UNUSUAL PRESENTATION OF CENTRAL NERVOUS SYSTEM METASTASES

Mechanisms of spread and radiological findings

Marcus André Acioly[1], Carlos Henrique Carvalho[1], João L. Pinheiro-Franco[1], Jens Schittenhelm[2], Ulrike Ernemann[3], Michael Weller[4], Jürgen Honegger[1]

Brain metastases are a well-known complication of systemic cancer, occurring in 20–40% of the patients suffering from cancer[1]. In adults, the lungs represent the most common source of brain metastases comprising 36–64% of the cases[1]. The cerebral hemispheres, cerebellum, brainstem[1], pituitary (sellar region)[2-4], cerebellopontine angle (CPA)/internal auditory canal (IAC)[2,5], and leptomeningeal metastases (LM)[1,2,6,7] are potential locations of dissemination.

We report an unusual case, in which solely the association of pituitary metastases (PM), bilateral CPA metastases and LM was found in a patient affected of a large cell neuroendocrine carcinoma (LCNEC) of the lung.

CASE

A 63-year-old woman presented with a 4-month history of emesis, anorexia, weight loss, and increasing thirst. After three months, the patient suddenly developed bilateral hearing loss, tinnitus and increased dizziness. Fluid intake and urine output were consistent with diabetes insipidus. The neurological examination revealed bilateral hearing loss, incomplete right peripheral facial palsy and unstable gait. Other motor or sensory deficits were not noted. The tendon reflexes were brisk.

Magnetic resonance imaging (MRI) revealed an intrasellar and suprasellar space-occupying lesion isointense in T1-weighted precontrast study with strong enhancement in contrast images infiltrating the pituitary gland, the pituitary stalk and the hypothalamus (Fig 1A and 1B), as well as bilateral CPA lesions. There was also loss of high-signal intensity of the pituitary posterior lobe.

A spinal tap showed a nonspecific lymphocytic pleocytosis. The patient underwent a transsphenoidal biopsy revealing a high-grade pleomorphic epithelial tumour, like a large-cell carcinoma. Besides, malignant cells were encountered on CSF cytology, confirming the diagnosis of LM (Fig 2A).

MRI also revealed the typical small nodular depot along the cauda, L4–L5 on the right side and L5–S1 on the left side, and

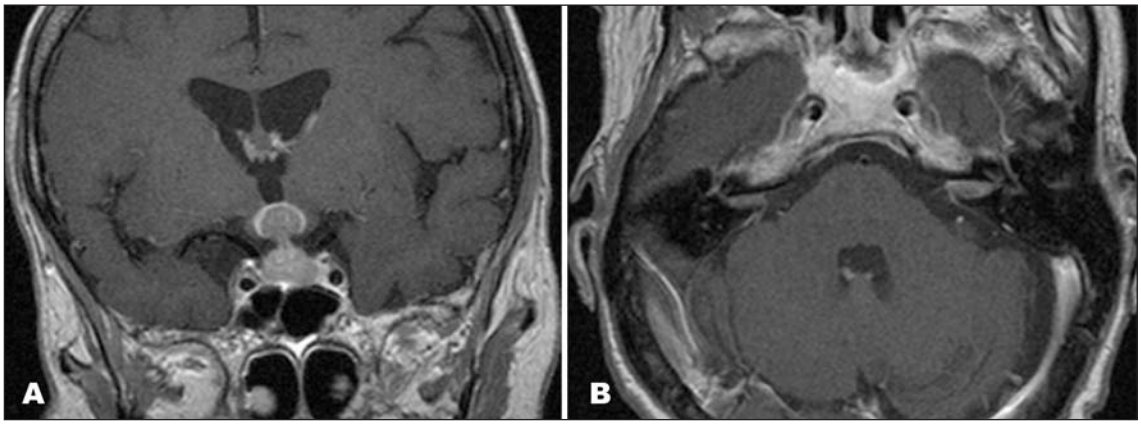

Fig 1. Cranial gadolinium-enhanced T1-weighted MRI. (A) Coronal image showing tumour extension to the hypothalamus. (B) Axial image showing bilateral CPA lesions.

METÁSTASES INCOMUNS DO SISTEMA NERVOSO CENTRAL: MECANISMOS DE DISSEMINAÇÃO E ACHADOS RADIOLÓGICOS

University Hospital, Tübingen, Germany: [1]Department of Neurosurgery; [2]Department of Neuropathology/Brain Research Institute; [3]Department of Neuroradiology; [4] Department of Neurology.

