb weakness. He was a non-smoker and non-drinker. Physical examination showed mild left proptosis. The cervical lymph nodes were not palpable. Neurological examination revealed left cranial nerve V_1, V_2 paraesthesia and VI palsy. Lower limb power, reflexes, and sensation were normal. Nasopharyngoscopy showed a tumour at the roof of the nasopharynx. Biopsy of the nasopharynx was positive for undifferentiated carcinoma. Magnetic resonance imaging (MRI) scan of the head and neck showed extensive tumour occupying the nasopharynx, eroding the base of the skull, the left petrous apex, and the pituitary fossa with intracranial extension. The intracranial portion was compressing and displacing the pons and the left temporal lobe. Extension into the left internal acoustic canal with bilateral cervical lymphadenopathy was seen. Positron emission tomography–computed tomography (PET-CT) showed focal activities adjacent to the posterior aspects of T12/L1 and S1/S2 that were suspicious of tumour involvement of the thecal sac. No other distant metastases were noted. MRI of the spine confirmed that there were multiple nodular-enhancing intrathecal lesions adhering to the conus medullaris and along the cauda equina from T11 to S1/2. Suspicious leptomeningeal nodular enhancement was also seen in the lower spinal cord from T9 to the conus (Figures 1 and 2). CSF obtained by lumbar puncture showed

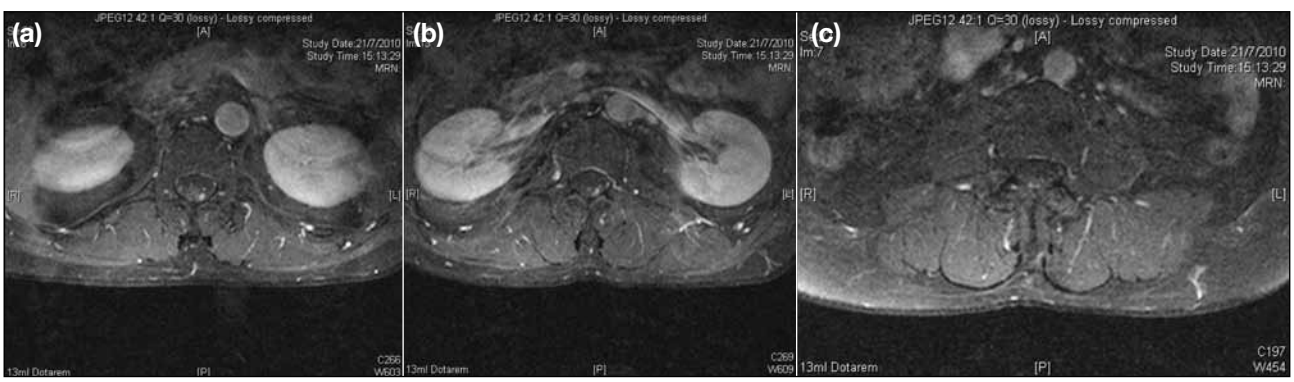

Figure 2. Axial cuts of pre-chemotherapy magnetic resonance imaging (gadolinium-enhanced T1-weighted sequences) showing leptomeningeal nodular enhancement at the levels of (a) T12, (b) L1, and (3) L3.

elevated protein and lowered glucose levels, but did not show any evidence of malignancy. The pretreatment Epstein-Barr virus (EBV) DNA was 26,750 copies/ml. The stage was T4N2M1.

The patient underwent six cycles of cisplatin-based chemotherapy. Progress PET-CT after six cycles of chemotherapy showed partial remission of the nasopharyngeal carcinoma, lymph nodes, and leptomeningeal metastases. MRI of the spine showed marked resolution of the multiple enhancing nodules adhering to the conus medullaris and along the cauda equina from T11 to S1/2. Only several small nodules were seen at the posterior aspect of the thecal sac from T9 to T11 (Figure 3). He was then treated by radiotherapy to T8 to T12 at a dose of 30 Gy over 10 fractions followed by high-dose palliative radiotherapy 60 Gy over 30 fractions to the nasopharynx and regional lymph nodes. His symptoms subsided after treatment except for mild paraesthesia over the left cranial nerves V_1 and V_2. The latest endoscopy performed 7 months after completion of treatment showed complete remission of the nasopharyngeal carcinoma and the EBV DNA level was 0 copies/ml. At 9 months after completion of treatment, he presented with unsteady gait. Physical examination showed wide-based gait with bilateral nystagmus, left cranial nerve V_1, V_2 paraesthesia, V motor, and VII palsy. CT of the brain and nasopharynx showed tumour relapse at the nasopharynx with intracranial extension at the left cerebellopontine angle, compressing and displacing the pons. The patient is now being treated with cisplatin-based palliative chemotherapy.

