Brain metastases in patients with diagnosed versus undiagnosed primary tumor

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ABSTRACT

الأهداف: من أجل الاقتراح لوضع فحص تشخيصي محدد للمرضى المصابين بالورم الأولي الذي لم يتم تشخيصه بعد (UDP).

الطريقة: شملت الدراسة 50 مريضاً تم تشخيص حالتهم بانتشار المرض في الدماغ في مستشفى الشهاداء – طهران – إيران، خلال الفترة ما بين يناير 2001م وحتى ديسمبر 2005م. تم إجراء التحليل المتغير لتقييم فرق المتغيرات المتعددة بين المرضى الذين تم تشخيص حالتهم (DP) والآخرين الذين لم يتم تشخيص حالتهم بعد (UDP).

النتائج: مثل المرضى الذين لم يتم تشخيص حالتهم 46% من العدد الإجمالي. كانت الحبسة عن الكلام أكثر شيوعاً بشكل ملحوظ بين مجموعة المرضى الذين لم يتم تشخيص حالتهم (UDP) (p=0.0008)، والترنح في مجموعة المرضى التي تم تشخيصها (DP) (p=0.04)، أكد مصدر الانتشار وجود الاختلاف بين المجموعتين (p=0.0006). كانت الرئة أكثر المواقع الأولية تكراراً لدى المجموعتين. بين جميع المرضى الذين لم يتم تشخيص حالتهم بعد (UDP)، تبين وجود الورم الأولي في موقع غير الرئة بنسبة 17% من المرضى. صادقت هذه الدراسة نظرية وجود اختلافات بين توزيع الأورام الأولية بين المرضى الذين تم تشخيص حالتهم (DP) والآخرين الذين لم يتم تشخيصهم بعد (UDP).

خاتمة: إذا فشلت فحوصات الرئة في الكشف عن الورم الأولي، فإن المريض على الأرجح لن يستفيد من الفحوصات السريرية المختلفة المكثفة. وفي مثل هذه الحالة، يجب أخذ الإجراءات الجراحية العصبية بعين الاعتبار كخطوة ثانية ملائمة للغاية.

Objectives: To propose a diagnostic work-up specifically tailored to the undiagnosed primary (UDP) tumor patients.

Methods: To investigate the distribution of primary tumors and presenting symptoms in UDP versus diagnosed primary (DP) patients, 50 consecutive patients with diagnosis of brain metastasis in Shohada Hospital, Tehran, Iran from January 2001 to December 2005 were included in this study. Univariate analyses were performed to assess the difference of various variables between DP and UDP patients.

Results: The UDP patients represented 46% of all. Aphasia was significantly more common in the UDP group (p=0.0008) and ataxia in the DP group (p=0.04). The source of the metastases proved to be different between the 2 groups of interest (p=0.0006). The lung was the most frequent primary site in both groups. Among all UDP patients, a primary tumor in a location other than the lung was only found in 17% of patients. This study validated the hypothesis that the distribution of primary tumors differs between DP and UDP patients.

Conclusion: If lung investigation fails to disclose the location of primary tumor, the patient is unlikely to benefit from extensive paraclinical investigation. In such a situation, a neurosurgical procedure should be considered the most appropriate second step to be taken.

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Brain metastases are among the most common brain neoplasms and account for some 20% of all brain tumors,[1,2] while affecting 20-30% of all patients with systemic cancer.[3] In more than 50% of patients with intracranial metastases, carcinoma of the breast or lung is the primary tumor.[4] However, in up to 15% of the patients presenting with brain metastases, the site of the primary tumor will not be detected despite thorough

investigation.[5] A histopathological diagnosis has first to be made in these undiagnosed primary (UDP) patients before any treatment plan can be determined. Two options of an intracranial procedure through stereotactic biopsy or open craniotomy or a thorough paraclinical search for an accessible primary tumor is then available.[6] There is little literature concerning UDP patients, and therefore the time sequence of the diagnostic studies and the timing of neurosurgical intervention remains controversial. A detailed knowledge of the distribution of primary tumors in UDP patients versus patients with diagnosed primary (DP) tumor is a necessity to establish an efficient investigation strategy.[6] The aim of this study was to investigate the distribution of primary tumors and clinical presentations of brain metastasis in patients with DP versus UDP tumor.

