Pathol. Oncol. Res. (2014) 20:215–220
DOI 10.1007/s12253-013-9732-z

COMMUNICATION

Gliomatosis Cerebri Type 1 with Extensive Involvement of the Spinal Cord and BRAF V600E Mutation

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Received: 19 June 2013 / Accepted: 4 December 2013 / Published online: 19 December 2013

Abstract Gliomatosis cerebri (GC) is a rare neoplasm in which there is a diffuse cerebral infiltration by malignant glial cells with relative conservation of the underlying structures. A 67-year-old lady was admitted complaining of balance problems, troubled breathing, stuttered speech, decreased mobility, progressive ataxia and also some mild cognitive problems. MRI demonstrated ill defined T2 hyperintensity with mild mass effect mainly involving the brain stem and cerebellar hemispheres, with minor signal abnormalities extending supratentorially along the corticospinal tracts. The imaging appearances were static over a year. No biopsy was performed. The patient received palliative care and died 2 years after initial presentation. Macroscopic examination of the brain showed an extensive firm white-grey lesion predominantly in the cerebellar white matter, the brainstem, spreading to the full length of the spinal cord and invading the sensory ganglia. Histology revealed an extensively infiltrating diffuse glioma with small elongated fusiform nuclei. Diagnosis of GC type 1 was made. Molecular genetic tests revealed BRAF V600E mutation, while no IDH1 & IDH2 mutations were found. GC should be taken into account in the differential diagnoses mainly when there is rapid clinical deterioration without clear evidence of radiological progression. Extensive spinal cord infiltration has been reported only in 9 % and BRAF V600E mutation was detected only in one case in GC previously. Future clinical trials should address whether BRAF V600E mutant brain tumour patients will benefit from BRAF V600E-directed targeted therapies.

Keywords Glioma · Gliomatosis cerebri · BRAF V600E · Brain · Spinal cord

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Introduction

Since Nevin first described gliomatosis cerebri (GC) in 1938, there have been about 300 cases, mainly in retrospective studies [1, 2]. It is a rare entity which has been defined as a diffusely infiltrating glioma involving more than two lobes of the brain. It is frequently bilateral and may extend into posterior fossa structures and even the spinal cord. It has a poorly defined clinical course and typically fatal outcome [3].

Distinction between GC and multifocal diffuse gliomas can be difficult in clinical practice. Multifocal gliomas disseminate from a primary site along nerve fibre bundles, and sometimes via CSF channels and blood. These tumours usually histologically correspond to glioblastomas and have no significantly different survival to patients with single lesion glioblastoma when taking into consideration age, Karnofsky performance score and extent of resection by multivariate analysis [4].

GC is divided into type 1 without evidence of tumour mass and type 2 in which tumour mass is also present [5]. The microscopic appearances of the tumour can be variable, with some neoplastic cells resembling astrocytes and others having more indeterminate features or rarely, oligodendroglial histology which can be distributed in rows parallel to those of myelin fibres. The nuclei usually show enough atypia to facilitate their identification as neoplastic, although mitoses may be minimal or even absent. Microvascular proliferation and necrosis are usually absent. Despite the relatively innocuous histological features, this tumour is considered grade III due to its aggressive clinical course.

We report a case of type 1 GC with extensive involvement of the spinal cord diagnosed by post mortem examination. We also detected BRAF V600E mutation in this tumour.

Clinical Summary

A 67-year-old lady presented with balance problems. She slowly and progressively deteriorated, developed troubled breathing, stuttered speech, decreased mobility, progressive ataxia and also some mild cognitive problems. MRI demonstrated ill defined T2-weighted and FLAIR hyperintensity mainly involving the brain stem and cerebellar hemispheres (Fig. 1a–c). Minor signal abnormalities were also noted extending supratentorially along the corticospinal tracts. There were further T2 hyperintense lesions within the hemispheric white matter and deep grey matter bilaterally. The imaging appearances were relatively static over 1 year time interval (Fig. 1d). FDG and MET PET showed no abnormal increased intake. The differential diagnosis included auto-immune/paraneoplastic encephalitis, neurodegenerative process and glioma. Although demyelinating diseases and lymphoma were also included in the differential diagnosis, they were rejected later. Possibility of surgical biopsy was considered but declined by neurosurgeons due to lack of definite mass lesion. The patient received palliative care only as no definite diagnosis was reached. She slowly deteriorated and died 2 years after the initial presentation.

