Miliary Brain Metastases

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1 Introduction

Postmortem examinations (Ogawa et al., 2007) showed that the brain metastasis covers approximately 12-25% of the cancer patients. Metastasis is being the most common brain tumor; where up to 40% of all the brain neoplasms are developed from metastatic origin (Nemzek et al., 1993). About 65-86% of all metastatic brain tumors are multiple, but almost always their number is less than five (Weisberg, 1979).

Most brain metastases are macroscopic parenchymal mass lesions with surrounding edema, and occur at the gray-white matter junction (Weisberg, 1979). Leptomeningeal carcinomatosis resulting from diffuse infiltration in the subarachnoid space also occurs in about 3% of the patients with lung, breast or gastric carcinomas (Ogawa et al., 2007). On the other hand, there is an extremely rare form of brain metastases which are characterized by the presence of tumoral spreading into the perivascular Virchow-Robin spaces, parenchyma, and as well as meninges. Several terms were proposed to describe this rare form of the brain metastasis, such as “miliary carcinoma”, miliary brain metastases”, “metastatic meningoencephalic carcinomatosis without tunefaction”. In 1951, Madow and Alpers, proposed the expression “carcinomatosis encephalitis” as the most adequate term. We, the authors of this chapter preferred to use the term “miliary brain metastases” because this term referred in the most recent publication and accepted by us as it defines the condition with clear terminology.

Miliary brain metastases are extremely rare conditions with poor prognosis. To our knowledge, in the English literature, there had been only 25 cases reported till today (Ara Callizo et al., 1989; Bhushan, 1997; Bugarho et al., 2005; Falk et al., 2012; Floeter et al., 1987; Fukuda et al., 1988; Iguchi et al., 2007; Inomata et al., 2012; Kahveci et al., 2012; Madow and Alpers, 1951; Mochizuki et al., 2012; Nakamura et al., 2001; Nemzek et al., 1993; Ogawa et al., 2007; Olsen et al., 1987; Ribeiro et al., 2007; Rivas et al., 2005; Ruppert et al., 2010; Shirai et al., 1997; Wong et al., 2007; Yamazaki et al., 1993). The aim of this chapter is to provide detailed information on this condition and review the recent literature.

2 Clinical Manifestations

Clinical manifestations of the miliary brain metastases vary widely. Clinically, miliary brain metastases are usually silent and the symptoms differ from patient to patient. Despite this silent clinical presentation some may present with various signs and symptoms of the central nervous system at the onset. The patients who were suffering from miliary brain metastases frequently demonstrate an organic mental syndrome, dementia in a subacute fashion, hemiparesis and convulsions (Ogawa et al., 2007; Rivas et al., 2005; Shirai et al., 1997). Early onset, rapidly progressing dementia is always prominent in the clinical course at an early point and may be a warning sign of this pathology.

However, neurological findings can strongly be minimal in majority of patients with miliary brain metastases. This indistinct clinical course may be due to weak edematous effect of the masses (Bhushan, 1997). Also speech abnormalities, gait disturbance can be the initial symptoms of miliary brain metastases. On the other hand, some patients do not have any neurological symptoms and were incidentally diagnosed during routine follow-up radiologic studies (Kahveci et al., 2012).
3 Radiological Diagnosis

Plain skull x-rays and brain computed tomography (CT) have very limited diagnostic value in miliary brain metastases. In some calcified lesions, CT can easily detect multiple calcified lesions in the central nervous system (Ara Callizo et al., 1989; Fukuda et al., 1988; Yamazaki et al., 1993). Furthermore, brain CT scan with contrast enhancement may demonstrate numerous tiny lesions (Floeter et al., 1987; Olsen et al., 1987). Also, the brain edema caused by multiple metastatic lesions can be evident in CT (Figure 1). Hydrocephalus that may result from meningeal and periventricular damage alters cerebrospinal fluid circulation can easily be detected by non-contrast CT.

Figure 1: Brain CT of a patient with miliary brain metastases revealing the edematous regions
Prior to magnetic resonance imaging (MRI), delayed double-dose contrast enhanced CT scans were consulted to be the optimal method to evaluate metastatic disease of the central nervous system (Shalen et al., 1981). Nowadays, MRI has proven to be more sensitive than CT in detection of any central nervous system pathology, and contrast enhanced MRI is the test of choice to evaluate metastatic disease of the brain and spinal cord (Brant-Zawadzki et al., 1984). Magnetic resonance imaging with gadolinium enhancement was further improved lesion detection especially for metastatic disease (Hesselink and Press, 1988; Sze et al., 1990).

