Management of unknown origin cerebral metastases

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Abstract

Aim: The present study attempts to determine the steps for obtaining the etiological diagnosis of brain metastases with unknown origin.

Material and methods: A total of 190 patients with brain metastases diagnosed in the Department of Neurosurgery in Emergency Hospital "N. Oblu" Iasi between 2007-2010 were included in this study. The clinical characteristics and pathological features were analyzed.

Results: There were 102 males and 88 females with a M:F ratio of 1.15:1. The median age of patients was 47.07 years (range 31-77 years). Females patients were older (mean age 57.21 years) than males patients (49.15 years). 154 patients (81.05%) had single brain metastasis, and 36 patients (18.95%) had more than two. The lesions were supratentorial in 142 patients (74.73%), infratentorial in 18 (9.47%), and both infratentorial and supratentorial in 30 patients (15.78%). Surgical treatment involved complete resection in 47.9% of cases, subtotal resection in 26.8%, and biopsy alone in the remainder (25.3%). Brain metastases originating in lung cancer represented the most common type (47.39%), followed by those from breast cancer (19.79%), then those from skin (melanoma) (8.33%), genitourinary carcinoma (6.30%), and gastrointestinal carcinoma (2.62%). In 16.31% of cases, the primary tumor remained unknown, despite extensive investigation.

Conclusion: The primary cancer leading to brain metastases can be detected either by obtaining a sample of tumoral tissue through a neurosurgical operation on the intracerebral tumor (total ablation or stereotactic biopsy) with histopathological examination, or by additional tests of the whole body. Taken into consideration the results of our own study, the management of the patients with brain metastases should include a thoracic CT scan or anteroposterior and lateral chest X-ray, clinical breast examination and mammography, abdominal ultrasound exploration, and skin, kidney and prostate examination. With the most sophisticated methods of diagnosis in approximately 16% of cases the origin of metastasis remains unknown. The identification of the primary site by the neuropathologist after stereotactic biopsy would clearly be advantageous.

Keywords: brain metastases, cerebral cancer treatment, stereotactic biopsy, tumoral type

Of all intracranial neoplasms, brain metastases represent 13.5-41% of all cases (4). Although most of these metastatic brain tumors can have a known primary site such as lung or breast carcinoma, there remaines a number of cases in which a thorough search failed to identify the primary site even at autopsy (26). Brain metastases of unknown origin become more frequently a problem for neurosurgeons as the expansion of computed tomograph (CT) network makes possible a cranio - cerebral exploration for any patient with neurological symptoms (20).

Intraparenchymal metastases are usually well-defined round masses, often with nodular or ring enhancement (due to central necrosis) and with peritumoral edema. If multiple masses are seen, the diagnosis is much easier (4).

Magnetic resonance imaging (MRI) with gadolinium is more sensitive than computed tomography for confirming the presence of brain metastases (18). It reveals single brain metastases in 1/3 of cases and multiple tumors in the remainders (28).

Thus, for patients complaining of indistinctive symptoms such as headache, dizziness, nausea or vomiting, a CT scan can provide the surprising discovery of a brain tumor which proves to be a metastasis after completion of exploration. From a clinically point of view, such a brain tumor can manifest through a major inaugural neurological symptom, such as localized or generalized seizures. The third situation is the discovery of such a brain tumor through a CT screening. In all these cases the patients did not complain of any other organ symptoms and they haven't been registered with a cancer (1).

This report details the experience at the Neurosurgery Department of "Prof. dr. N. Oblu" Clinic Emergency Hospital, Iasi, in the management of patients in whom the only evidence of malignancy at presentation was the metastatic disease of the brain. The aim of the present study was to evaluate this patient group in order to develop guidelines for further diagnostic and treatment procedures.

Material and method

Between 2007-2010, 190 consecutive patients with brain metastases, but with unknown primary site and no other evidence of metastases were treated in the Neurosurgery Department of "Prof. dr. N. Oblu" Clinic Emergency Hospital, Iasi.

All the patients were admitted in the hospital due to a previous general and neurological screening. Imaging investigation (CT or MRI) confirmed the diagnosis of a brain metastasis and gave information about their number. Surgical removals or stereotactic biopsies were carried out in all of them.