Pathological Findings

Full autopsy examination was performed after acquiring consent for hospital post mortem and research from the relatives. There was evidence of aspiration pneumonia, which was the direct cause of death. The brain was moderately swollen but no obvious mass effect or herniation was seen by external examination (Fig. 2a). Formalin fixed brain weight was 1338 g while the separated brainstem and cerebellum weight was 241 g in keeping with increased weight ratio of the infratentorial compartment (normal ratio=1/8). Coronal sectioning of the brain revealed an acute cortical infarct, measuring approximately 2.5×3.0×1.5 cm, in the superior medial part of the occipital lobe which appeared to be a terminal event. The cerebellum revealed firm ebony-like areas in the white matter and the outline of the dentate nucleus was blurred (Fig. 2b, c). Although no obvious mass lesion was seen elsewhere, the firmness was also detected throughout the brainstem and the full length of the spinal cord, suggesting an infiltrative tumour.

Histology revealed extensively infiltrating diffuse glioma in almost all examined areas. The tumour cells had small elongated fusiform nuclei, in keeping with astrocytic character (Fig. 3). In places, perivascular accumulation of the glial tumour cells was noted. In most areas the tumour had low cellularity; however, there were multiple areas with increased cellularity and nuclear pleomorphism (Fig. 3b). In latter areas, the mitotic activity was evident (Fig. 3b). There was no evidence of vascular proliferation or necrosis. No significant neuronal loss was seen in any of the infiltrated grey matter nuclei.

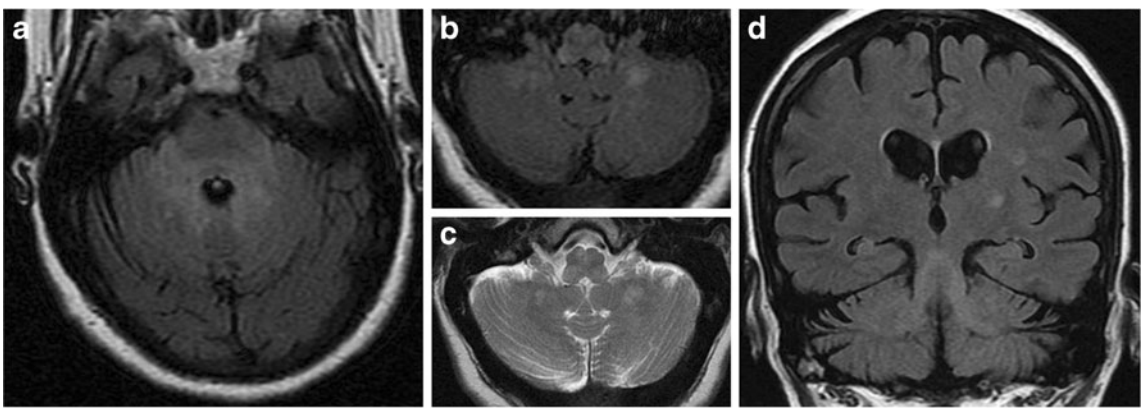

Fig. 1 Initial MRI reveals diffuse and relatively symmetrical FLAIR (**a**, **b**) and T2-weighted (**c**) hyperintensity in the cerebellar white matter extending to the brainstem. Similar appearances in the cerebellum and brainstem 5 months later, with mild FLAIR hyperintensity also seen in the cerebellar peduncles and the internal capsule (**d**)

