Commentary

In this issue of Journal of Neuroscience in Rural Practice, Kahveci R *et al*,[1] present a rare report of 52-year-old male patient with "Miliary brain metastases from an occult lung Adenocarcinoma " who died within one month following palliative whole brain radiation. I would like to take this opportunity to discuss the recent advances in the management of Miliary brain metastases from Lung Adenocarcinoma.

Miliary brain metastases remain a diagnostic challenge mimicking central nervous system parasitosis. Miliary brain metastases are rare and correspond to CNS

metastases with a hematogenous perivascular spread without intraparenchymal invasion and focal edema.[2, 3] Initial symptoms of the military brain metastases are diverse and may include cerebellar syndrome, motor or sensory defects, cognitive impairment and disorientation followed by unconsciousness.[2, 4] The rising incidence is most likely to be related to several factors including neuro-imaging facilities, an ageing population and better systemic treatment for the primary disease.[5]

The location of the brain metastases is of great interest and probably reflects the biologic dissemination of the metastatic seeds in area of borderline vascular supply. About 85% of brain metastases are found in the cerebral hemispheres, usually at the watershed areas between the middle and posterior cerebral arteries, 10-15% in the cerebellum and 3% in the brain stem. Miliary brain metastases however, are found in the perivascular Virchow-Robin(VR) spaces, subpial space and subcortical white matter and pial sheath plays an important role in their development.[6]

The histological diagnosis of metastases in most cases is adenocarcinoma from a lung primary. Motoi *et al*,[7] have reported that epidermal growth factor receptor (EGFR) mutations are frequent in adenocarcinoma of the papillary type. These mutations are associated with sensitivity to EGFR TKI (tyrosine kinase inhibitors) gefitinib therapy and are usually located at Exon 19 and 21.

The MRI scanning with gadolinium enhancement is the most sensitive imaging modality because of multiplanar imaging capabilities, superior tissue contrast, and elimination of bony artefacts. Iguchi *et al*,[4] describe multiple enhancing miliary nodules in the cerebral cortex, basal ganglia, thalamus, cerebellum, and brainstem after MRI scanning using Gd-DTPA. Ribeiro *et al*,[8] however, recorded the presence of tumoral micro nodules spreading into the perivascular Virchow-robin (VR) spaces, parenchyma, as well as meninges, without constituting a tumoral mass as a characteristic feature of miliary metastases. The authors suggested that MRI using gadolinium was able to reproduce the pathological features of this uncommon pattern of cerebral dissemination in the VR perivascular spaces. CT brain is usually normal in miliary metastases or shows oedema of the brain.

Sekine *et al*,[3] evaluated the correlation between non-small cell lung cancer patients with brain metastases and epidermal growth factor receptor (EGFR) mutations on molecular studies, as well as the radiological findings. They found that patients with Exon 19 deletion have more, multiple small brain tumors with smaller peritumoral brain oedema on MRI scanning. A regular evaluation with Brain MRI was recommended by the authors regardless of the presence of neurologic symptoms in this group of patients.

The management of patients with cerebral metastasis should involve a multi-disciplinary team with contribution from neurosurgeons, clinical/radiation Oncologists, palliative care physicians, specialist nurses and neuro-radiologists. The benefits of loco regional control as a means to potentially prolong overall survival must be balanced against patient quality of life and neurological function.[9]

Given the poor prognosis for patients with brain metastases and median overall survival 7 months,[10] careful selection of suitable patients for treatment of brain metastases is essential to avoid unnecessary risk to those unlikely to benefit from aggressive local treatment. Clinical and functional status, histology and primary disease control and imaging features should all contribute to clinical decision making. Local therapy should depend on the number, the size, and the site of brain metastases.

Sperduto *et al*,[10] report that patients with more than 3 brain metastases and non-small cell lung cancer as a primary have poor prognosis with a median survival of 3-6 months. The patient in this report was 52-year-old with multiple brain metastases and presumably KPS <70 and no information regarding extra cranial metastases would have had a disease specific graded prognostic assessment score (DS GPA score) of 1.0 with a median survival of 3(2.6-3.8) months.

Major areas of investigation should include a) Improving the outcome of whole brain radiation by adding new radio sensitizers; b) Using methods to reduce the potential neurotoxicity of the treatment such as IMRT with avoidance of hippocampus and sub ependymal areas and c) Assessing the possibility of synchronous boost treatment to multiple target areas with whole brain radiation.[11] Accumulation of the knowledge about specific pattern of brain metastases will help approach to individual management. It is recommended that opinion should be taken from centers with more experience in management including diagnostic capabilities so that unnecessary invasive investigations, surgical interventions with increased morbidity and mortality can be avoided.

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References

1. Kahveci R, Gürer B, Kaygusuz G, Sekerci Z. Miliary brain metastases from occult lung adenocarcinoma: Radiologic and histopathologic confirmation. J Neurosci Rural Pract 2012;3:386-9.
2. Rupert AM, Stankoff B, Lavole A, Gounant V, Milleron B. Miliary Brain Metastases in lung cancer. J Clin Oncol 2010;28:e714-6.
3. Sekine A, Kato T, Hagiwara E, Shinohara T, Komagata T, Iwasawa T, *et al*. Metastatic brain tumours from non- small cell lung cancer with EGFR mutations: Distinguishing influence of exon 19 deletions on radiographic features. Lung Cancer 2012;77:64-9.
4. Iguchi Y, Mano K, Goto Y, Nakano T, Nomura F, Shimokata T, *et al*. Miliary brain metastases from adenocarcinoma of the lung: MR imaging findings with clinical and post-mortem histopathologic correlation. Neuroradiology 2007;49:35-9.
5. Soffietti R, Ruda R, Trevisan E. Brain metastases: current management and new developments. Curr Opin Oncol 2008;20:676-84.
6. Ogawa M, Kurahashi K, Ebina A, Kaimori M, Wakabayashi K. Miliary brain metastasis presenting with dementia: Progression pattern of cancer metastases in the cerebral cortex. Neuropathology 2007;27: 390-5.
7. Motoi N, Szoke J, Riely GJ, Seshan VE, Kris MG, Rusch VW, *et al*.Lung adenocarcinoma: Modification of the 2004 WHO mixed subtype to include major histologic subtype suggests correlations between papillary and micro papillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. Am J Surg Pathol 2008;32:810-27.
8. Ribeiro HB, De Paiva TF, Mamprin GP, Gorzoni ML, Rocha AJ, Lancellotti CL. Carcinomatous encephalitis as clinical presentation of Occult Lung Adenocarcinoma. Arq Neuropsiquiatr 2007;65:841-4.
9. Jenkinson MD, Haylock B, Shenoy A, Husband D, Javadpour M. Management of Cerebral metastasis: Evidence based approach for surgery, stereotactic radiosurgery and Radiotherapy. Euro J Cancer 2011;47: 649-55.
10. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, *et al*. Diagnosis –specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: A multi-institutional analysis of 4259 patients. Int J Radiat Oncol Biol Phys 2010;77:655-61.
11. Rodrigues G, Eppinga W, Lagerwaard F, de Haan P, Haasbeek C, Perera F, *et al*. A pooled analysis of arc-based image guided simultaneous integrated boost radiation therapy for oligometastatic brain metastases. Radiother Oncol 2012;102:180-6.

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