A search for the primary site of the tumor was made in each case during hospital stay. These included detailed history taking, thorough physical examination, routine chest radiographs, urine and blood investigations. Also, tissue samples taken through surgical removal or stereotactic biopsy have been processed in the Department of Pathology of the same hospital using the standard histopathological technique. Microscopical examinations have been done in all cases in order to determine the tumoral type of cerebral neoplasia and to identify the primary cancer due to some histopathological similarity between metastases and their "parental" malignancies.

Results

Personal experience in the Neurosurgery Service of the Hospital "N. Oblu" Iasi showed that in a three years period of time have been diagnosed 190 patients with cerebral metastasis. There were 102 males and 88 females with a M:F ratio of 1.15:1. The mean age of entire population was 47.07 years with a range of 31 – 77 years. Females ranged in age from 49 to 77 years with a mean of 57.21 years, whereas males had a mean age of 49.15 years with a range of 31 to 75 years. The highest incidence of brain metastases was in the sixth and seventh decades of life (Table 1).

Brain CT was performed in 135 patients (71.05%), MRI in 36 patients (18.94%), and CT plus MRI in 19 (10%). 154 patients (81.05%) had single brain metastasis, and 36 patients (18.95%) had more than two. The lesions were supratentorial in 142 patients (74.73%), infratentorial in 18 (9.47%), and both infratentorial and supratentorial in 30 patients (15.78%).

Surgical treatment involved complete resection in 47.9% of cases, subtotal resection in 26.8%, and biopsy alone in the remainder (25.3%).

Primary malignancies were diagnosed after surgical removal. Taken all cases together, brain metastases originating in lung cancer represented the most common type (47.39%) (Figures 1 and 2), followed by those from breast cancer (19.79%), then those from skin (melanoma) (8.33%) (Figure 3), genitourinary carcinoma (6.30%), and gastrointestinal carcinoma (2.62%). In 16.31% of cases, the primary tumor remained unknown, despite extensive investigation (Table 2).

TABLE 1

Brain metastases frequency by patients' age

Age (years)	30-39	40-49	50-59	60-69	70-79	Total
No. of cases	12	23	65	74	16	190
Percentage	6.31%	11.97%	**34.21%**	**38.54%**	8.33%	100%

TABLE 2

Brain metastases frequency by primary cancer site

Organ of origin	**Lung**	**Breast**	**Skin**	**Colo-rectum**	**Stomach**	**Testicul**	**Prostate**	**Kidney**	**Unknown**
No. of cases	91	38	16	3	2	3	7	2	31
Per –centage (%)	**47.39**	19.79	8.33	1.57	1.05	1.57	3.68	1.05	16.31

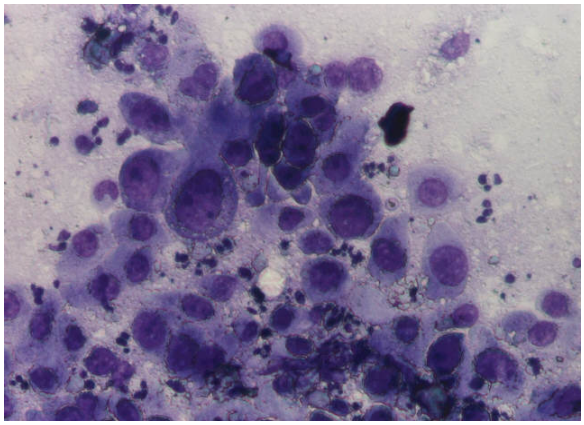

Figure 1 Smear of a brain metastasis originating in an epidermoid squamocelullar carcinoma of the lung (toluidine blue, 10x20)

