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Second Cancer affecting the Central Nervous System: Systematic Literature Review Exploring the Link between Malignant Melanoma and Glioblastoma

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Short title: The link between Malignant Melanoma and Glioblastoma.

Keywords: Collision Tumor, Malignant Melanoma, Glioblastoma, Neurooncology

Abbreviations: CNS=Central Nervous System; GBM=Glioblastoma; MM=Malignant Melanoma

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ABSTRACT

Background: Glioblastoma (GBM) is a malignant primary brain cancer, among the most devastating and lethal diseases of the central nervous system. Similarly, malignant melanoma (MM) is responsible for most skin cancer-related deaths. A link between those two aggressive cancers has not yet been established. We present here a systematic review of the literature and an exemplificative case.

Methods: A systematic review of the literature was conducted to assess possible commonalities between MM and GBM. An exemplificative surgical vignette of a 73-year-old patient with occurrence of a fronto-basal GBM after surgical removal of a metastasis of MM in the same location was then detailed.

Results: Fifteen studies currently published in the English international literature support a link between MM and GBM, both based on epidemiological and pathophysiological/genetic aspects. This constatation is reinforced by our surgical vignette of a collision tumor with the occurrence of both tumors in the same location several years apart.

Conclusion: The evidence reported in the literature, as well as our surgical vignette, support a likely link between pathogenesis of GBM and MM.

Keywords: Collision Tumor, Malignant Melanoma, Glioblastoma, Neurooncology

INTRODUCTION

An association between aggressive cancers is an unfortunate, but well-known clinical scenario: the American Cancer Society (www.cancer.org) defines second cancer as an entirely new cancer developing in an oncology patient who survived a previous cancer diagnosis. Second cancers can be concomitant if they co-exist, or subsequential if they appear one after the other. To progress in our understanding of second cancers, we should keep on studying the commonalities between multiple cancers affecting the same individuals, this is a challenging undertaking from a biostatistical and pathogenetic perspective.

Cancer registries are particularly useful to investigate the standardized incidence ratio (SIR) for second cancers: a cohort study conducted through data from the Finnish Cancer Registry concluded that the SIR for new cancers type in patients with brain tumors was 1.2 (95% confidence interval (CI) 1.1–1.3) [1]. A significant excess risk of second cancers affecting the CNS has been described, among others, for gliomas, meningiomas, lymphomas (particularly non-Hodgkin's ones), and skin melanomas: in this article, we will focus our attention on the former and latter types of cancers from this list.

Glioblastoma (GBM) is a malignant primary brain cancer and is considered one of the most devastating and lethal diseases of the central nervous system (CNS) [2]. GBM belongs to the family of brain gliomas, a group of tumors originating from glial cells (namely astrocytes, oligodendrocytes, and ependymal cells), and represents the most aggressive form (WHO Grade IV) of those tumors. Noteworthy, it can either originate as a *de novo* lesion or result from the aggressive transformation of an initially benign glioma [3]. GBM can occur at any age, however two peaks are usually seen in the fourth and sixth decades of life. GBM typically bears a very poor prognosis, with life expectancy ranging between few months and few years since original diagnosis [4].

Similarly, malignant melanoma (MM) is the most aggressive form of melanomas, a tumor group responsible for most skin cancer-related deaths [5]. MM originates from a malignant transformation of melanocytes, which are derived from the neural crest: this is why MM occurs not only on the skin but wherever neural crest cells migrate, including the gastrointestinal tract and the CNS. Of note, the five-year relative survival rate for patients with MM is just about 10% [5].

Given the very low rate of second cancers affecting the CNS, exploring a possible link in terms of genetic and epigenetic traits would be relevant for the neuro-oncology community [1,6–8]. Through a systematic literature review we will explore the features of those tumors and the commonalities they share, which have implications for their treatment and overall prognosis. We additionally illustrate this link with a vignette of the first case reported to our knowledge of a collision tumor consisting of a GBM occurring in the same site of a previously excised MM.

METHODS

In order to have an overview of the commonalities in terms of genetic background, diagnostic and therapeutic management, and overall prognosis, between GBM and MM, a systematic literature review has been conducted in accordance with the PRISMA statement [9].

