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Glioblastoma multiforme in patients with history of extracranial cancer: Case series

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ABSTRACT

Objectives: Significant progress in treatment strategies improves the expectations of patients with extracranial cancers. Metastases are the primary consideration in patients with cancer history. In the case of neurologic disorders, the patient should undergo brain MRI. A rationale is presented for surgery, whole-brain or stereotactic radiotherapy, or chemotherapy. Recently, we have encountered misdiagnosed primary malignant brain tumours in patients with oncologic history who had been admitted for surgery for brain metastases. The aim of our study is to evaluate the incidence of concurrent cancers, to assess the relationship between previous cancer staging and primary brain tumour evaluation as well as to determine treatment efficiency.
Methods: From January 2007 to December 2011, we prospectively followed up patients with concurrent history of both extracranial cancer and subsequent glioblastoma multiforme. Information was collected on the clinical condition, imaging, history of extracranial cancer, previous and present surgical and oncologic procedures, and GBM histologic, cytogenetic, and molecular genetic investigations.
Results: Five patients were recruited: three females and two males. The average patient age at the time of GBM diagnosis was 65.6 years. Three patients had a history of breast carcinoma, one of renal carcinoma and one of colorectal carcinoma. Following the diagnosis of carcinoma, three patients received chemotherapy and radiotherapy, one patient had radiotherapy alone, and one had no adjuvant therapy. In all the cases, surgery revealed primary GBM, with a standard occurrence of genetic abnormalities (Table 1). The average time from the diagnosis of extracranial cancer to that of GBM was 4 years. Four patients underwent chemoradiotherapy and one had palliative radiotherapy. Two patients completed oncotherapy and their OS was 27 months and 19 months, respectively. One patient had post-surgical progression of hemiparesis. One patient had pulmonary embolism during oncotherapy and one had paraplegia caused by a pathological fracture of vertebras T5 due to breast carcinoma metastases. The OS was 11.8 months (range 3–27 months). All the patients succumbed to GBM progression.

1. Introduction

Metastases are the most frequent brain tumours, accounting for 50–60% of all intracranial neoplasms [1]. Currently, advanced treatment strategies, including surgery, radiotherapy, chemotherapy, and biologic treatments, are available for the most common cancers, such as those arising from the lung, breast, and colon and rectum. Significant progress in this field improves the expectations of these patients. Brain metastases have been found in 10–50% of patients with cancer history. When a neurologic deficit or epileptic seizures develop, these patients should undergo brain MRI. Silent brain metastases are detected only rarely. A rationale is presented for surgery, whole-brain or stereotactic radiotherapy, or chemotherapy [2–8]. Recently, we have encountered an unanticipated histologic finding of primary malignant brain tumours in patients with cancer history who had been admitted for surgery for brain metastases [9]. The aim of our study is to evaluate the incidence of concurrent tumours, to assess the relationship between

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previous cancer staging and primary brain tumour evaluation as well as to determine treatment efficiency.

2. Materials and method

From January 2007 to December 2011, we prospectively followed up patients with concurrent history of both extracranial cancer and glioblastoma multiforme (GBM). Information was collected on the clinical condition, imaging, the history of extracranial cancer, previous and present surgical and oncologic procedures, and GBM histologic, cytogenetic and molecular genetic investigations. Indication for the surgery was Karnofsky score more than 70, single brain metastasis, which is eligible for resection on MRI, and primary cancer under control confirmed by PET-CT FDG. All patients underwent early post-surgical MRI (up to 72 h) to determine resection radicality. Whenever possible, patients were recommended to the Stupp oncotherapy protocol. Tumour tissue was sampled as both formalin-fixed, paraffin-embedded and fresh-frozen material. All tumour samples were submitted to histologic analysis and were investigated for the genetic aberrations of *TP53, EGFR1, PTEN, MDM2, RB1, CCND1, BCR,* 9p21 (*CDKN2A,* p16), 10p11, 19q13, 1p36, *IDH1* mutation, and *MGMT* promoter methylation. Clinical and MRI follow-up information was gathered at regular intervals of 3 months. All patients signed the informed consent and the study was approved by the local ethics committee.

2.1. Pathology

Formalin-fixed, paraffin-embedded samples were submitted to a local neuropathologist. Ten-μm thick sections were cut and conventional haematoxylin and eosin and basic immunohistochemical reactions for protein expression including GFAP (polyclonal rabbit antibody, DAKO, Glostrup, Denmark, 1:1000 dilution, microwave pre-treatment with citrate buffer pH 6.0), p53 (monoclonal mouse anti-human, clone DO7, DAKO, Glostrup, Denmark, 1:100 dilution, microwave pretreatment with citrate buffer pH 6.0), and Ki67 (monoclonal mouse anti-human, clone MIB-1, DAKO, Glostrup, Denmark, 1:200 dilution, microwave pretreatment with citrate buffer pH 6.0) were performed. This was followed by Dako EnVision + Dual Link System-HRP secondary antibody (DAKO, Glostrup, Denmark) incubation. The immunoreactivity was visualized by the liquid DAB + substrate-chromogen system (DAKO, Glostrup, Denmark). GFAP staining was evaluated as either positive or negative. The number of p53 positive nuclei was recorded as was the intensity of the staining (weak–medium–strong). The proliferation activity was calculated using the Ki67 proliferative index. All tumours were classified according to the latest WHO classification of CNS tumours.

2.2. FISH analyses

FISH analysis was performed on formalin-fixed, paraffin-embedded (FFPE) tissues according to the manufacturers' instructions with LSI 1p36.3/1q25.2, LSI 9p21.3/CEP9, LSI 19q13/19p13.42, LSI *EGFR*/CEP7, LSI *MDM2*/12p12.1, LSI *PTEN*/10p11.1, LSI BCR/22q12.2, LSI CCND1/CEP11 (IntellMed, Ltd., Prague, Czech Republic) and LSI *p53*/CEP17, LSI *RB1*/13q12.11 (Vysis, Downers Grove, IL, USA) probes. The signals were observed and counted using fluorescence microscopy. At least 100 non-overlapping nuclei were selected in each sample. Aberration was described when a non-physiological number of signals was present in >20% nuclei or the average number of signals was >2.5 or <1.8.

Table 1

No	Carcinoma	ca oncoTh	Age of GBM dg.	GBM oncoTh	n-myc	bcr	cep7	EGFR	CEP11	CCND1	9p21.3	1q25.2	1p36.3	13q12.11	Rb1	p53	10p11.1	PTEN	19q13	MDM2	MGMT promotor metylation	IDH 1,2 mutation
1.	Colorectal	RT + ChT	67	RT + ChT			Norm	Gain			Norm		Norm	Norm	Norm	Gain	Norm	Loss	Norm	Norm	No	No
2.	Breast	RT + ChT	60	RT + ChT	Loss	Loss	Norm	Norm	Gain	Gain	Loss		Norm	Loss	Loss	Norm	Norm	Norm	Loss	Norm	Yes	
3.	Kidney	0	57	RT + ChT			Gain	Gain			Norm		Gain	Norm	Loss	Gain	Norm	Loss	Gain	Gain	No	
4.	Breast	RT + ChT	71	RT + ChT			Norm	Gain			Norm		Norm	Norm	Norm	Norm	Loss	Loss	Norm	Norm	No	No
5.	Breast	RT	71	RT		Loss	Norm	Norm			Loss	Norm	Norm	Loss	Loss	Norm	Norm	Norm	Loss	Norm	Yes	