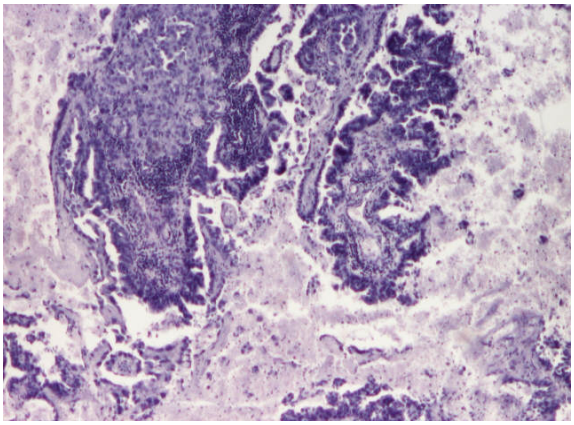

Figure 2 Microphotograph of the microscopic features of a brain metastasis originating in a papillary carcinoma of the lung (Hematoxylin&Eosin, 10x10)

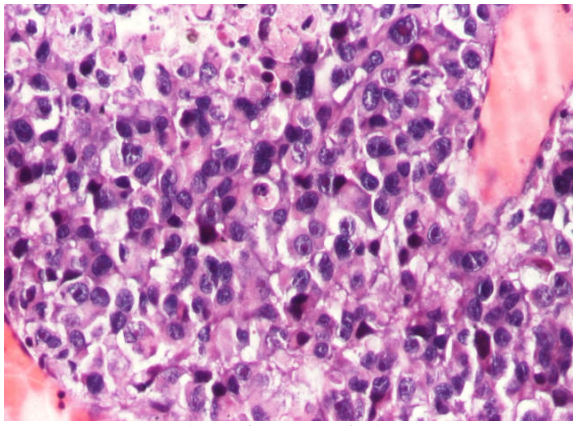

Figure 3 Histologic features of a brain metastasis from an epithelioid melanoma of skin (Hematoxylin-eosin, 10x20)

Discussion

In 33-66% of patients, solitary cerebral metastasis give rise to the symptoms preceding even the primary lesion. Furthermore, in a significant number of cases the primary malignancy can not be diagnosed during life and in some cases remains unknown even at autopsy (26). The incidence and primary source of brain metastases vary with patient age. The highest incidence of brain metastases (over 60%) is observed in patients 50 to 80 years old. In our study, the highest incidence of all cerebral metastases (72.75%) appeared in a younger group of patients (50-69 years) and the peak incidence (38.56%) was encountered in the sixth decade (50-59 years).

In the present research, there is no predilection of brain metastases for males or females. The histology of the primary cancer 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. However, in decreasing relative frequency, lung cancer, breast cancer, melanoma, renal cancer, and colon cancer account for most brain metastases (27).

In 1889, an English pathologist, Stephen Paget, analysed the organ distribution of metastases produced by different human neoplasms in order to determine the pattern of metastasis process. He concluded that certain tumor cells (the "seed") had a specific affinity for the milieu of certain organs (the "soil") because metastases resulted only when the seed and soil were compatible (9). It is consider that 30% to 60% of brain metastases originate from lung cancer (12). 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 (7). Melanoma ranks third among primary tumors giving rise to brain metastases. Of patients with brain metastases, approximately 5% to 21% will have melanoma as their primary tumor (29). Metastatic brain tumors from colorectal cancer are relatively rare, with a reported frequency of 1.8% to 4.8% of all metastatic brain metastases (24). Brain metastases from gastric cancer are extremely rare. Patients with gastric cancer account for less than 1% of all cases of brain metastases in autopsy and clinical series (27). Intracranial metastases from prostate cancer are rare (0.6% to 4.4% of cases) (8). The incidence of brain metastases in patients with testicular cancer ranges from 2% to 25% in clinical series and was 20.7% in an autopsy series. However, brain metastases are extremely rare in surgical series of patients with testicular cancer (2%) (27). The incidence proportion of metastatic brain tumors from renal cancer in patients with primary renal tumors ranges from 5.5% to 11% (16) In 1999,

Taddei et al. investigated a group of patients with brain metastases with clinical characteristics similar with our study. In their group, made up of 211 patients with age ranging from 33 to 79 years, lung tumors (47%) and breast tumors (9%) were the most frequently responsible for brain metastases. In 17% of patients, the primary lesion was unknown (33).

In our study, most of the patients with an identified underlying malignancy had a primary lung cancer (49.69%). This cancer also ranked first in other studies, although le Cesne et al found gastrointestinal tumours to be the most frequent (6).