Received 22 January 2008, received in final form 9 June 2008. Accepted 7 July 2008.

Dr. Marcus Andre Acioly – Department of Neurosurgery, University Hospital, Hoppe-Seyler-Strasse 3.D - 72076 Tübingen, Germany. E-mail: marcusacioly @yahoo.com.br

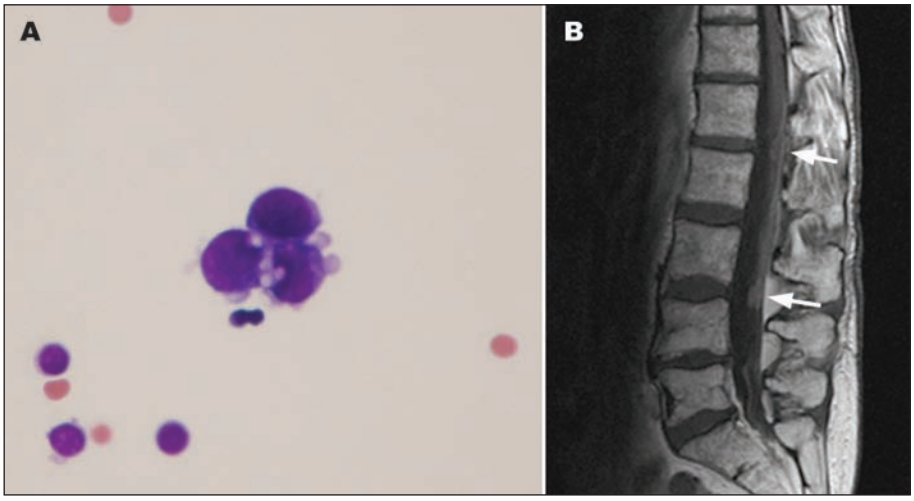

Fig 2. (A) Cytological findings. Photomicrograph showing cerebrospinal fluid sample with a cluster of three atypical cells (Pappenheim stain, original magnification × 400). (B) Spinal gadolinium-enhanced T1-weighted MRI. Sagittal image showing lesions on conus medullaris and cauda equina (white arrows).

ventral of conus medullaris with strong enhancement in contrast images consistent with the diagnosis of LM (Fig 2B). Thoracic computed tomography (CT) scans showed a mass (measuring 1.4 × 1.1 cm) on the right side located within the retrotracheal space and a single increased lymph node (0.7 × 1.0 cm) near the right hilus. The bone scintigraphy revealed metastases exclusively to the skull base. A bronchoscopy was performed showing few nonspecific inflammatory cells.

The immunohistochemical profile of the tumour cells revealed a large-cell neuroendocrine carcinoma (LCNEC) with expression of cytokeratin 7 (CK7), thyroid transcription factor-1 (TTF-1) and synaptophysin with probable origin in the lung. The treatment was conducted with whole brain palliative radiotherapy and chemotherapy.

This publication was authorized by the ethical committee at our institution.

DISCUSSION

Morita and colleagues reported on a patient with PM who developed LM after a transsphenoidal procedure[4]. In another study, Lee and colleagues[2] described a case with bilateral CPA lesions and a suprasellar mass, nonetheless without evidence of intrasellar or spinal involvement. Several combinations of PM and CPA metastases are encountered in literature[3,5] including *postmortem* studies[3]. We described a unique case of metastases of LCNEC of the lung solely to the pituitary, LM and CPA at the time of diagnosis. This is an unusual presentation of central nervous system metastases in a patient affected of LCNEC lung cancer.

Metastases can reach the sella via several routes[3,4]: 1) direct hematogenous spread to the pituitary parenchyma or diaphragma sellae; 2) spread from a hypothalamo-hypophyseal or stalk metastases through the portal vessels; 3) direct extension from the skull base or juxtasellar metastases; and 4) meningeal spread through the suprasellar cistern.

