Long delay cerebral metastases

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Abstract

In adults, cerebral metastases are the most common intracranial tumors, and their incidence has been rising in the last decades. The median interval between the diagnosis of the primary cancer and the detection of brain metastasis is relatively short, generally around one or two years.

This study made a selection of six cases with a more than five years delay until the diagnosis of a cerebral metastases, from over 246 patients with brain metastases, admitted in our department, between 2006-2010. All six patients underwent surgery for their primary neoplasm, prior to neurosurgical diagnosis and treatment.

We found 6 patients, having renal, breast or lung cancer, in which the delay between diagnosis of the primary tumor and that of the brain metastases started from 5 years and reached even 18 years.

In all cases, this delay was longer than the median interval found in the most neurosurgical series. Very probably the immune system plays a major role in controlling recurrences and new metastases in the nervous system

Keywords: cancer, cerebral metastases, long delay cerebral metastases, prognostic factors

Introduction

Brain metastases represent a significant source of morbidity and mortality in patients with systemic cancer. Nowadays, cancer patients have a longer life expectancy because of the important advances in cancer diagnosis and therapy.

The incidence of brain metastases is difficult to determine with precision. In earlier neurosurgical series the overall incidence of cerebral metastases was 20%-30% for all patients with systemic cancer (20). Estimates based on more recent series and autopsy studies show a much higher incidence of brain metastases, with incidences varying between 8.3 to 11.1 per 100.000 individuals (12). Approximately 40% of intracranial neoplasms are metastatic (10, 23). These estimates place brain metastases first in frequency among all intracranial tumors, before intracranial glioma and meningioma (18, 21, 27).

The histological type of the primary tumor appears to be the major factor of the frequency and pattern of intracranial spread. Multiple, large autopsies series suggest that, in order of decreasing frequency, lung, breast, melanoma, renal and colon cancer are the most common primary tumors that metastasize to brain (10, 12, 21, 27). Primary lung tumors account for 30% to 60% of all brain metastasis cases (13, 15). Breast cancer ranks second, contributing 10% to 30% (13, 15) of all brain metastases among women (21), and renal cancer has a frequency of 11% (2, 23). When the ability of a primary

tumor to spread to the brain is considered, melanoma ranks first followed by lung and breast cancers (1, 16, 19).

The median interval between the diagnosis of the primary cancer and the detection of brain metastasis is relatively short, generally around one or two years (4, 24). This study made a selection of six cases with a more than five years delay.

Material and methods

We made a retrospective study over 246 patients with brain metastases, which were admitted and operated in our department, the Neurosurgery Clinic of the Institute of Cerebrovascular Diseases "Prof. Dr. V. Voiculescu" – Bucharest, between 2006-2010. In this series, we found 6 patients, having renal, breast or lung cancer, in which the delay between diagnosis of the primary tumor and that of the brain metastases was longer than the median interval found in the most neurosurgical series. The time interval was measured between the month recorded from the primary cancer surgery and that for the cerebral tumor surgery. All patients underwent surgery for their primary neoplasm, prior to the diagnosis of the intracranial tumor. We performed a radical surgical treatment with removal of the entire cerebral metastases, proved by postoperative contrast CT scans.

Ilustrative case

Patient C.L., female, 69 years old, was admitted in our clinic in October 2010. She complained of persistent headache and balance disorders. Neurological examination revealed a right pyramidal syndrome and motor aphasia. Contrast cerebral CT scan showed a large, relatively well-circumscribed tumor, located in the left frontal lobe, with nonhomogenous contrast enhancement and important peritumoral edema.

From her previous pathological history we noted that in 1992 she underwent surgery for a left breast carcinoma when a left mastectomy was achieved. The histological exam showed an infiltrating ductal carcinoma. Postoperatory, the patient underwent radiation therapy and followed a chemotherapy protocole. In 1998, she was operated for a right breast mastosis, when a Pattey-type mastectomy was performed.

The patient underwent surgery for her left frontal lobe tumor. We performed a frontal craniectomy, located on the lesion, and achieved a total gross removal of a 6 cm. in diameter tumor, with central necrosis. The histological exam revealed a metastasis from a breast ductal carcinoma. The patient followed postoperative radiation therapy with a total radiation dose of 60Gy.

The last clinical examination, performed 12 months after surgery, proved a good general and neurological health condition of the patient. Control cerebral CT scan showed absence of any tumor recurrences.