Methods. Between January 2001 and December 2005, 50 patients with brain metastases were diagnosed at the Department of Neurosurgery, Shohada Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran. Inclusion criteria included single or multiple metastases detected on CT scan of the brain or MRI. Although there are no pathognomonic features that distinguish brain metastases, however, a peripheral location, spherical shape, ring enhancement with prominent peritumoral edema and multiple lesions, all suggest metastatic disease.[7] Patients' demographic data were obtained from case notes and a computer database. Clinical examination included analytical history taking and a standard physical neurologic examination, including motor and sensory examination as well as cranial nerves. Primary tumor histology and site as well as number and localization of brain metastases were also recorded. The UDP was assumed if no primary tumor could be detected after thorough clinical examination and complete staging within 3 months after the diagnosis of brain metastases. Routine investigations in UDP patients consisted of chest x-ray and thoracoabdominal CT scan. Further exams such as bone scan, mammography, bronchoscopy, gastrointestinal endoscopy, or colonoscopy, were performed only when indicated by clinical suspicion, histological characteristics of the brain lesion and in the patients finally diagnosed as having an unknown primary. This was a retrospective study with no interventions. Written informed consent was obtained from all patients and the research committee of the faculty of medicine approved the study.

To compare the distribution of variables between the 2 groups of interest, univariate analysis was performed using the chi-square test. We considered a *p*-value of <0.05 to be statistically significant. The statistical Package for Social Sciences (SPSS Inc, Chicago, Illinois) for Windows version 10.0 was used for all statistical analyses.

Results. Demographic data as well as the presenting symptoms in the 2 groups are shown in **Table 1**. We had 27 DP (54%) and 23 UDP (46%) patients. There was 29 male (58%) and 21 female (42%) patients in our study, ranging in age from 29-80, with a median age of 54 years. In the univariate analysis, no difference was found between the 2 groups according to gender distribution (p=0.77) and proportion of patients older than 65 years (p=0.73). The most frequent symptoms occurring as a result of intracranial pathology were headache, paresis, and papilledema, encountered in more than 50% of patients in both groups. However, aphasia was significantly more common in the UDP group (p=0.0008) and ataxia in the DP group (p=0.04). As shown in **Table 2**, there was no significant difference between the 2 groups according to the number of brain metastasis (p=0.73), however, the localization of brain metastasis was significantly different between the 2 groups (p=0.04). Primary tumor distribution is summarized in **Table 3**. The source of the metastases proved to be different between the 2 groups of interest in the univariate analysis (p=0.0006), where the source were grouped as lung, breast, gastrointestinal tract, other, and unknown.

Table 1 - Characteristics of patients with known versus unknown primary tumor.

Characteristics	Undiagnosed primary tumor (n = 23)	Diagnosed primary tumor (n = 27)	*P*-value
	n (%)		
Gender			
Male	14 (60.9)	15 (55.5)	0.77
Female	9 (39.1)	12 (44.5)	
Age (year)			
≤ 65	17 (73.9)	22 (81.5)	0.73
> 65	6 (26.1)	5 (18.5)	
Clinical presentation			
Headache	14 (60.8)	22 (81.5)	0.12
Seizure	4 (17.4)	2 (7.4)	0.39
Paresis	16 (69.5)	15 (55.5)	0.38
Cranial nerve deficit	7 (30.4)	14 (51.8)	0.15
Aphasia	9 (39.1)	0 (0)	0.0008
Ataxia	2 (8.7)	9 (33.3)	0.04
Sensory loss	1 (4.3)	0 (0)	0.46
Incontinence	2 (8.7)	1 (3.7)	0.58
Higher cortical function disorder	5 (21.7)	3 (11.11)	0.44
Visual disturbance	3 (13.1)	3 (11.11)	1
Loss of consciousness	0 (0)	1 (3.7)	1
Papilledema	13 (56.5)	19 (70.4)	0.38

Table 2 - Characteristics of brain metastasis in UDP versus DP patients.

Characteristics	Undiagnosed primary tumor (n = 23)	Diagnosed primary tumor (n = 27)	*P*-value
	n (%)		
Number of brain metastasis			
1	12 (52.2)	14 (51.8)	0.73
2	5 (21.7)	8 (29.6)	
> 2	6 (26.1)	5 (18.6)	
Localization of brain metastasis			
Supratentorial	19 (82.6)	19 (70.4)	0.04
Infratentorial	0 (0)	6 (22.2)	
Supra and infratentorial	4 (17.4)	2 7.4)	

UDP - undiagnosed primary, DP - diagnosed primary

Table 3 - Localization of the primary tumor in UDP versus DP patients.

