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Clinical Article

The origin of brain metastases in patients with an undiagnosed primary tumour

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Summary

Background. In patients presenting brain metastases as the first manifestation of a previously undiagnosed primary tumour (UDP) histopathological confirmation of the diagnosis can be obtained by either direct surgical sampling of the brain lesion or paraclinical search for an accessible primary tumour. The sequence of the diagnostic work-up and the timing of an eventual neurosurgical intervention are a matter of debate and are mainly influenced by the distribution of primary tumours in UDP patients. The aim of this study was to verify the hypothesis that the distribution of primary tumours differs between UDP patients and the rest of the patients with brain metastases (DP), and to propose a diagnostic work-up specifically tailored to the UDP population.

Methods. Retrospective study on 342 patients admitted to the Lausanne University hospital between 1983 and 1998 with the diagnosis of cerebral metastases.

Findings. UDP patients represented 36% of the whole group. Primary tumour location was significantly different between the two groups ($p = 0.001$). Although the lung was the most frequent primary tumour location in both groups (UDP: 60%, DP: 43%), in UDP 14% only of the primaries were found outside of the lung and as much as 26% remained unknown despite thorough investigations.

Conclusions. Our study confirmed the hypothesis that the relative frequency of primary tumours differs between DP and UDP patients. This difference therefore mandates a diagnostic strategy specifically tailored for UDP patients: if a radiological lung investigation clearly remains the best initial step in the work-up of these patients, extensive paraclinical investigations without a clear clinical suspicion should probably not be undertaken if this first survey fails to disclose the primary tumour as only 14% of the patients will actually benefit from it. In this situation, a neurosurgical procedure should probably be considered the most appropriate next step to be taken in order to provide a definitive diagnosis without unnecessary delays.

Keywords: Brain tumours; metastases; diagnosis.

Introduction

In patients with no known primary tumour who present with brain lesions of potentially metastatic nature, an histopathological diagnosis has first to be established before any treatment plan can be determined. Two options are then available: a direct neurosurgical approach through stereotactic biopsy or open craniotomy or a thorough paraclinical investigation searching for a primary location accessible to biopsy or resection. The time sequence of the diagnostic studies and the timing of an eventual neurosurgical intervention are a matter of debate due to the potential complications of any intracranial procedure but also to the low yield of several of the systemic investigative modalities. A detailed knowledge of the distribution of primary tumours in undiagnosed primary patients (UDP) and the awareness that primary tumours distribution might differ between UDP and the rest of the patients with brain metastases (DP) is a prerequisite for a safe and efficient investigation strategy. In order to provide a detailed description of primary tumours in UDP patients and to test the hypothesis that such a distribution differs between DP and UDP patients, we reviewed 342 cases

of newly diagnosed cerebral metastases that were treated at our hospital.

Materials and methods

In this report, the wording ⟪at presentation⟫ will indicate the moment when cerebral metastases were diagnosed.

Patient population

Because the work-up and evaluation of patients with brain metastases has improved vastly with the advent of computer tomography (CT) scanning, we restricted our study to only the years after CT-Scan was introduced and became routinely available at our institution, not only for diagnosis but also for systemic work-up and follow-up of these patients.

Between January 1983 and December 1998, 342 patients with cerebral metastases were treated at the Lausanne University Hospital. Our institution is the main regional hospital and referral centre for the Canton of Vaud (626,200 catchement population) but also represent one of three tertiary referral centres in a catchement area of 1,350,000 people. The patients of the study were identified through hospital computer analysis of discharge diagnostic codes, of the 342, 122 (36%) had an undiagnosed primary tumour at presentation (UDP) and 220 (64%) a diagnosed primary tumour at presentation (DP). Follow-up from presentation until the time of death was obtained in 306 (90%) cases, 21 (6%) were still alive at the time of analysis and 15 (4%) were lost to follow-up.