The literature search has been performed on PubMed, Google Scholar, Scopus and Cochrane databases. The keywords used for the search included a combination of the terms of interest in the following research equation: (glioblastoma) AND ((intracranial melanoma) OR (metastatic melanoma)) AND ((management) OR (genetic profile) OR (prognosis) OR (second tumor) OR (concomitant tumor) OR (collision tumor)).

All relevant case reports and case series were identified. Articles written in any other languages than English were excluded from the analysis. After full screening of articles content, all articles that did not contribute to evidencing the link between both tumors were excluded as well.

RESULTS

The search strategy has been summarized in the PRISMA Flow diagram (Fig. 1). The related studies have been summarized in Table 1. A total of 15 studies, including 220 patients, supported a connection between MM and GBM. These studies included in the present review consisted in relevant case reports, epidemiologic and genetic studies. Relevance and significance of the key features found in the literature are further detailed within the discussion section.

Surgical Vignette

We report the case of a 73-year-old patient, active smoker with a medical history of ulcerated melanoma (Clark Level 5, Breslow 3.1 mm) requiring amputation of the right 3rd fingernail, followed by adjuvant treatment with low-dose Interferon. Five years later, the patient showed tumor progression with the occurrence of a right fronto-basal lesion (Fig. 2AB) managed with craniotomy and radical surgical excision (Fig. 2CD); histology confirmed the diagnosis of metastatic melanoma (Fig. 3). Given the complete tumor removal, it was decided, during our neuro-oncology multidisciplinary meeting, that radiation therapy was not necessary.

Two years after the brain surgery, the patient presented colic and peritoneal diffusion of the disease that was treated by Pembrolizumab, nonetheless six months later the patient further progressed, showing a subcutaneous occipital localization of the melanoma. His chemotherapy, at this stage, was promptly switched to Ipilimumab with complete clinical remission within 3 months. Discussion during multidisciplinary general oncology meeting led to the decision to stop immunotherapy and to consider a restaging through a total body 18-FDG-PET scan. This investigation was repeated after three and six months and did not show any pathological uptake of the radiotracer.

Two years later, a follow-up body 18-FDG-PET scan and a cerebral MRI scan with spectroscopy revealed the recurrence of a right nodular fronto-basal lesion (Fig. 4AB) located in the same surgical bed of the previously excised intracranial MM. The neuroradiological features raised the suspicion of a recurrent MM, and considering this as the most likely working diagnosis the patient was referred to the neuro-oncology multidisciplinary meeting, where a re-do surgery was proposed. Surgical excision of the recurring lesion was uneventful (Fig. 4CD); of note, the intraoperative findings suggested a very aggressive lesion, highly vascularized, without clear demarcation from the surrounding brain parenchyma. With much surprise, the histological diagnosis revealed the lesion to be a WHO grade IV, IDH wild type, GBM (Fig. 5). To rule out any doubt of diagnosis between both entities, immunohistochemical analysis and NGS mutations panel were performed again on stored sample from the first surgery. Mutational and immunohistochemical profiles allowed for a clear confirmation of melanoma in the first case and glioblastoma in the second one (Table 2).

The patient subsequently underwent, due to his age and low personal tolerance/acceptance, an accelerated STUPP protocol by 42 Gray stereotactic radiotherapy administered within 3 weeks with concomitant Temozolomide. He recovered well and is currently still alive (15 months after surgery) in a relatively good shape. No recurrence of melanic mole were found at all different clinical follow-up.

DISCUSSION

Emerging scientific research has indicated a potential association between malignant melanoma (MM) and glioblastoma (GBM), although the exact nature of this connection is still a subject of investigation. Our clinical observation, that represents to date, to our knowledge, the first case of a MM/GBM collision tumor ever reported, along with the literature review, points out this likely connection between melanomas and glioblastomas, as these tumors share potential pathophysiologic pathways and evidence therapeutic response to temozolomide.

96 While various reports[10,11] showed a significant association between MM and GBM, suggesting the possibility of an
97 underlying neural crest abnormality, there are some contradictory details worth discussing. Arcega et al. reported
98 diagnosis of a metastatic melanoma after surgical removal of the expected recurrence of a priorly resected glioblastoma,
99 but interpreted it as an initial diagnosis mistake [12]. Tucker et al. [13], who investigated the risk of second cancers in
100 Connecticut between 1935 and 1982, observed that among patients with brain cancer there was an increased incidence of
101 melanoma, although no excess of brain cancer was seen after skin melanoma.