Miliary metastasis are seen as nodular, tiny, multiple lesions with perivascular spreading; showing iso-to low intensity on T1 and high intensity signals on T2-weighted sequences of MRI and may present a nodular or peripheral (ring-like) contrast enhancement following gadolinium injection (Iguchi et al., 2007) (Figure 2). In some cases in which brain MRI were performed did not show any abnormalities (McGuigan et al., 2005; Nakamura et al., 2001; Ogawa et al., 2007; Rivas et al., 2005). Furthermore some miliary brain metastases did not enhance with contrast media (McGuigan et al., 2005; Nakamura et al., 2001; Nemzek et al., 1993; Yamazaki et al., 1993). It is speculated that the contrast-enhanced MRI could fail to delineate the metastatic lesions because the blood-brain barrier remains intact at the early stages of the clinical course (Inomata et al., 2012; Nemzek et al., 1993; Ogawa et al., 2007).

![Figure 2: Gadolinium-enhanced axial, and coronal T1-weighted MRI section revealed multiple millimetric nodular lesions with homogenous enhancement in both cerebral hemispheres and the brainstem](image)

On the other hand, a large number of infectious and non-infectious diseases such as miliary tuberculosis, neurocysticercosis or toxoplasmosis, can cause multiple enhancing lesions in the brain, and mimic miliary brain metastases (Garg and Sinha, 2010). So, differential diagnosis with proper imaging techniques is mandatory.

Proton magnetic resonance spectroscopy (MRS) is a potent instrument to analyze tissue metabolism noninvasively. It reflects alterations of the intracellular metabolite concentrations such as choline (Cho), creatine (Cr), N-acetylaspartate (NAA), lipids and lactate on pathological tissues (Hollingworth et
This technique may help to distinguish pathological tissue from normal brain tissue in means of differences of the intracellular metabolites (Hollingworth et al., 2006). On proton MRS imaging, non-neoplastic lesions such as cerebral infarctions and brain abscess have noticeable decreases in Cho, Cr and NAA levels. While tumors have generally elevated Cho and decreased levels of Cr and NAA, it had been shown that intracranial metastatic lesions showed strong elevations in levels of lipids. This elevation of the levels of lipids in metastatic tumors was significantly higher than any brain lesion except tuberculosis, abscess and toxoplasmosis (Möller-Hartmann et al., 2002). On the other hand Cho, Cr and NAA levels were shown to decrease in tuberculosis, abscess and toxoplasmosis may help to distinguish infectious pathologies from miliary brain metastases (Kahveci et al., 2012) (Figure 3). Kahveci et al. (2012) reported that Cho levels were increased with elevated Cho/NAA and decreased NAA/Cr ratios on proton MRS in a patient with miliary brain metastases. Proton MRS may contribute to make differential diagnosis of the miliary enhanced lesions of the central nervous system.

Figure 3: Proton MRS showed an increase in choline peak

4 Pathological Features

Parenchymal cerebral metastases are usually characterized by nodules or single masses in white and gray matter junction, as a result of hematogenic dissemination. It is estimated that up to 30% of patients with solid cancer have cerebral metastasis at the time of death (Ribeiro et al., 2007). Miliary metastatic pattern
describes the occurrence of several disseminated nodules in the brain parenchyma. It is quite uncommon and invades the perivascular Virchow-Robin spaces, parenchyma and meninges (Ribeiro et al., 2007).

Since the clinical features are frequently non-specific and radiological studies often fail to make a correct diagnosis, neuropathological examination is essential to establish the diagnosis. In histopathologically proved cases, the most common site of metastasis to the brain in miliary brain metastases was the lung and the most common pathology was adenocarcinoma (Table 1). Although in macroscopic examination the gross evidence of tumor involvement is usually minimal. Light microscopic examination generally reveals outnumbered foci of metastases with a perivascular distribution (Figure 4).

The metastatic cascade, whereby cancer cells escape from the primary tumor site, invade surrounding tissue, intravasate into the bloodstream or lymphatics, and arrest, extravasate, survive and proliferate within a secondary site is an inherently inefficient process. Certain tumor types demonstrate an organ-specific pattern of spread (Talmadge and Fidler, 2010). Once metastatic cancer cells enter the brain circulation, they might arrest in sites of slow flow within the capillary bed at vascular branch points. The arrested cancer cells encounter brain vascular endothelial cells, which seems to promote metastatic tumor cell growth and invasion (Kienast et al., 2010)

Kienast et al. (2010) used multiphoton laser scanning microscopy and a mouse cranial window model to follow in real time brain metastasis formation from both lung cancer and melanoma cell lines. After extravasation, there was a persistent correlation between tumor cells with micro-vessels, and either vessel co-option (with melanoma) or angiogenesis (with lung carcinoma). Previous studies showed a similar association between metastasizing tumor cells and blood vessels.

Recently, the importance of cellular adhesion molecules, which attach carcinoma cells to vascular endothelium, has been identified in metastatic processes. Ogawa et al. (2007), reported that in a miliary brain metastases case adhesion molecules were expressed abnormally and caused to trap carcinoma cells in the vessels. It has been hypothesized that perivascular pial sheath (adventitia) plays an important role for the development of the miliary brain metastases.

