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CASE REPORT

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Sudden unexpected death due to undiagnosed glioblastoma

Report of three cases and review of the literature

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Abstract Although glioblastomas are among the most common primary cerebral neoplasms, sudden death due to these tumors is an uncommon event. Due to the usual rapid increase in intracranial pressure, patients develop symptoms rather early, leading to medical attention in time. A search for cases of sudden unexpected death due to undiagnosed glioblastoma from a total of 14,482 cases from the archives of the Institute of Legal Medicine in Hamburg in the period of 1991–2003 revealed only one such case. Out of a total of 5,432 cases from the Institute of Neuropathology, Hamburg, during the same period, two further cases were found. A comprehensive literature review on cases of sudden death due to primary cerebral neoplasms published so far revealed a total of 83 cases with only ten cases of glioblastoma (12%), whereas 55 of these cases were due to histological benign tumors (66%).

Keywords Sudden death · Brain neoplasms · Glioblastoma · Forensic neuropathology

Introduction

Primary intracranial neoplasms are relatively rare, with an annual incidence of 14.0 per 100,000 reported in the USA [1]. Nevertheless, the mortality due to primary intracranial neoplasms is high, particularly in young adults aged 20 to 39 years, representing the third leading cancer-related death during these two decades [2]. Since patients with intracranial neoplasms present rather early in the course of their disease—typically with headaches, seizures, nonspecific cognitive or personality changes, or focal neurological signs [3]—sudden unexpected death due to intracranial neoplasms is an uncommon event seen only exceptionally in medicolegal autopsy practice. Moreover, as a result of increasingly widespread access to modern and sensitive imaging technology (e.g., magnetic resonance imaging), sudden deaths due to undiagnosed intracranial neoplasms probably account for significantly lower percentages in forensic autopsy series nowadays than in similar series prior to 1980 [2]. We report three cases of sudden unexpected death due to undiagnosed glioblastoma according to WHO grade IV from our own archives and present a review of the literature from 1966 through 2003.

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Materials and methods

Review of autopsy files

A retrospective chart review of 14,482 autopsies carried out at the Institute of Legal Medicine, University of Hamburg, Hamburg, Germany, during 1991–2003 was performed to identify outpatient fatalities due to primary brain tumors which presented as sudden unexpected death. During this period, there were six cases of sudden unexpected death due to a primary brain tumor (accounting for 0.04% of all cases). In four of these cases, paraffin sections of the respective tumors were available and reevaluated according to the latest WHO classification of tumors of the nervous system [4] as glioblastoma WHO grade IV (case no. 1), atypical meningioma WHO grade II, pilocytic astrocytoma WHO grade I, and epidermoid cyst, respectively. Unfortunately, in the remaining two cases, neither paraffin sections nor wet material was still available. In one of the cases, diagnosis could be gathered with reasonable certainty from the protocol of the legal autopsy as meningioma (drowning following epileptic seizure in the bath tub; firm, well-demarcated lobulated dural tumor with im-

pression of adjacent frontal lobe measuring 10×3× 2 cm). In the last case, the patient was a man with a history of renal carcinoma, who suddenly collapsed while at lunch. Autopsy revealed signs of central dysregulation and increased intracranial pressure. Macroscopically, a tumor of the right parietal lobe measuring 5×7×5 cm was described. Bleeding or necrosis was not described. Because of the infiltrative nature of the tumor with blurred and indistinctive boundaries, a diagnosis of "benign glioma" was given. Histology, however, was not done. Admittedly, this last case remains somewhat uncertain, since we are not able to exclude totally metastasis or even glioblastoma.

In addition, the files of the Institute of Neuropathology, University of Hamburg, Hamburg, Germany, from the period 1991–2003 were reviewed. From a total of 5,432 brain autopsies performed during this period, five cases of sudden unexpected death due to undiagnosed brain tumors were found (accounting for 0.09% of all cases), two of which were due to glioblastoma (case nos. 2 and 3). Here, the diagnoses in the remaining three cases were anaplastic oligodendroglioma according to WHO grade III, medulloblastoma WHO grade IV, and primary cerebral lymphoma (malignant non-Hodgkin's lymphoma).