Source of the primary tumor	Undiagnosed primary tumor (n = 23)	Diagnosed primary tumor (n = 27)	*P*-value
	n (%)		
Lung	5 (21.8)	7 (26.0)	
Breast	0 (0)	6 (22.2)	
Gastrointestinal tract	1 (4.3)	4 (14.8)	0.0006
Others	3 (13.0)	10 (37.0)	
Unknown	14 (60.9)	0 (0)	

UDP - undiagnosed primary, DP - diagnosed primary

Discussion. In our series, 46% of the patients treated for brain metastases presented with an unknown primary. This percentage is inferior to the 64% UDP patients reported by Ebels et al[8] on 36 brain metastasis patients, but is comparable to the 36% UDP patients reported in a recent study on 342 patients with brain metastases by Agazzi et al.[6] This could reflect the impact of modern diagnostic tools like CT scan or MRI in recent studies. Clinical characteristics in our study proved to be similar between DP and UDP patients concerning gender and age at presentation. This finding is in agreement with other studies.[6,9,10] The overall distribution of the presenting symptoms was reported in a previous study to be different between DP and UDP patients,[8] however our study is the first to compare the frequency of each individual symptom between the 2 groups. We showed that aphasia and ataxia are significantly more common in UDP and DP groups, respectively. A possible explanation for this difference is the observation that supratentorial metastases were significantly more common in UDP patients, while infratentorial metastases were more common in DP patients.

Our study demonstrated that the source of the metastases in UDP patients was significantly different from DP patients (p=0.0006). Lung was the most frequent primary site in both DP and UDP patients. However, breast as a primary location of tumor, which was relatively frequent in DP group, was absent from the UDP group. Differences in the origin of the brain metastasis between DP and UDP patients had already been reported based on comparison of UDP groups with literature data on brain metastasis patients in general.[8,11-18] However, Agazzi et al[6] conducted the first study of this kind to provide a statistical comparison between DP and UDP patients from the same institution. Although the lung was the most frequent primary site in both DP and UDP patients in their study, its relative frequency was significantly higher in the UDP group (60%) than in the DP group (42.7%). They also found that some primary locations such as breast and melanoma were less frequent in the UDP group, a finding replicated by our study. Among all UDP patients in our study, a primary tumor in a location other than the lung was only found in 17% of patients. It is also noticeable that as much as 60.9% of the primary tumors in our UDP patients eventually remained unknown. This finding shows that a primary tumor is very unlikely to be detected through non-invasive tests when the lung investigation remains negative.

To investigate the degree and type of delays in performing diagnostic biopsies in medical patients with suspected malignancy, an interesting retrospective survey was carried out by internists[19] among a general oncologic population. They reported that in 67% of patients the biopsied lesion was detected by the second day of evaluation, however, there was an 8-10 day delay before a biopsy was carried out. Although logistic and other unavoidable delays occurred in 40% of the cases, in 60%, delays could only be attributed to continued, frequently low yield, noninvasive tests. The overall yield in detecting a lesion of all those non-invasive tests was 24% with a particularly low figure for lower gastrointestinal tract endoscopy and cytological examinations.

Several studies have suggested that patients with brain metastases as the only site of disease besides the primary location have a comparable survival to patients with limited disease, when whole brain radiotherapy has been started early together with combination chemotherapy.[20-23] This warrants a diagnostic and management strategy without unnecessary delays for

patients with brain metastases. Based on the differences in the distribution of primary tumors between DP and UDP patients, we suggest that if the first step in evaluation of patients with unknown primary metastases, namely, chest radiography or CT scan failed to detect the primary location, an intracranial procedure, therapeutic or just diagnostic should be considered the most appropriate second step in management of these patients. The sample size of the present study was not large, and further prospective investigation is required to assess the independent difference of all the factors studied here and those studied previously between DP and UDP patients.

In conclusion, the results of the present study suggest that the diagnostic evaluation of UDP patients should be tailored according to specific distribution of primary tumors in the UDP population rather than just adapted from the guidelines for the work-up of brain metastases patients in general. If lung investigation fails to disclose the location of primary tumor, the patient is unlikely to benefit from extensive paraclinical investigation. In such a situation, a neurosurgical procedure should be considered the most appropriate second step to be taken.

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