In UDP patients, the diagnosis of cerebral metastasis was established during surgical removal of the lesion in 46 patients, by stereotactic cerebral biopsy in 33 patients and in 43 cases, most of them with two lesions or more, tissue diagnosis was obtained from the extracerebral location of the primary tumour discovered on the initial work-up. Routine investigations of those patients consisted of chest X-ray and thoraco-abdominal CT-Scan. Further exams such as bone scan, mammography, bronchoscopy, or gastro-intestinal endoscopy, 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.

Discharge destination after diagnosis and treatment of the cerebral metastasis was recorded and dichotomised in home versus another hospital, nursing home or rehabilitation centre. The Karnofsky Performance Status (KPS) at the time of the diagnosis of the cerebral metastases was either recorded as found on the hospital admission chart or calculated retrospectively from the pertinent admission data.

Statistical methods

When comparing continuous and categorical variables between the two groups of interest the chi-square and Kruskal-Wallis test have been used respectively [2, 3]. For explorative purposes, a multivariate logistic regression [2] was performed to simultaneously compare all the characteristics of interest between DP and UDP patients. In all regressions the variables describing the patient characteristics presented in this report were considered and appropriately coded in terms of binary indicators. To arrive to the final model, backward stepwise selection was used, with variables entering the model if their P-value was smaller than 5% and leaving the model if it was bigger than 10%. All reported P-values are two-sided. All statistical analyses were performed using the Stata® computer package [1].

Results

Patients characteristics

A comparison of patients' characteristics between DP and UDP group is displayed in Table 1a and 1b. In the *univariate* analysis, no difference was found between the two groups according to sex distribution ($p = 0.071$), median age at presentation ($p = 0.21$), proportion of patients older than 65 at presentation ($p = 0.071$), number ($p = 0.47$) and location ($p = 0.35$) of cerebral metastases. Significant differences were demonstrated according to the clinical presentation of the brain lesion ($p = 0.017$), the KPS at presentation ($p = 0.001$) and the presence of systemic metastases ($p = 0.013$), with UDP

Table 1a. *Characteristics of patients with known versus unknown primary tumour at presentation*

	Undiagnosed primary nb of patients (column %)	Diagnosed primary nb of patients (column %)	Total
Male	40 32.8%	94 42.7%	134 39.2%
Female	82 67.2%	126 57.3%	208 60.8%
			p = 0.071
Age < 65	83 68%	152 69%	235 68.7%
Age ≥ 65	39 32%	68 30.9%	107 31.3%
			p = 0.84
KPS ≥ 70	80 66%	112 52%	192 57%
KPS < 70	41 34%	104 48%	145 43%
			p = 0.001
Discharged to hospital	22 18.2%	57 26.3%	79 23.4%
Discharged home	99 81.8%	160 73.7%	259 76.6%
			p = 0.092
Clinical presentation of cerebral metastasis			
– Focal neurological deficit	78 64.4%	108 50.5%	186 55.5%
– Epilepsy	22 18.2%	37 17.3%	59 17.6%
– Intracranial hypertension	10 8.3%	23 10.8%	33 9.8%
– Headache	7 5.8%	17 7.9%	24 7.2%
– Asymptomatic	4* 3.3%	29 13.5%	33 9.9%
			p = 0.017

The tables where the total does not match 342 indicate missing values.
* Intracranial lesion diagnosed during brain imaging for unrelated reasons (i.e. trauma etc.).

Table 1b. *Characteristics of the brain metastasis in patients with known versus unknown primary tumour at presentation*

	Undiagnosed primary nb of patients (column %)	Diagnosed primary nb of patients (column %)	Total
Number of cerebral metastasis			
– 1	63 52.1%	118 54.6%	181 53.7%
– 2	12 9.9%	28 13%	40 11.9%
– >2	46 38%	70 32.4%	116 34.4%
			p = 0.4
Localisation of cerebral metastasis			
– Supra-tentorial	83 69.2%	139 66.2%	222 67.3%
– Infra-tentorial	7 5.8%	22 10.5%	29 8.8%
– Supra and infratentorial	30 25%	49 23.3%	79 23.9%
			p = 0.35
Systemic metastasis			
– No	68 60.7%	98 46.2%	166 51.2%
– Yes	44 39.3%*	114 53.8%	158 48.8%
			p = 0.013

The tables where the total does not match 342 indicate missing values.
* Presence of metastases as determined *after* the complete oncological work-up.