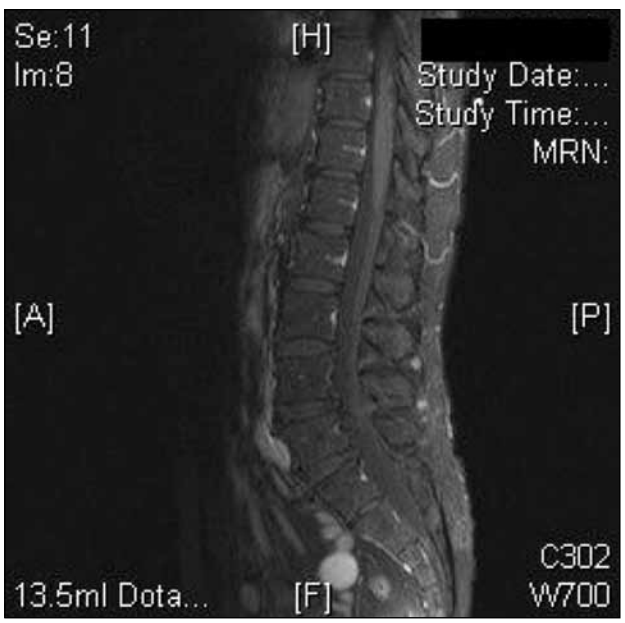

Figure 3. Post-chemotherapy magnetic resonance imaging with previously noted enhancing nodules adhering to the conus medullaris and along the cauda equina from T11 to S1/2 showing marked resolution; only several small nodules are now seen at the posterior aspect of the thecal sac at the T9 to T11 levels.

DISCUSSION

Nasopharyngeal carcinoma rarely presents with leptomeningeal carcinomatosis. In this patient, leptomeningeal metastases probably occurred by direct infiltration of the nasopharyngeal carcinoma into the brain. The tumour cells then followed the CSF flow down to the spinal cord. The presenting symptoms of leptomeningeal carcinomatosis are usually non-specific and related to increased intracranial pressure, such as headache, nausea, vomiting, altered mental status, and seizure. Cerebral leptomeningeal metastases can cause dysphasia, apraxia, hemiparesis, and personality change. Cranial nerve involvement can cause decreased visual acuity, diplopia, trigeminal sensory or motor loss, cochlear dysfunction, and facial weakness. Spinal cord meningeal involvement may give rise to back pain, limb weakness, paraesthesia, and incontinence. Meningismus is only present in 13% of patients.[8] This patient presented with only vague symptoms of lower limb weakness, without clinically detectable neurological deficit of the lower limb. Clinicians should be on the alert for the possibility of distant metastases in patients with T4 nasopharyngeal carcinoma.

Cytological examination of CSF is the gold standard for diagnosing leptomeningeal carcinomatosis. However, CSF cytology is not a highly sensitive diagnostic method. A sensitivity of only 54% for a single lumbar puncture has been reported,[9] although over 90% have been achieved with repeated tests.[8,10] Increased opening CSF pressure, elevated protein, decreased glucose concentration, and increased cellularity are additional non-specific findings. The detection rate of CSF cytology can be improved if the sample is promptly placed in preservative (ideally within 1 hour) and an adequate sample (5 ml or more) is evaluated.[11] There is a positive correlation between disease burden and the number of tumour cells present in the CSF, thus early diagnosis requires more sensitive tools. Biochemical markers, immunohistochemistry, and molecular biology techniques applied to the CSF have been explored in an attempt to find a reliable biological marker of disease. Tumour markers such as α-fetoprotein and β-human chorionic gonadotropin can be relatively specific for