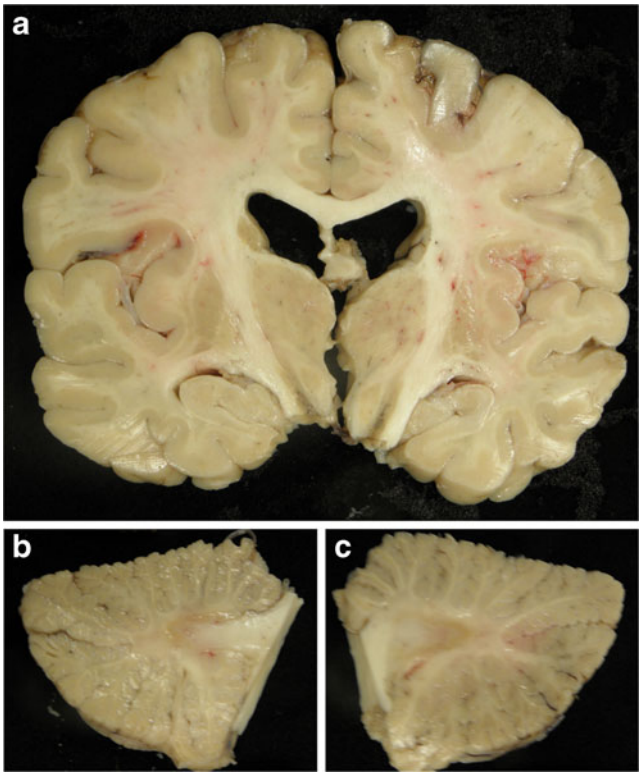

Fig. 2 Macroscopy. There is no mass effect or herniation but the brain is moderately swollen and the ventricles are mildly dilated (**a**). The cerebellar white matter was firm to touch and ebony-like (**c**, **d**). The outline of the dentate nucleus is blurred

The diffuse gliomatous infiltration was very marked in the cerebellum (Fig. 3a) and the whole brainstem (Fig. 3b, c), although the involvement appeared to be asymmetrical (Fig. 3d, e). The infiltration extended mainly through the pyramidal tract to the spinal cord. At least focal infiltration of the white matter and the anterior horn was observed in all spinal cord segments, even showing involvement of cauda equina and the lumbar sensory ganglia (Fig. 3f, g). Focal gliomatous infiltration was further detected in the internal capsule, basal ganglia, hippocampus and, in small areas, in the frontal and occipital white matter.

Immunohistochemistry revealed strong background staining of the gliofibrillary processes and probably in some tumour cells by GFAP and S100, although these were not helpful to identify tumour cells. IDH1 was negative. Some of the cells within the infiltrated areas were labelled by bcl2, p53 and cyclin D1 although distinction between reactive and neoplastic cells were not possible (Fig. 4a–c). The proliferation activity was focally increased up to 8 % by Ki67 (Fig. 4d).

The overall features were consistent with GC type 1 with extensive involvement of the cerebellum, brain stem, spinal cord, cauda equina and sensory ganglia. The tumour cells had astrocytic character and were IDH1 negative.

Molecular Genetic Tests

Genomic DNA were extracted from formalin fixed paraffin embededd tissue of cerebellum and lumbar sensory ganglion using the QIAamp DNA FFPE Tissue kit (Qiagen GmbH - Hilden, Germany). Bisulphite conversion was performed using an EpiTect kit (Qiagen GmbH - Hilden, Germany). O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status and BRAF V600 mutation were determined using the therascreen MGMT Pyro Kit and therascreen BRAF Pyro Kit respectively using a Q24 MDx Pyrosequencer (Qiagen GmbH - Hilden, Germany). Sequencing of IDH1 and IDH2 was also performed by pyrosequencing methods [6, 7].

Investigations revealed BRAF V600E mutation. No IDH1 & IDH2 mutations were found. The MGMT gene promoter was unmethylated.

Discussion

In the World Health Organization (WHO) classification of central nervous system tumours, GC is defined as a neuroepithelial neoplasm of unknown origin that involves more than 2 cortical lobes and often extends into infratentorial structures of the brain with preservation of anatomic architecture and sparing of neurons [5]. Two types of GC can be distinguished. Type 1 is the classical lesion with diffuse infiltration and possible enlargement of involved structures but without evidence of tumour mass formation. Type 2 is characterised by, in addition to presence of diffuse component, an obvious tumour mass, usually showing features of a malignant glioma. Although the morphological features are more likely to correspond to a low grade neoplasm, GC is an aggressive neoplasm with an average survival of 14 months from onset of symptoms [2, 3, 8]. Based on the poor prognosis GC is classified as grade 3 according to the WHO.