There are two possibilities to discover the location of primary cancer:

- neurosurgical intervention and sampling of tumoral tissue in order to determine the histopathological features of tumoral architecture and tumoral cells;
- general clinical examination and laboratory tests for discovery of primary neoplasm.

Neurosurgical intervention may be classical ablation of the tumor or stereotactic biopsy. Total ablation intervention addresses to patients who have a good general state, single metastases, which is located in a non-eloquent area. In cases with multiple metastases total removal will address to the voluminous formation with herniation tendency. Indications for stereotactic biopsy refer to patients with deterioration of the general state, and with multiple metastases located in eloquent areas (Rolando area, central gray nuclei, corpus callosum, and brain stem). To obtain a valuable result it is necessary to make multiple samples within the tumor. As a consequence, fine needle biopsy could be a source of errors.

After completing all explorations, including neurosurgical intervention, the discovery of the initial site of the primary cancer could rise to 85%. Pavlidis et al. (25) found that primary neoplasias remain unknown in 3% of all cases of cancers and Greco and Hainsworth (15) reported even less (2% of all cases).

In our study, the primary site remained unknown in 16.44%patients, that represents a comparable group with those in other studies, in which the underlyning malignancy could not be detected in 15%-50% of the patients with brain metastases. To have certainty it is mandatory to see a well-differentiated tumoral tissue that repeats the architecture of the tissue where the cancer developed initially. For poorly differentiated tumors, the origin of neoplasia couldn't be identified. Moreover, there are two situations: in some cases existed similarity between the microscopic appearances of the brain metastasis and those of primary cancer, but in other cases the histopathological features of the brain metastasis does not coincide with those of the primary cancer. So, surgical intervention can offer a tumor sample that will be analyzed by the neuropathologist who could identify the histological type and the location of the primary cancer, but when there are poorly differentiated tumoral cells, than the pathological diagnosis could be difficult. In these cases it is necessary to use further investigations such as immunohistochemistry, electron microscopy and genetic analysis.

A second possibility to identify the origin of a brain metastasis is to explore the whole body when there isn't the necessity of an emergency operation for decompression. This is the situation of small brain metastases, with no tendency of herniation and no signs of intracranial

hypertension.

The easier examination and more comfortable for the patient is a positron emission tomography (PET scan), but it has high costs. A study comprising 3000 asymptomatic subjects have been found the existence of at least one brain metastasis in 3% of cases. Brain metastases with unknown origin can be detected with Fluorodezoxyglucoze 18 (18F) which allowed the discovery of the primary cancer in 29% of cases (19, 22, 23).

If there isn't PET scan in the hospital, then it can be used classical explorations (radiograph, CT, MRI, laboratory testing). The ranking of these explorations could be based on statistics which showed how often can be encounter an organ as the origin of the primary cancer which can lead to a brain metastasis. Taken into consideration statistics from the literature (21) and the results of our own study, the management of the patients with brain metastases should include a thoracic CT scan or anteroposterior and lateral chest X-ray, clinical breast examination and mammography, abdominal ultrasound exploration, and skin, kidney and prostate examination.

The treatment of brain metastases have to be complex in order to provide the longest survival for the patients (Figure 4). So, the management of brain metastases represents a formidably challenge. The first place in the panoply of treatment methods is neurosurgical complete removal of single metastases. The second method is the whole brain radiotherapy with or without pharmacological agents (such as motexafin gadolinium) which enhance the effect of radiation on brain metastases remnants (10). Another possibility for intracerebral metastases treatment is stereotactic radiosurgery which use several types of radiation-therapy devices: cobalt-60–based machines, linear accelerators, and cyclotrons, which use gamma rays,x-rays, and proton, respectively (32). It can be used also brachytherapy with Iodine - 125 (17) or laser induced thermal therapy (31).

The goal of discovering the site of primary cancer would be the use of a specific type of chemotherapy for achieving cure of cerebral metastases. Unfortunately it should be noted that the existence of blood-brain barrier prevents chemotherapy drug action (9). However, there are studies (3) indicating the size reduction of brain metastases in some cases with lung or breast origin after using temozolomide, efaproxiral, metoxafin (13). In carcinomatous meningitis we can use intrathecal cytarabin and methotrexate (5). The maximum dose intravenous methotrexate also can be used (14).