The most common route of spread for LM is hematogenously to cerebrospinal fluid (CSF) via small meningeal vessels[2]. Furthermore, direct extension, transport through valveless venous plexus, escape from subependymal tumours or iatrogenic (postoperative) are also reported[8]. Once in the CSF, tumour cells can also lodge in the sulci, the brain surface or on nerve roots growing into a thin diffuse coating of the meninges or focal nodules that are centered on the pia[2,8], frequently involving regions in the basilar cisterns and cauda equina, where the slow CSF flow and gravity promote deposition of cells[8]. This direct leptomeningeal involvement and/or dissemination through the CSF are the likely mechanism for metastatic CPA lesions[5]. In the presented case, no single mechanism could explain such an unusual presentation. Thus, we could assume that a combination of hematogenous route and CSF spreading is the potential mechanism of dissemination. Due to clinical presentation of pituitary involvement followed by cranial nerve impairment, it is possible that malignant cells reached pituitary hematogenously and spread through CSF to CPA and LM.

Concerning the radiological findings, high-resolution cranial CT and MRI are sensitive for the diagnosis of PM[9]. Rapid growth of a sellar tumour with invasion of the infundibular recess remits to the diagnosis of PM. MRI is the technique of choice for LM[6]. Cranial nerve enhancement on cranial imaging and spinal intradural extramedullary (most frequently seen in cauda equina) enhancing nodules may be considered diagnostic of LM in cancer patients[6]. Infundibular invasion, loss of high-signal intensity of the pituitary posterior lobe, along with cranial nerve and spi-

nal enhancing nodules suggested metastatic disease in the presented case.

Of relevance is the concept of loculated intracranial LM well studied by Lee and colleagues[2] in MRI, a pattern that was also found in our patient imaging. Occasionally, collections of tumour cells can lodge in some portions of the intracranial arachnoidal space, including the ventricles, forming a rather distinct extra-axial lesion. When it occurs without diffuse pattern, it may cause a diagnostic dilemma and delay proper management[2]. The most frequent locations are the suprasellar cistern, the lateral ventricles, the lateral recess of the fourth ventricle, the CPA cistern and the fourth ventricle, where there are abundant CSF collections. Initially the tumour cells infiltrate the leptomeninges as a single layer or as thicker multilayered aggregates[2,8] that are not detectable by radiological imaging. When a mass of tumour accumulates within the subarachnoid spaces cited above, a subarachnoidal extra-axial mass develops (Type A). Further tumour growth can lead to parenchymal infiltration. When the main tumour mass remains extra-axial and without edema, it is classified as type B. Once the tumour extends beyond the pial surface with vasogenic edema, it is considered type C. The tumour can also grow along the cranial nerves, in a dumbbell fashion, mimicking schwannomas in type D. The loculated LM is observed in 80% of the patients and may present in an associated fashion[2].

In conclusion, the association of PM, bilateral CPA/IAC metastases and LM is a rare clinical presentation of central nervous system metastases. The hypothesis of metastatic disease should be remembered in patients with sudden development of cranial nerve palsies, and CPA or sellar region lesions, alone or in combination. Besides, investigation of CSF in such patients should be done routinely to evaluate the presence of concomitant LM.

ACKNOWLEDGMENTS – We are grateful to Mr. Gerd Pfister for his assistance with figure production.

REFERENCES

1. Soffietti R, Ruda R, Mutani R. Management of brain metastases. J Neurol 2002;249:1357-1369.
2. Lee YY, Tien RD, Bruner JM, De Pena CA, Van Tassel P. Loculated intracranial leptomeningeal metastases: CT and MR characteristics. AJNR Am J Neuroradiol 1989;10:1171-1179.
3. Matsuda R, Chiba E, Kawana I, et al. Central diabetes insipidus caused by pituitary metastasis of lung cancer. Intern Med 1995;34:913-918.
4. Morita A, Meyer FB, Laws ER Jr. Symptomatic pituitary metastases. J Neurosurg 1998; 89:69-73.
5. Yuh WT, Mayr-Yuh NA, Koci TM, et al. Metastatic lesions involving the cerebellopontine angle. AJNR Am J Neuroradiol 1993;14:99-106.
6. Chamberlain MC. Neoplastic meningitis. J Clin Oncol 2005;23:3605-3613.
7. Straathof CS, de Bruin HG, Dippel DW, Vecht CJ. The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. J Neurol 1999;246:810-814.
8. Kesari S, Batchelor TT. Leptomeningeal metastases. Neurol Clin 2003;21: 25-66.
9. Komninos J, Vlassopoulou V, Protopapa D, et al. Tumors metastatic to the pituitary gland: case report and literature review. J Clin Endocrinol Metab 2004;89:574-580.