The interval of time between the diagnosis of the breast cancer and that of cerebral metastasis was18 years.

Results

As we mentioned, our selection criteria was a long delay between the diagnosis of the cancer and the detection of the cerebral metastases. Two patients with renal cancer had the same 7 years delay between the diagnosis of the cancer and that of cerebral metastasis. Two patients, operated for a breast cancer, had a delay of 8, respectively 18 years.

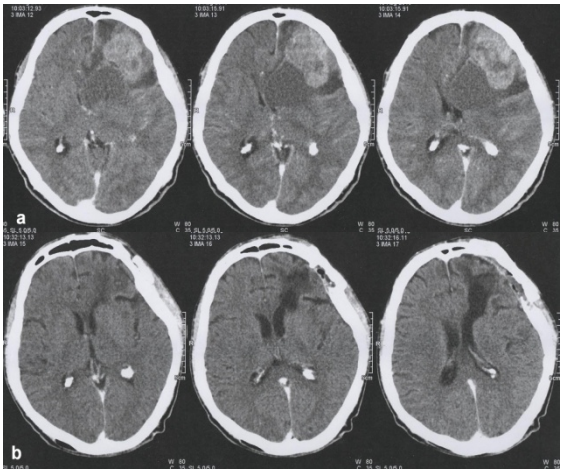

Figure 1 A Preoperative contrast cerebral CT scan showing a large left frontal tumor, with important peritumoral edema and shifting of the midline; **B** Postoperative contrast CT scan (12 months after surgery) showing a total gross resection of the frontal metastases and lack of local recurrence.

One patient with a laryngian neoplasm, than operated on for a lung metastasis, showed two cerebral tumors with a delay of 7 years from the diagnosis of his cancer. The last patient, operated for a lung cancer, presented a cerebral metastasis after 5 years from the diagnosis of his lung neoplasm.

Statistic dates	**Case1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Sex	F	M	F	F	M	M
Age	57	57	50	69	54	50
Primary cancer (date of surgery)	Renal cancer (02. 2002)	Renal cancer (10.2002)	Breast cancer (12.2000)	Breast cancer (03.1992)	Laryngian cancer (06.2002)	Lung cancer (04.200 5)
Cerebral metastasis surgery	11.2009	10.2009	10.2008	10.2010	05.2009	07.2010
No. of cerebral metastases	1	1	1	1	2	1
Length of time interval (years)	7	7	8	18	7	5
Postoperative follow-up (months)	19	14	26	12	10	10
Systemic metastases	No	Yes (bone metastasis; 02.2007)	No	No	Yes (lung metastases; 09.2007)	No
Postoperative cerebral radiotherapy/ systemic chemotherapy	Yes/yes	Yes/no	No/no	Yes/no	Yes/yes	Yes/no

Discussion

The histology of the primary tumor appears to be the major dictator of the frequency and pattern of intracranial extension. Virtually any type of cancer has the ability to produce brain metastases. Half of the patients with brain metastases in autopsy series had lung or breast cancer as the primary tumor (14, 22).

The process of tumor metastasis is highly selective and consists of a series of sequential, interrelated steps. To produce clinically relevant lesions, metastatic cells must complete all steps of this process. More than a century ago, Stephen Paget questioned whether the organ distribution

of metastases produced by different human neoplasms was due to chance. He analyzed more than 1.000 autopsy records of women with breast cancer. His research documented a nonrandom pattern of metastasis, suggesting that the process was not due to chance but rather, that certain tumor cells (the "seed") had a specific affinity for the milieu of certain organs (the "soil"); metastases resulted only when the seed and soil were compatible (17). Some 40 years later, J. Ewing challenged Paget's "seed and soil" theory and hypothesized that metastatic dissemination occurs by purely mechanical factors that are a result of the anatomical structure of the vascular system (7). These explanations have been evoked separately or together to explain the metastatic site preference of certain types of neoplasms. It is proved today, that only certain cancer cell lines (cell clones) could cover all the stages of the metastatic cascade process (8). Also, the development of a metastasis in certain area of the central nervous system is specific to selected clone cells depending on the histology of the primary tumor (8, 9).

In our study were reviewed brain metsteses from lung, breast and renal cancers. Therefore, we selected few informations about these neoplasms.

Primary lung tumors account for 30% to 60% of all cases of brain metastasis (14, 16). Lung cancer ranks second among all cancers in its tendency to invade the brain (5,14).