Historically, the diagnosis of GC was only based on autopsy procedure. The first successful intra vitam diagnosis was reported in 1987 by Troost et al. [9]. Because of clinical and radiological non-specific features, patients with GC are easily misdiagnosed with other neurological diseases, such as CNS inflammatory diseases, arteriopathies or leucoencephalopathies [2]. In general, the clinical disturbances are usually mild compared to the large extension of the lesions visible on MRI, although MRI findings are not always characteristic enough to raise the diagnosis of GC.

Our patient received palliative care because no definite ante mortem diagnosis was reached. There is no standard treatment protocol for GC due to the small number of cases. However, there is evidence that external whole-brain radiotherapy alone or concomitant temozolomide may stabilize clinical symptoms and prolong survival in some patients [10–12]. In a small number of GC, cases with IDH1-mutation, particularly

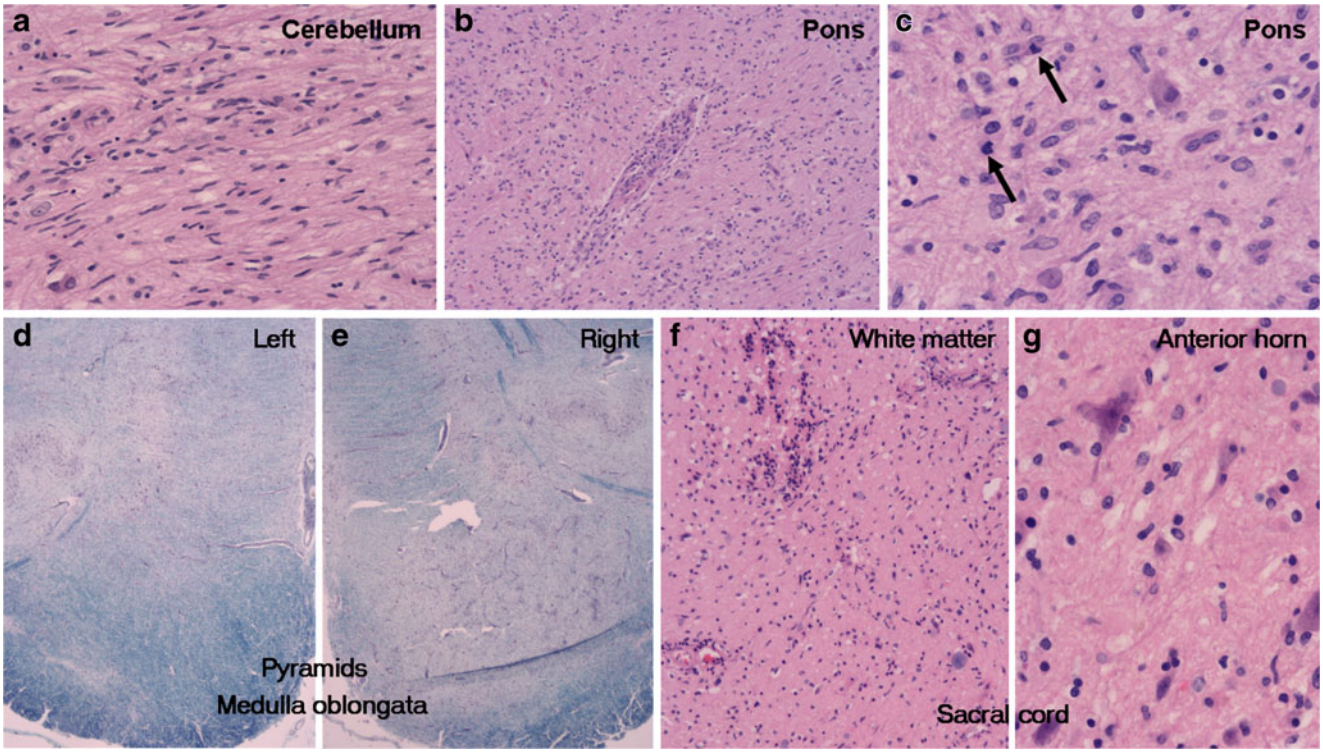

Fig. 3 Microscopy. Diffuse gliomatous infiltration in the cerebellum (**a**), pons (**b**, **c**), medulla oblongata (**d**, **e**), the white matter (**f**) and the anterior horn of the sacral cord (**g**). The tumour cells are fusiform or elongated. Perivascular accumulation of the glial tumour cells is evident (**b**). Focal hypercellularity and a few mitotic figures are noted (**c**, *arrows*). The right side of the pyramids shows loss of myelin staining, suggesting asymmetrical involvement (**d**, **e** – Luxol fast blue/Nissl). No significant neuronal loss was seen in any of the infiltrated grey matter nuclei