102 Three pathological processes can be considered to explain the occurrence of second cancers: a) an underlying genetic
103 profile exposing to the risk of multiple cancers, b) second cancers related to exposure to radiation treatment, and c)
104 second cancers triggered by chemotherapy and targeted therapy.

105 First, the fact that GBM has a higher occurrence in combination with MM compared to other cancers such as breast or
106 prostate cancer suggests the existence of a possible genetic link, which might predispose patients to develop those
107 cancers. Genetic studies have provided further evidence supporting a potential association between GBM and MM.
108 Killela et al.[14] found remarkably high levels of telomerase reverse transcriptase (TERT) promoter mutations in GBM.
109 Consistently with previous works, these mutations were associated with significantly lower survival rates in patients with
110 GBM, particularly de novo ones rather than those resulting from a subsequent transformation of originally histologically
111 confirmed low grade glioma [15]. Noteworthy, such genetic feature has been described also in MM patients[16–18].

112 In addition, others observed that both cancers, GBM and MM, tend to have a higher rate of mutations in the protein
113 tyrosine phosphatase receptor type D (PTPRD) gene, a tumor suppressor gene on chromosome 9 [19]. According to a recent
114 meta-analysis of 12 studies[20] MGMT promoter methylation was found to be higher in both primary melanomas and MM
115 compared to normal controls. This finding suggests that MGMT promoter methylation could potentially serve as a useful

116 biomarker for metastatic MM in blood samples, as the incidence of MGMT promoter methylation was found to be higher
117 in MM blood samples compared to tissue samples [18].

118 With regards to the association between GBM and MM, Yang et al. reported the case where those cancers occurred
119 concomitantly, and backed the idea that such association might have a genetic basis [21]. It is also worth noting that BRAF
120 V600E mutations are typically found in low frequencies in GBM, with only 2% of the cohort described in a study by
121 Schindler et al. [22,23] showing these mutations. However, higher frequencies of BRAF V600E mutations can be found also
122 in other tumors [24], and have been known to promote tumorigenesis in several malignancies via a similar pathway through
123 the constitutive activation of BRAF protein. Of note, in our case negative staining for BRAF V600E was observed in first
124 resection of MM and second surgical excision of GBM, further supporting an association between those two lesions.

125 Second, radiation treatment is widely recognized as a possible cause of cancer, in fact past radiation exposure increases
126 the risk of developing most kinds of leukemia, as well as sarcomas, melanomas, and CNS tumors such as meningioma
127 and gliomas. Second cancers may develop 10 years or more after radiation therapy, and this risk seems to be highest in
128 patients who were exposed during their childhood to conventional radiotherapy [25]. Occurrence of a high-grade glioma has
129 been particularly reported as linked to radiation in patients with prior systemic malignancies.[26] This is not incidental
130 because the radiation dose and the relative radiosensitivity of specific tissues and organs are two parameters known to
131 influence the risk of developing second cancers. With regards to second cancers affecting the CNS, the transition from
132 conventional to stereotactic radiotherapy and the much safer use of stereotactic radiosurgery should hopefully reduce the
133 incidence in the future [27]. This is even truer when one considers the impact that radiosensitizers, meant to increase the
134 effect of radiation dose on the target while sparing the surrounding healthy brain parenchyma, will have on the
135 management of patients harboring brain tumors [28].

Third, anytime a patient is consented for chemotherapy, the consenting process covers the risk of second cancers: for instance, chemotherapy is known to be a greater risk factor than radiation therapy in causing leukemia. Alkylating agents (cyclophosphamide, lomustine, carmustine, etc.), Platinum-based drugs (cisplatin, carboplatin), Anthracycline topoisomerase II inhibitors (etoposide, etc.) are all known to increase the risk of second cancers. For this, strategies to reduce their toxicity and simultaneously enhance bioavailability of chemotherapy for high–grade gliomas and other brain malignancies have been suggested, for instance by using biodegradable nanocarriers to bypass the blood brain barrier and favor direct uptake by cancer cells [29]. Immunotherapy agents that target the BRAF protein (vemurafenib, dabrafenib, etc.) deserve a separate discussion. Those latter immunotherapy regimens have certainly increased the survival rate of MM, however their side effects need to be kept into account and might have played a role in the exemplificative case described in this article. While for chemotherapy the risk gets higher with cumulative doses over longer treatment time or high intensity over a shorter period, not much is known regarding the long-term effects of many newer immunotherapy protocols. The hypothesis that the GBM developed following the therapies used to treat MM may not be excluded as it could be the result of an immune depression syndrome. Furthermore, it is a matter of fact that, the progressively increased overall survival rate of cancers, recorded over last decade, allowed to observe many patients developing concomitant or delayed multiple cancers.