Table 2. *Origin of the primary tumour in UDP versus DP patients*

	Undiagnosed primary nb of patients (column %)	Diagnosed primary nb of patients (column %)	Total
Localisation of primary tumour			
Grouped for statistical analysis			
– Lung	73 59.8%	94 42.7%	167 48.8%
– Non-Lung	17 14%	123 55.9%	175 41%
– Unknown	32 26.2%	3* 1.4%	35 10.2%
			p < 0.001
Detailed			
– Lung	73 59.8%	94 42.7%	167 48.9%
– Breast	2 1.6%	34 15.4%	36 10.5%
– Melanoma	3 2.5%	32 14.6%	35 10.2%
– Unknown	32 26.2%	3* 1.4%	35 10.2%
– Other**	5 4.1%	29 13.2%	34 10%
– Colon	3 2.5%	18 8.2%	21 6.1%
– Kidney	4 3.3%	10 4.5%	14 4.1%

⟨*⟩ Three patients who presented with systemic metastasis but no primary isolated.
⟨**⟩ Bladder, uterus, thyroid, lymphoma, soft tissue sarcoma, epidermoid of ENT origin.

patient presenting less frequently asymptomatic brain lesions and less frequent extracerebral metastatisation at the time of presentation. The *multivariate* logistic regression further demonstrated that UDP patients were more frequently discharged home ($p = 0.01$), and had less frequently asymptomatic cerebral metastases ($p = 0.0001$).

In the DP group, the median interval between diagnosis of the primary tumour and of the brain metastases was 7.3 months for lung cancer, 14 months for kidney and colon, 37 months for breast and 47 months for melanoma.

Origin of the primary tumour

Primary tumour distribution is illustrated in Table 2. The origin of the metastases proved to be different between DP and UDP patients in the univariate analysis ($p < 0.0001$), where the origin were grouped as lung, breast, melanoma, colon, kidney, other and unknown. In the multivariate analysis, due to the very small number of patients in the UDP group having a primary tumour other than in the lung, location of the primary tumour was coded as ⟨⟨lung⟩⟩, ⟨⟨non lung⟩⟩ and ⟨⟨unknown⟩⟩. Once again, the difference in primary tumour origin appeared as statistically significant with a p value of 0.001. In the UDP group, 60% of the primaries were in the lung, 26% remained unknown until the time of death and 14% of the patients had a primary tumour discovered outside of the lung.

In the 17 UDP patients whose primary tumour was found outside of the lung, the diagnosis was established by surgical resection in 10 cases and by stereotactic biopsy of the brain lesion in one. Of the remaining 6 patients, 5 had a primary tumour detected on clinical examination (3 breast, 1 testicle, 1 melanoma and 1

large uterine tumour) and one had a colon tumour that was diagnosed only one month after the diagnosis of the brain metastases.

Discussion

Presentation with a brain metastasis from a previously undiagnosed primary tumour is not a rare event. In our study, 36% of the patients treated for brain metastases belonged to this group. This percentage is inferior to the 64% UDP patients reported by Ebels [6] in his study on 36 brain metastasis patients who underwent surgical removal of their lesion, but is comparable to more recent series where modern diagnostic tools like CT-Scan or MRI were routinely available [5, 13].

Clinical characteristics in our series proved to be similar between DP and UDP patients especially concerning the age at presentation and the proportion of single versus multiple brain metastases. The KPS at the time of diagnosis of the cerebral metastases and the discharge destination after their treatment appeared nevertheless to be different, with UDP patients being in a better general condition and being more frequently discharged directly home after the diagnosis and treatment of the brain lesion. This could reflect a minor primary disease activity in our UDP group also confirmed by the higher proportion of UDP patients free from systemic metastases at presentation compared to their counterparts of the DP group.

Differences in the origin of the brain metastasis between DP and UDP patients had already been reported based on the comparison of UDP groups with literature data on brain metastasis patients in general [4–6, 9–14], nevertheless our study is the first one providing a statistical comparison between DP and UDP patients from the same institution.