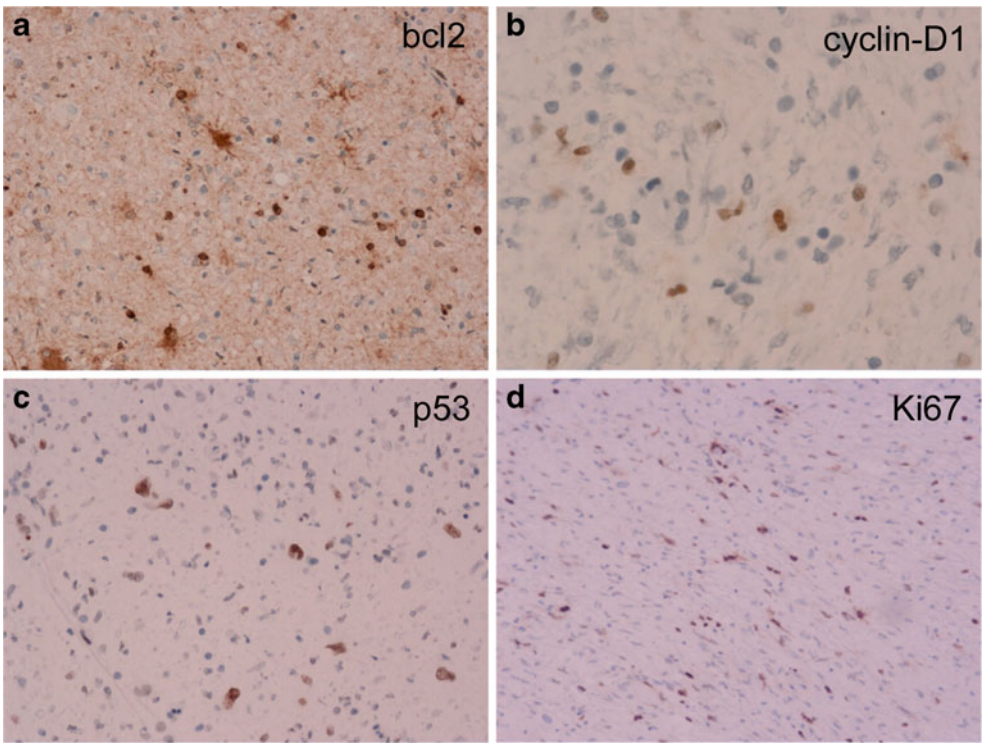

Fig. 4 Immunohistochemistry. Some of the cells within the infiltrated areas are labelled by bcl2 (**a**), p53 (**b**) and cyclin D1 (**c**) although distinction between reactive and neoplastic cells is uncertain. The proliferation activity is focally increased up to 8 % by Ki67 (**d**)

oligodendroglial phenotype with concomitant 1p/19q loss, had longer overall survival compared to non-mutated ones after targeted chemotherapy [13].

In our case post mortem examination revealed widespread infiltration of the cerebellum, brain stem, spinal cord, cauda equina and sensory ganglia, with focal involvement of white matter in the cerebral hemispheres. Our patient suffered progressive focal neurological deficits, particularly due to the widespread involvement of the cerebellum and the corticospinal tract. Spinal cord involvement in GC is reported only 9 % of the cases [14]. In our case the full length of the spinal cord was infiltrated, even with involvement of the cauda equina and sensory ganglia. The rate of spinal metastasis from intracranial glioblastoma is uncommon (0.4–2.0 %) and, despite the limited number of well-documented cases, there has been an increase in the frequency of spinal cord involvement in recent years [15–17]. Invasion of the cauda equina and sensory ganglia indicates that GC and high grade gliomas may break the glial barrier of CNS-PNS junction at the nerve roots.