leptomeningeal metastasis of primary central nervous system (CNS) germ cell tumours when elevated in CSF in the absence of markedly elevated serum levels. EBV is associated with acquired immunodeficiency syndrome (AIDS)–related primary CNS lymphoma and nasopharyngeal carcinoma. Polymerase chain reaction for EBV DNA in the CSF was reported to be an extremely sensitive and specific diagnostic marker for AIDS-associated primary CNS lymphoma.[12] EBV DNA can also be explored as a diagnostic marker of leptomeningeal metastases in nasopharyngeal carcinoma.

MRI is regarded as the imaging study of choice for the diagnosis of leptomeningeal metastases. A gadolinium-enhanced T1-weighted sequence detects abnormal meningeal enhancement characteristic of leptomeningeal disease. Meningeal enhancement is not specific for leptomeningeal metastases, as it may also be present in infectious and inflammatory diseases. However, focal areas of linear enhancement, especially in a nodular pattern, in cancer patients are highly suggestive of leptomeningeal metastases. As a diagnostic tool for leptomeningeal metastases, MRI has its limitations, as its sensitivity and specificity are only 76% and 77%, respectively.[13] In this patient, fluorodeoxyglucose (FDG) PET enabled early diagnosis of leptomeningeal carcinomatosis along the spinal cord, which was later confirmed by MRI. This patient illustrates the utility of FDG-PET in the detection of unexpected metastases at unusual sites. However, the sensitivity and specificity of PET-CT for detection of leptomeningeal carcinomatosis is unclear at this stage and requires further evaluation.

The mainstay of therapy for meningeal carcinomatosis has been intrathecal chemotherapy delivered through an intraventricular reservoir or by lumbar puncture, together with focal radiotherapy to major sites of involvement. Unfortunately, the choices of intrathecal agents are limited to methotrexate, cytosine arabinoside, and thiotepa. Methotrexate is the most commonly used agent for solid tumours. Toxicity related to the administration of methotrexate can be serious and includes seizures, acute chemical arachnoiditis with headache, nausea, vomiting, mental changes, subacute onset of motor and sensory abnormalities, and delayed necrotising leukoencephalopathy. Clear clinical data on the effect of systemic chemotherapy in leptomeningeal carcinomatosis are lacking. Traditionally, it is believed that the blood-brain barrier may protect malignant cells in the CSF from systemic chemotherapy. A few case reports have demonstrated that systemic chemotherapy with carboplatin and docetaxel (plus trastuzumab), and hormonal therapy could be effective in the treatment of leptomeningeal carcinomatosis from breast cancer.[14,15] This patient demonstrates that leptomeningeal carcinomatosis can respond to systemic chemotherapy. The authors hypothesise that the blood-brain barrier may have been disrupted by tumour cells and, thus delivery of systemic drugs to the CSF was possible. The use of systemic chemotherapy for treatment of leptomeningeal metastases deserves formal study and comparison to standard intrathecal treatments. Systemic therapy can potentially control the disease outside the CNS and prevent neurotoxicity related to intrathecal therapy. The role of radiotherapy in addition to intrathecal chemotherapy is uncertain due to the absence of any prospective randomised trial. When radiotherapy is considered, it is usually given at a dose of 30 Gy over 10 fractions to the brain and / or to the symptomatic, bulky, or obstructive sites to relieve CSF flow obstruction.

The prognosis for patients with leptomeningeal metastases is usually grave, with a mean survival of 6 weeks following diagnosis. With treatment, the mean survival increases to 4 to 6 months.[2] The prognosis is poor because leptomeningeal carcinomatosis is usually a late presentation in patients who have already had extensive and multiple metastases. This patient demonstrated a good response to treatment and had a relatively long survival of more than 1 year after diagnosis.

CONCLUSION

Leptomeningeal metastases are rare in nasopharyngeal carcinoma and have a poor prognoses. While the most effective treatment is yet to be defined, systemic chemotherapy and palliative radiotherapy may achieve good symptom control and improve survival in these patients.

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