Finally another hypothesis that could be considered in the development of the GBM in our report is the role played by the neural stem and glial progenitor cells that are notably present in multiple regions of the adult human brain [30]; Such cells that are, multipotent and self-renewing, could potentially be susceptible to transformation following different onco-genetic stimuli; in this specific case these cells could have probably been activated by the MM constituting what some authors define a singular entity the “collision tumor” that in this case occurred one after the other in the same site. This latter entity are rare and well documented lesions characterized by the occurrence of two benign, a benign and a malignant and/or two malignant tumors respectively in the same site or very close to each other [31].

158 Interestingly, the patient reported here showed a quite long survival with good quality of life so far, which appears
159 unusual for someone undergoing successively the management of metastatic melanoma and glioblastoma. Metastatic
160 melanoma has indeed a median survival of 9 months [32], whereas glioblastoma's median survival is around 12 months,
161 with 3-5% of "long-survivor" patients surviving more than 3 years [33]. The good therapeutical response in our case
162 questions the potentially different behavior of such collision tumors that may involve different pathophysiological
163 mechanisms, or that the patient is just an exceptional responder of which real reasons are still unknown being under
164 research (National institute of Cancer trial number: NCT02243592).

165 **Limitation of the study**

166 Our systematic review failed to identify a genetic syndrome that might justify an association between GBM and MM;
167 nonetheless we are convinced that in the exemplificative case described the occurrence of those two aggressive tumors
168 developing exactly in the same site at few years of distance might not be exclusively explained by chance. Given the
169 paucity of cases described so far it will be difficult to disclose a pathogenetic process or establishing a formal syndrome.
170 In depth biostatistical analysis of existing cancer registries and advances in basic research, particularly biomarkers and
171 biosignatures [34], will hopefully facilitate in the future a better understanding of the specific association between
172 aggressive lesions such as GBM and MM, and more generally will help guiding clinical decision-making process in
173 patients with second cancer diagnosis.

174 **Conclusion**

175 The findings from this systematic review allowed to better clarify the risk of second cancers affecting the CNS and the
176 article has been enriched by the report of a very rare case involving a patient diagnosed with MM and GBM occurring in
177 the same surgical site one after the other. The evidence reported in the literature as well our surgical vignette suggests a

strong association between MM and GBM, raising the suspicion that in the case reported the GBM did not simply occur by chance in the surgical bed of a previous MM metastasis. Further research is certainly necessary to better understand the underlying mechanisms and any genetic factors involved in second cancers affecting the CNS.

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TABLES

Table 1. Studies identified in the PRISMA review and features found supporting the connection between glioblastoma (GBM) and malignant melanoma (MM).

Study	*Type of study*	*Number of patients supporting a link between GBM and MM (n)*	*Main connections evidenced between GBM and MM*
Arcega et al	Case report	1	MM can mimick giant cell GBM and challenge histopathological diagnosis.
Yang et al	Case report	1	MM and GBM occur concomitantly in one patient.
Maluf et al	Case series	3	GBM occurs in 3 patients with a prior primary melanoma.
Desai et al	Epidemiologic study	7	Concomitant MM are over-represented in a large GBM population.
Scarbrough et al		208	Gliomas have greater incidence rate among MM cases than in the general population.
Tucker et al		*Unknown*	Risk of MM is increased among patients with brain cancer
Killela et al	Genetic study	/	Melanomas and GBM both evidence high level of TERT promoter mutations.
Nonoguchi et al		/	
Huang et al		/	
Horn et al		/	
Qi et al		/	
Solomon et al		/	GBM and MM have a high rate of mutations in the PTPRD gene
Schindler et al		/	MM and GBM can present BRAF mutations (rare in GBM).
Davies et al		/	
Horbinski et al		/	

MGMT : methylguanine DNA-methyltransferase ; PTPRD : protein tyrosine phosphatase receptor type D ; TERT : telomerase reverse transcriptase

Table 2. Anatomopathological characteristics of both tumors leading to diagnosis of metastatic melanoma and glioblastoma.