Histological diagnosis of GC can be challenging, particularly in small biopsy material. Typically the infiltrating tumour cells are formed by a population of spindle-shaped atypical cells, resembling astrocytoma, but GC composed of predominant oligodendroglial cells has been also described [18]. GC can be mistaken for non-neoplastic white matter disease as the differentiation of reactive astrocytes from atypical tumour cells can be very difficult. Immunohistochemistry for GFAP and S100 may label some of tumour cells but, as in the present case, the strong background staining of the gliofibrillary processes may prevent recognition of the true tumour cells. The recently introduced IDH1 appears to be the most helpful immunostain in the neuropathological practise, which labels up to 80 % of diffuse low grade gliomas [19]. It appears that IDH1 mutations are mainly identified in 30-42 % of GC cases with solid tumour mass but not in type 1 GC [20–22]. Our case was IDH1 negative and no IDH1 or IDH2 mutations were detected. This is in accordance to the literature that type 1 GC is more likely to represent an IDH1 negative diffuse glioma which is genetically distinct from the mass forming diffuse astrocytomas. Combined chromosomal losses of 1p and 19q are usually not found in GC [20]. IDH1 (R132H) mutation in GC, particularly with co-expression with α-internexin, appears to be associated with response to chemotherapy [21, 22].

We detected immunoreactivity for p53, Bcl2 and cyclin D-1 in some of the cells within the infiltrated areas; however, distinction between reactive and neoplastic cells were not possible. Some alterations of cell cycle regulators have been described in GC and others malignant gliomas, such as the down-regulation or the suppression of cyclin D1 gene expression [23, 24]. On the other hand, cyclin D1 expression in neurons and glia has been described after traumatic brain injury [25] and we have also seen it in reactive brain (personal observation). Bcl2 expression is an anti-apoptotic protein uniquely associated with neoplastic transformation and for that, it could be an interesting target in futures therapies on GC [26]. Furthermore, p53 mutation are well known in malignant gliomas but only rarely observed in GC [20, 27].

We detected the missense mutation of the BRAF V600E type in our case. More than 95 % of BRAF mutations are of the V600E type, which leads to the substitution of valine by glutamic acid in the activating segment of the kinase domain of BRAF. The mutated BRAF protein is constitutively activated and enhances the proliferative potential through activation of the mitogen-activated protein kinase (MAPK) pathway [28]. BRAF point mutations are found frequently in pleomorphic xanthoastrocytoma (60–70 %), and ganglioglioma (~20 %) and extra-cerebellar pilocytic astrocytomas (30–40 %) [29, 30]. For primary glioblastomas this alteration is altogether rare (<5 %) but is more frequent in the subset of paediatric glioblastomas (~10 %) [31]. Schindler et al. found BRAF V600E mutation in one of their 5 GC cases [30]. The positive case was histologically diagnosed as astrocytoma grade II in biopsy and no further details were given about the negative GC cases. These findings implicate BRAF V600E mutation as a valuable diagnostic marker even for rare tumor entities. The BRAF(V600E) inhibitor PLX4720 significantly increased survival of mice after intracranial transplant of genetically relevant murine or human astrocytoma cells[32, 33]. It remains to be seen whether BRAF V600E mutant brain tumour patients will benefit from BRAF V600E-directed targeted therapies.

Conclusion

We described a case of GC type 1 with extensive spinal cord infiltration diagnosed by autopsy. In spite of its rareness, GC should be taken into account in differential diagnoses mainly when there is rapid clinical deterioration without clear evidence of radiological progression. Macroscopic examination of the brain revealed firm white-grey lesions predominantly in the cerebellar white matter and the brainstem, spreading to the full length of the spinal cord, cauda equina and the sensory ganglia. Histology revealed an extensively infiltrating, IDH1 negative, diffuse glioma with BRAF V600E mutation. Future clinical trials should address whether BRAF V600E mutant brain tumour patients will benefit from BRAF V600E-directed targeted therapies.

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