Our study demonstrates that the origin of the metastases in patients presenting with an undiagnosed primary tumour is significantly different from the general population of brain metastases patients ($p = 0.001$) and explains why the diagnostic work-up of UDP patients should not be accomplished by just applying the guidelines for the DP group.

Although the lung is the most frequent primary site in both DP and UDP patients, its relative frequency is significantly higher in the UDP group (60%) than in the DP group (42.7%). In addition, some primary locations, such as breast and melanoma, that are relatively frequent in the DP group, are almost absent from the UDP group. It is also important to notice that as much as 26% of the primary tumours in the UDP group will finally remain unknown. This figure is probably partially influenced by the diagnostic tools available (as suggested by the higher percentages in older series [5, 6, 9]), but seems fairly stable and comparable in more recent studies [15]. Those results reveal that among all UDP patients, a primary tumour in a location other than the lung will only be found in 14% of the cases, irrespective of the thoroughness of the ancillary investigation.

These data not only confirm the generally accepted view that chest radiology (radiograph and/or CT-Scan) should be the first step in the evaluation of suspected brain metastases but most importantly they demonstrate that a primary tumour is very unlikely to be diagnosed through non-invasive tests when the lung investigation remains negative.

Van de Pol [15] who reviewed 72 patients with symptomatic brain metastases from undiagnosed primaries, arrived at the same conclusion when he was able to diagnose a lung primary in 48 of his 72 patients, and reported 19 patients in whom the primary remained unknown until death, leaving only four patients who benefited from paraclinical investigations beyond chest X-ray and CT-Scan. Similarly, Latief [8] investigated 32 patients who presented with brain metastases without a known primary tumour and who were investigated with both chest radiograph and CT-Scan. In all but one case, the primary tumour was diagnosed in the lung by means of chest X-ray or CT-Scan: 61% had a primary lesion visible on both chest radiograph and CT-Scan, 13% had a chest radiograph interpreted as non-specific although the CT-Scan showed a definite primary lesion and in the final 26%, the initial chest X-ray was interpreted as normal whereas the CT-Scan showed a primary lung carcinoma. The only patient with both chest X-ray and CT-Scan interpreted as normal, was later diagnosed as having a breast cancer by mammography and finally biopsy.

The question as to when a tissue diagnosis should be obtained was addressed by a very interesting study conducted by internists [7] among a general oncological population. The authors quantified the unnecessary delays due to the continuation of non-invasive tests beyond the time point when a potentially biopsiable lesion was found. They reported that although 67% of the lesions that eventually provided the definitive diagnosis were detected by the second day of investigation, a biopsy was only performed an average of 8 to 10 days later. If part of the reason for this delay was related to logistics problems, in 60% of the cases it was the direct consequence of continued non-invasive investigations. 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.

In UDP patients, a potentially biopsiable (and/or resectable) lesion is by definition diagnosed from the day of presentation and if present, a biopsiable lesion in the lung can be readily diagnosed by means of simple radiological examinations. If no primary tumour is disclosed by this first day of work-up and if no specific clinical signs or symptoms are present, further paraclinical investigations will most likely result in unnecessary costs and delays for the majority of patients. We therefore believe that in case of negative chest investigation, an intracranial procedure, therapeutic or just diagnostic should be considered the most appropriate second step to be taken.

Conclusion

This study validated the hypothesis that the distribution of primary tumours differs between DP and UDP patients. Given those differences we believe that the work-up of UDP patients should be specifically tailored rather than just adapted from the guidelines for the evaluation of brain metastases patients in general. Chest radiography and CT-Scan should definitely represent the first step in their evaluation, nevertheless if the results of this initial survey remain negative, the specific distribution of primary tumours in the UDP population speaks against performing any other non invasive investigation. In such a situation and in the absence of specific clinical signs or symptoms, an intracranial procedure, therapeutic or just diagnostic should be considered the most appropriate second step to be taken in order to reliably, safely and cost-effectively arrive at the final management strategy without unnecessary delays.