When brain metastases are discovered, it should be initiated a symptomatic corticosteroid therapy and treatment for prevent seizures or thromboembolism. After interdisciplinary cooperation, primary cancer should be treat in tandem and in function of vital emergency. Complex treatment of cerebral metastases provides the longest survival.

The median survival of patients with cerebral metastases would be 7 months when they are treated with whole brain radiotherapy, 15 months when radiosurgery is associated, 14 months when radiosurgery is used alone, 14 months when brain radiotherapy is associated with surgical ablation, and 21 months when all three treatment methods are used together (2, 11, 30, 34).

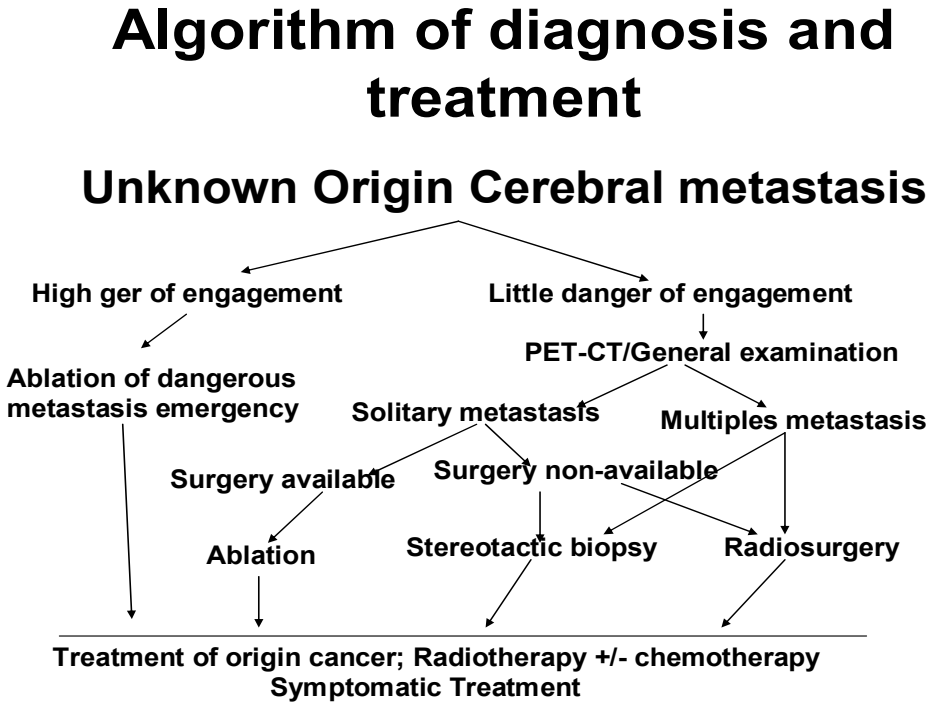

Figure 4 Algorithm of diagnosis and treatment for unknown origin cerebral metastases

Depending on the number of cerebral metastases, it is noted that single metastasis treated by surgical ablation and radiotherapy has a median survival time of 13 months while those multiple will have a median survival time of 7 months, with 0% survival at 2 years. Surgical ablation combined with radiosurgery offers an average survival of 10 months (15% surviving at 2 years).

Conclusions

The discovery of a brain metastasis in a routine computed tomography examination or for minor neurological symptoms become more frequently. The primary cancer leading to brain metastases can be detected either by obtaining a sample of tumoral tissue through a neurosurgical operation on the intracerebral tumor (total ablation or stereotactic biopsy) with histopathological examination, or by additional tests of the whole body. Taken into consideration the results of our own study, the management of the patients with brain metastases should include a thoracic CT scan or anteroposterior and lateral chest X-ray, clinical breast examination and mammography, abdominal ultrasound exploration, and skin, kidney and prostate examination. With the most sophisticated methods of diagnosis in approximately 16% of cases the origin of metastasis remains unknown. The identification of the primary site by the neuropathologist after stereotactic biopsy would clearly be advantageous.

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