	First tumor	Second tumor
Immunohistochemical profile		
HMB 45	+	-
Sox10	+	-
Melan-A	+	-
ps-100	+	-
Olig-2	-	+
GFAP	-	+
ATRX	-	+
Mutations		
IDH1 3132H	-	-
BRAF L597R	+	-
TP53 G244C	+	-
CTNNB1 Q726R	+	-
NRAS F156L	+	-
Diagnosis retained	Metastatic melanoma	Glioblastoma

FIGURES

Figure 1. PRISMA flow-chart.

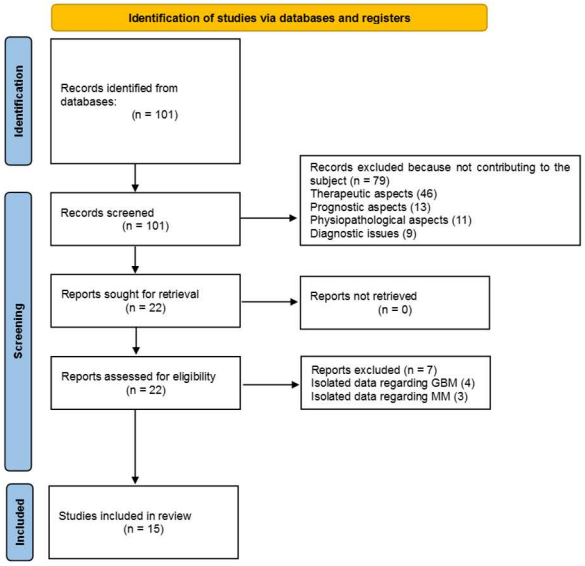

***Figure 2*:** Comparison of initial pre-operative T1-enhanced MRI sequences showing a right fronto-basal lesion in coronal (A) and axial (B) views, with post-operative (4 months check), T1-enhanced MRI in coronal (C) and axial (D) views showing complete resection.

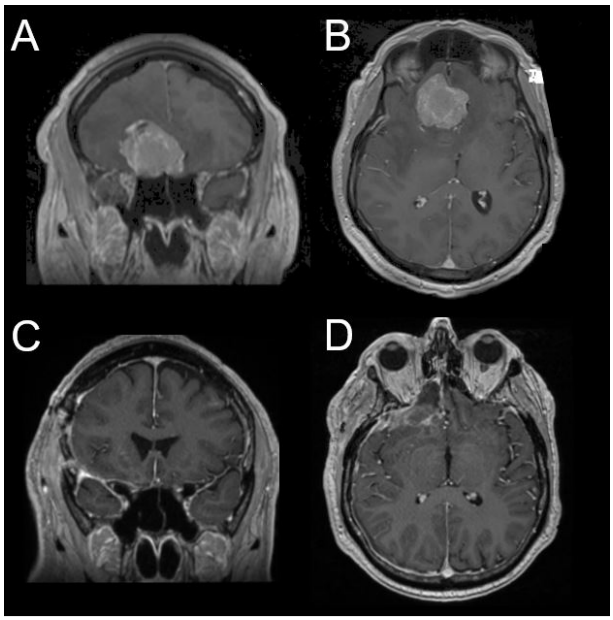

***Figure 3. Diagnosis of melanoma metastasis*:** Histology shows a proliferation of solid architecture, composed by cohesive cells, containing very irregular size and shape nucleus often including a bulky nucleolus (A, B). Cytoplasm size is variable and eosinophilic or clarified. Melanin brown pigment deposition and areas of necrosis are objectivized. Immunohistochemistry shows tumor cells positive to HMB 45 (C) and Melan-A antibodies (D). All these findings lead to the diagnosis of brain metastasis of melanoma.