Literature search

A MEDLINE literature search with restriction to English, French, and German languages was performed for the period of 1966 through 2003, using the thesaurus' terms "sudden death" and "brain neoplasm" in combination. Citations in these papers were reviewed for further published cases. After dismissing tumors not listed in the latest WHO classification of tumors of the nervous system [4] and those not fulfilling the criteria of sudden unexpected death as one occurring in a hitherto asymptomatic person with a time interval of maximal 24 h from beginning of onset of symptoms, 83 cases remained. The tumors were then classified as benign (WHO grade I or II) or malignant (WHO grade III or IV), respectively. The results of this classification are shown in Table 1.

Case reports

Case no. 1

A 33-year-old woman was found dead in her apartment. She was lying in her bed with the sheets underneath the body being voided. At the scene, no clues toward suicide or external violence could be established by law enforcement officers. Reportedly, the woman had been in a good health status prior to death. A medicolegal autopsy was performed. Here, signs of central dysregulation (moderate brain edema with a weight of 1,450 g, massive hemorrhagic pulmonary edema and terminal aspiration of stomach contents) together with fresh tongue biting marks were found. Macroscopically, a brain tumor of the right frontoparietal region was suspected. Laboratory investigation did not detect any drugs or controlled substances in the woman's body fluids. The blood alcohol concentration was 0.00 g/l.

The brain was fixed unsliced in buffered formaline and dissected after 3 weeks fixation. Here, a tumor of the right hemisphere with numerous cystic spaces, extending into the corpus callosum and the contralateral white matter, was found (Fig. 1). Histologically, the tumor was composed of mostly poorly differentiated pleomorphic astrocytic cells with moderate degree of nuclear atypia. At the periphery of the tumor, extensive calcification was seen. Incipient microvascular proliferation was also present. Focally, the tumor featured necroses with nuclear pseudopalisading (Fig. 2). Immunohistochemical staining was performed with antibodies against glial fibrillary acidic protein (GFAP; DAKO Z334), synaptophysin (DAKO M776), neurofilaments (NF; Zymed), p53 protein (DAKO M7001), epidermal growth factor receptor (EGFR; DAKO M3563), and the proliferation-associated antigen Ki 67 (MIB1; DAKO M7240), using standard protocols with positive controls for each antibody. The tumor cells were GFAP-positive and negative for the neuronal markers NF and synaptophysin as well as EGFR negative. Ki67/MIB1-labeling index was 5.6% (five positively stained nuclei in 89 nuclei in 0.1 mm^2). The percentage of nuclei with accumulation of p53 was 1.0%

Table 1 Cases of sudden death due to undiagnosed primary intracranial neoplasms, classified as benign or malign (a total number of cases 83)

Benign	*n*=55	Malign	*n*=28
Astrocytoma (grade II)	*n*=17	Glioblastoma (grade IV)	*n*=10
Meningioma (grade I or II)	*n*=8	Anaplastic astrocytoma (grade III)	*n*=6
Oligodendroglioma (grade II)	*n*=8	Medulloblastoma (grade IV)	*n*=4
Pilocytic astrocytoma (grade I)	*n*=4	Malignant lymphoma	*n*=3
Ependymoma (grade II)	*n*=4	Germinoma	*n*=1
Lipoma (benign)	*n*=3	Gliosarcoma (grade IV)	*n*=1
Subependymoma (grade I)	*n*=3	Malignant glioma	*n*=1
Teratoma (mature/benign)	*n*=2	Anaplastic oligodendroglioma	*n*=1
Ganglioglioma (grade I or II)	*n*=2	Anaplastic ependymoma	*n*=1
Schwannoma (grade I)	*n*=1		
Hemangioblastoma (grade I)	*n*=1		
Subependymal giant cell astrocytoma (grade I)	*n*=1		
Central neurocytoma (grade II)	*n*=1		