References

1. Stata Statistical Software: 5.0 Edition. College Station, TX: Stata Corp, 1997
2. Armitage P, Berry D (1987) Statistical methods in medical research. Blackwell Science
3. Conover W (1971) Practical nonparametric statistics. John Wiley and Sons Inc, New York
4. Debevec M (1990) Management of patients with brain metastases of unknown origin. Neoplasma 37: 601–606
5. Dhopesh VP, Yagnik PM (1985) Brain metastasis: analysis of patients without known cancer. South Med J 18: 171–172
6. Ebels E, van der Meulen J (1978) Cerebral metastasis without known primary tumor: a retrospective study. Clin Neurol Neurosurg 80: 195–197
7. Farag S, Green M, Morstyn G, Sheridan W, Fox R (1992) Delay by internists in obtaining diagnostic biopsies in patients with suspected cancer. Annal Internal Med 116: 473–478
8. Latief KH, White CS, Protopapas Z, Attar S, Krasna MJ (1997) Search for a primary lung neoplasm in patients with brain metastasis: is the chest radiograph sufficient? AJR 168: 1339–1344
9. Le Chevalier T, Smith FP, Caille P, Constans J-P, Rouesse JG (1984) Sites of primary malignancies in patients presenting with cerebral metastases. A review of 120 cases. Cancer 56: 880–882
10. Maesawa S, Kondziolka D, Thompson T, Flickinger J, Lunsford L (2000) Brain metastases in patients with no known primary tumor. The role of stereotactic radiosurgery. Cancer 89: 1095–1101
11. Merchut MP (1989) Brain metastases from undiagnosed systemic neoplasms. Arch Intern Med 149: 1076–1080
12. Nguyen L, Maor M, Oswald M (1998) Brain metastases as the only manifestation of an undetected primary tumor. Cancer 83: 2181–2184
13. Salvati M, Cervoni L, Raco A (1995) Single brain metastases from unknown primary malignancies in the CT-era. J Neuro-Oncology 23: 75–80
14. Trilliet V, Catajar J-F, Croisile B, Turjman F, Aimard G, Bourrat C, Bret P, Carrie C, Chassard J-L, Chauvin F, Confavreux C, Cordier J-F, Deruty R, Duquesnel J, Fischer G, Gamondes J-P, Gerard J-P, Goutelle A, Lapras C, Loire R, Mornex J-F, Perrin G, Sindou M, Tommasi M, Trilliet M, Trouillas P, Brune J (1991) Cerebral metastases as first symptom of bronchogenic carcinoma. A prospective study of 37 cases. Cancer 67: 2935–2940
15. Van de Pol M, Van Aalst VC, Wilmink JT, Twijnstra A (1996) Brain metastases from and unknown primary tumor: which diagnostic procedure are indicated? J Neurol Neurosurg Psychiatry 61: 321–323

Comments

Although this study is retrospective, the data provided are of practical interest for establishing strategy when confronted with patients harbouring brain metastasis(es) from undiagnosed primary tumour. The authors' conclusion is that radiological lung investigation remains sufficient in the absence of clear clinical suspicion of other organ origin. We personally would prefer that the investigation in such patients be "thoracic and abdomino-pelvic CT scan". In the authors series about 9% of primary tumours located in the abdomen or pelvic cavities. Perhaps in the near future entire body PET – scan will be the solution.

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This paper represents an audit of 342 patients with cerebral metastases, referred to Lausanne University Hospital which is one of three tertiary referral centres with a catchment population of 1.35 million. They found that as many as 36% of patients with presumed brain metastases were not known to have a systemic primary tumour at presentation. Histological confirmation of the brain lesion was performed in 79 patients, and 43 patients had tissue diagnosis obtained from the extracerebral location of a primary tumour discovered on work up. The most useful tests were chest x-ray and CT scan of the chest. The site of the primary tumour remained undiagnosed in 26% of patients.

The frequency of undiagnosed primaries depends on the referral population referred by the tertiary referral centre/district general hospital. The paper confirms that in the absence of clinical signs to help localise primary site, chest x-ray or CT scan of the chest is the appropriate first line investigation.

Robin Grant

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