5 Differential Diagnosis

In the differential diagnosis of the miliary brain metastases, the diagnosis of paraneoplastic encephalopathy, vascular dementia, infectious encephalitis, and adverse effects of chemotherapy must be considered. The main MRI differential diagnosis is meningitis by Criptococcus sp because of the distribution pattern of the lesions in the perivascular spaces of Virchow-Robin in the diencephalon, centrum semiovale, leptomeninges, and the presence of hydrocephalus. But cerebrospinal fluid analysis of the miliary brain metastases patients is generally non-specific (Ribeiro et al., 2007).

A variety of infective and non-infective etiologies can produce multiple ring-like enhancing lesions of the brain. It is a diagnostic challenge to make a correct diagnosis in such situations (el-Sonbaty et al., 1995; Garg et al., 2000; 2008; Oncul et al., 2005; Tosomeen et al., 1998). Also it is observed that infectious pathology is the most common etiology in patients with multiple ring enhancing lesions of the brain (Garg et al., 2008). Of these infectious etiologies, tuberculosis and neurocysticercosis are the most common infections. Furthermore, metastatic etiology is the commonest of the non-infectious etiology (el-Sonbaty et al., 1995; Garg et al., 2000; 2008; Oncul et al., 2005; Tosomeen et al., 1998).
<table>
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**Table**: Presented cases of miliary metastases in the English literature.
Figure 4: Pathologic specimen of cerebral biopsy of a patient with miliary brain metastases originating from lung adenocarcinoma. Microscopic examination with H and E staining revealed infiltrating glial tissue by neoplastic cells (original magnification \( \times 4 \)) (a), Microscopic examination with H and E staining revealed solid nests of atypical cells having pleomorphic nuclei and eosinophilic cytoplasm (original magnification \( \times 40 \)) (b), Immunohistochemical examination of tissue sections showed neoplastic cells cytoplasms staining positively for cytokeratin 7, and nuclear TTF-1 expression of neoplastic cells (c, d)

In HIV-infected patients, infections like toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy and certain neoplastic disease must be considered in the differential diagnosis (Porter and Sande, 1992; Thurnher et al., 2001). Even so, no possible cause can be determined of an approximately 40% of patients with multiple ring enhancing brain lesions (Garg et al., 2008).

As the most common presenting symptom of the miliary brain metastases is progressive dementia, a precise diagnosis is mandatory for clinical assessment and treatment. Dementia with Lewy bodies, Crutzfeldt-Jakop disease or Alzheimer Disease must be considered in differential diagnosis of miliary brain metastases.
6 Treatment

Prognosis of miliary brain metastases is poor without a significant effect attributed to chemotherapy or radiotherapy. When the paucity of the cases is considered, it is natural that there is not a standard treatment regimen for miliary brain metastases.

Whole brain radiation at 300 cGy per fraction X 10 fractions is the standard treatment for patients with brain metastases, particularly for those patients with poor performance status.

Gefitinib, a small molecule tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), has significant antitumor activity in advanced non-small-cell lung carcinoma. Gefitinib achieves dramatic radiologic and clinical regression in 10% of patients with non-small-cell lung carcinoma (Kris et al., 2003). Partial response with gefitinib is associated with sensitivity mutation of EGFR. Epidermal growth factor receptor tyrosine kinase inhibitor treatment may be thought to be having some beneficial effects in treating miliary brain metastases (Wong et al., 2007). The authors think that combination of whole brain radiation and gefitinib may be the only treatment of miliary brain metastases to our recent knowledge.

7 Outcome

Miliary brain metastasis is a seldom reported condition. To the best of our knowledge only 25 cases had been reported in English literature until mid-2013s (Ara Callizo et al., 1989; Bhushan, 1997; Bugalho et al., 2005; Falk et al., 2012; Floeter et al., 1987; Fukuda et al., 1988; Iguchi et al., 2007; Inomata et al., 2012; Kahveci et al., 2012; Madow and Alpers, 1951; Mochizuki et al., 2012; Nakamura et al., 2001; Nemzek et al., 1993; Ogawa et al., 2007; Olsen et al., 1987; Ribeiro et al., 2007; Rivas et al., 2005; Ruppert et al., 2010; Shirai et al., 1997; Wong et al., 2007; Yamazaki et al., 1993) (Table). Prognosis of this uncommon condition is poor. The overall survival was reported to be as high as 24 months and as low as 14 days from the initial diagnosis. All reported cases of the miliary brain metastases were summarized in the Table.

8 Conclusion

Miliary brain metastases are somehow uncommon pattern of cerebral neoplastic metastasis which are difficult to diagnose the condition. This poor-prognosed disease must be considered in the differential diagnosis of progressive dementia and multiple enhancing lesions of the central nervous system.

References