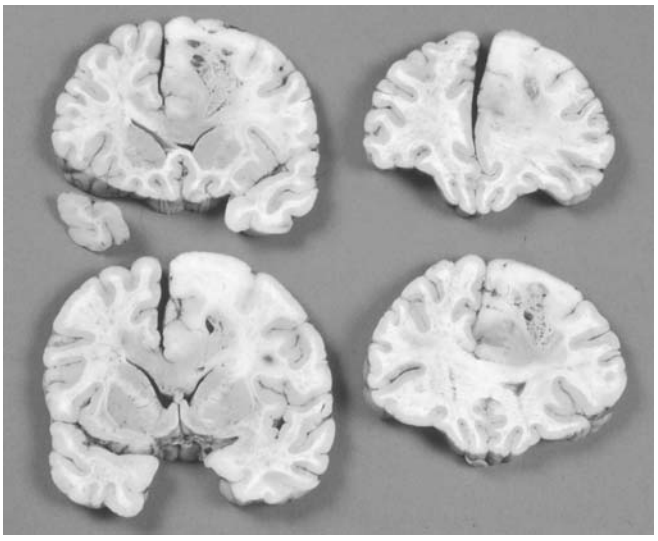

Fig. 1 (Case no. 1): Macroscopic view showing diffuse enlargement of frontoparietal regions on the right side with blurring of junction of grey and white matter, numerous cystic spaces, and tumorous infiltration of the corpus callosum

(one positively stained nucleus in 96 nuclei in 0.1 mm^2). The final diagnosis was glioblastoma corresponding to WHO grade IV.

Case no. 2

A 52-year-old man suddenly collapsed at home. He was transported to the Emergency Department where he was clinically described as comatose and unresponsive. The pupils were dilated and not reacting to light. Clinically, thrombosis of dural sinus was suspected. Since the man was officially declared as brain-dead, no further diagnostic or therapeutic measures were initiated. Reportedly, the man had been in a complete good health status prior to death. Pathological findings of the clinical autopsy were of no significance relevant to the man's death; the immediate cause of death was given as "brain edema". Neuropathologically, a tumor of the left cingulated gyrus with infiltration of the thalamus and adjacent white matter was found. The surrounding structures showed marked edema. There were signs of marked brain swelling (brain weight 1,520 g, flattened gyri, hemorrhagic necroses of cerebellar tonsils). Histologically, a small-cell astrocytic neoplasm with marked endothelial proliferation, necroses, and pseudopalisading was seen (Fig. 3). Immunohistochemically, the tumor was GFAP-positive and negative for neuronal markers and for EGFR. Ki67/MIB1-labeling index was 7.3% (7/96 nuclei). The percentage of nuclei with accumulation of p53 was 7.7% (7/90 nuclei) Final diagnosis was glioblastoma according to WHO grade IV.

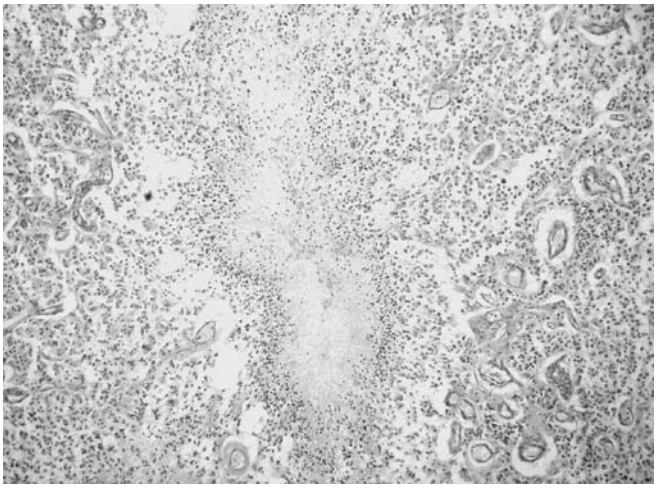

Fig. 2 (Case no. 1): Glial neoplasm with central necrosis surrounded by pseudopalisading (haematoxilin and eosin, original magnification 10×)