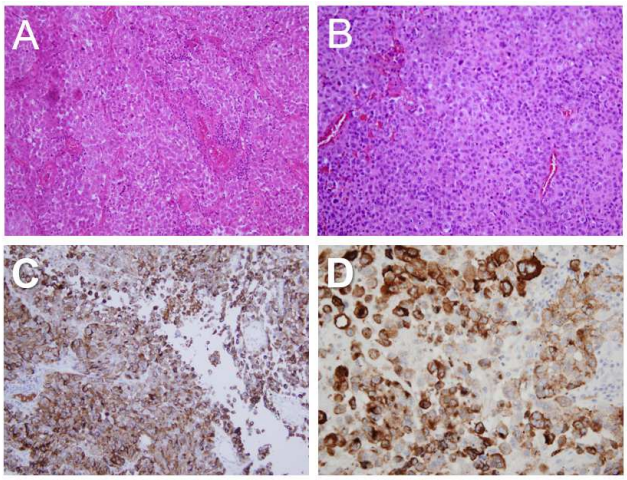

Figure 4. Comparison of pre-operative T1 enhanced MRI sequences showing a nodular lesion in the right frontal lobe suspected for recurrence, coronal (A), axial (B), with post-operative T1 enhanced MRI sequences in coronal (C) eand axial (D) views, showing resection of the recurrent right frontal lesion that with surprise was a wild type grade IV glioblastoma.

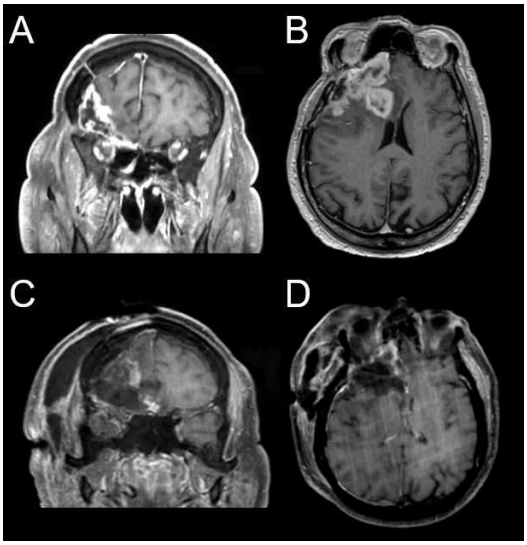
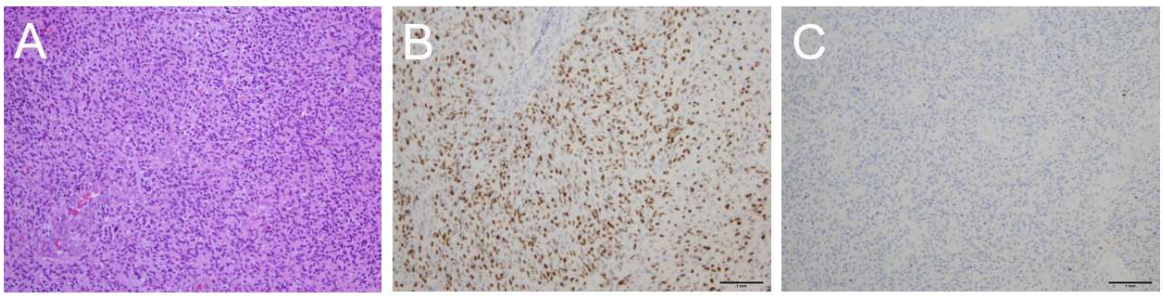
Figure 5. Diagnosis of glioblastoma: Histology shows a glial-like proliferation tissue with an astrocytic phenotype, composed by cells with moderate cytonuclear atypia and eosinophilic cytoplasm. This tissue contains large areas of necrosis and of pathological endothelial-capillary proliferation (A). Immunohistochemical investigations show that the tumor cells are positive to Olig-2 (B) and GFAP antibodies. They are negative to HMB 45, SOX10 (C), Melan-A and pS-100. ATRX is retained. They do not express the mutant IDH1 variant R132H. NGS is performed with paraffine blocks of the first tumor and several mutations were found as follow: BRAF L597R exon 15, TP53 (G244C exon 7 and splicing zone 3' TP53 c.993+3A>T.p exon 9, CTNNB1 Q726R exon 15 and NRAS F516L exon 5. Another NGS is performed for the second tumor. None of these mutations are found but the analyses suggested EGFR amplification and CDKN2a deletion, consistent with the diagnosis of glioblastoma, IDH WT.