Of patients with lung cancer, 18% to 65% will develop brain metastases and the specific histology of the primary lung tumor is very important in determining metastatic frequency (5, 22). There are five histological subtypes of lung cancer: small cell lung cancer, squamous cell carcinoma, adenocarcinoma, large cell cancer and carcinoid tumor.

Indeed, more than 40% of patients with small cell lung cancer and lung adenocarcinoma have brain metastases in clinical series or at autopsy (5). It represents more than twice the rate of metastasis found with the other types of lung cancer such as squamous cell carcinoma (5,22).

In a clinical series of patients with brain metastases from lung cancer in Turkey (22), adenocarcinoma, epidermoid carcinoma, and small cell carcinoma gave rise to 84% of these metastatic lesions. In a clinical series of patients presenting with brain metastases as the first sign of their malignancy at the Gustave-Roussy Institute, France, 44% had adenocarcinoma and 30% had undifferentiated or small cell lung carcinoma, compared with only 12% who had squamous cell lung carcinoma (12).

The median interval between the diagnosis of lung cancer and the detection of brain metastasis falls between two and nine months and is shorter than is seen for other cancers (16, 22). In our study, the delay was a few times longer, 5 years for the lung tumor and respectively 7 years for the laryngian one. For the lung neoplasm the histological result was adenocarcinoma.

Primary breast cancer ranks second to lung cancer as the most frequently occurring primary tumor in patients with brain metastases. Among women, breast cancer is the most common cause of brain metastasis, resulting in 5% to 30% of all brain metastases (25, 26). Breast cancer ranks third, after lung cancer and melanoma, among primary cancers in its tendency to metastasize to the brain, and approximately 20% to 30% of patients with breast cancer will develop a brain metastasis (21, 26).

Brain metastases from breast cancer typically occur late in the course of the disease, between 2 and 3.3 years after diagnosis (16,22). In our study, both patients had a breast ductal adenocarcinoma metastasis, and had an 8 respectively 18 years delay.

Primary renal cancer frequently metastasizes to the brain. In an autopsy series, the frequency of brain metastases in renal adenocarcinoma patients was 11% (2, 23). In a clinical series by Harada et al. 5.5% of 325 patients who had renal cell carcinoma that was treated at Osaka University Hospital from 1957 to 1993, developed brain metastases (11).

The median interval between diagnosis of renal cancer and brain metastasis caused by it ranges from 1 year to 2.3 years (3, 11). In our study both patients showed a same 7 years time interval and had clear cell carcinoma metastases on histological exams.

Long delay between diagnosis of the primary tumor and the development of the brain metastasis represents, in most series, a favorable prognostic factor associated with a longer median survival (6, 19, 24). Other favorable prognostic factors are: primary cancer under control, absence of extracranial metastases, Karnofsky score > 70, age under 60, female gender and, of course, gross total resection of the metastasis.

The median patient survival time after surgical excision of a single brain metastasis is 9 to 14 months, depending on such factors as the type of primary cancer, length of time between diagnosis of the primary tumor and diagnosis of brain metastasis, neurological performance status, and presence or absence of systemic disease (6, 19).

Contrary to classical teaching, recent reports demonstrated that surgery improves the survival of patients with multiple brain metastases, so long as all the lesions can be removed. These good results are achieved only in patients with two or three metastases and it must be emphasized that for resection to be beneficial, all the lesions must be resected (4).

Conclusions

Generally, the longest survival intervals were recorded in patients operated on for breast, renal and lung cerebral metastases, and the shortest intervals in patients with melanoma metastasis. All our six patients demonstrated at their last control registered in our clinic records, a good general and neurological performance status. None of them presented cerebral recurrences at the control CT scan examination. In all cases we performed a radical surgical treatment with removal of the entire tumoral mass. Because a long interval between the diagnosis of the primary cancer and that of cerebral metastases plays an important role in obtaining a longer patient survival an aggressive surgical approach should be encouraged in these selected cases.

In the articles that we had reviewed we did not find a clear explanation of this long delay in metastatic process. Very probably the immune system plays a major role in controlling recurrences and new metastases also in the nervous system. Conceivably in such cases (as, probably, in ours), some neoplastic nidi were kept dormant by an uncertain balance between the neoplastic aggressiveness and the defensive factors of the organism. As long as this balance operated, the metastases were prevented from developing enough to give rise to clinical symptoms and hence detection.

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