Case no. 3

A 75-year-old man presented to the Medical Department with a history of "cardiac syncope" and coronary atherosclerosis. During his stay, extensive studies of cardiac functions were done. Reportedly, no neurological findings or symptoms were apparent. On the 10th day of his hospital stay, the man was found lying dead in his bed. Pathological findings at clinical autopsy were consistent with ischemic cardiomyopathy due to moderate coronary atherosclerosis. Histology showed slight bronchopneumonia. Since the clinical pathologist did not find any suspicious cerebral findings, death was "most probably attributed to biventricular heart failure". Neuropathologically, a tumor of the left cerebellar hemisphere with infiltration of adjacent brainstem structures was found. There were only mild signs of brain swelling. Further, dilatation of the lateral and third ventricle, attributed to tumorous occlusion of the aqueduct, was seen. Histologically, a small-cell astrocytic neoplasm with focal gigantocellular differentiation featuring necroses was described (Fig. 4). Infiltration of tegmental lower brainstem structures was seen. Immunohistochemically, the tumor was GFAP-positive and negative

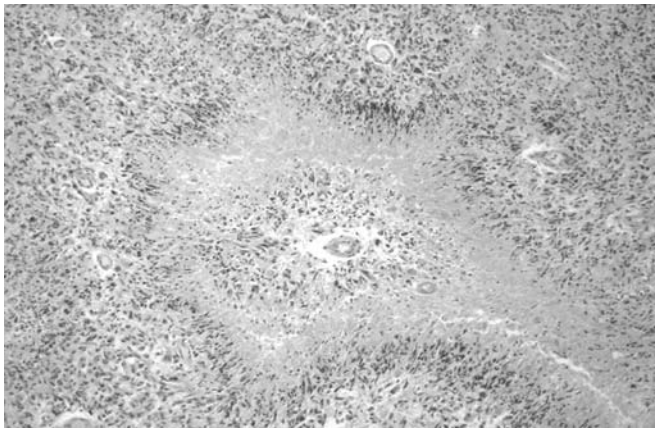

Fig. 3 (Case no. 2): Glial neoplasm with necrosis and pseudopalisading (H&E, original magnification 10×)

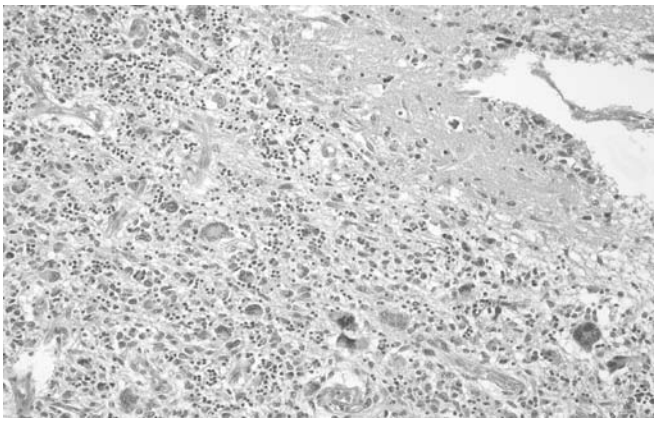

Fig. 4 (Case no. 3): Glial tumor with numerous bizarre pleomorphic multinucleated tumor cells (H&E, original magnification 20×)

for neuronal markers and for EGFR. Ki67/MIB1-labeling index was 8.9% (14/157 nuclei). The percentage of nuclei with accumulation of p53 was 5.5% (7/127 nuclei). The final diagnosis was glioblastoma according to WHO grade IV.

Discussion

Glioblastoma, defined as the most malignant astrocytic tumor and corresponding to WHO grade IV, is a relatively frequent intracranial neoplasm, representing about 12–20% of all intracranial tumors and accounting for about 50–60% of all astrocytic gliomas. In the USA, the incidence is reported as two to three new cases per 100,000 population/year. Generally, their peak age is between 45 and 75 years; if exceedingly rare before the age of 30, they exempt no age and may even occur in childhood or prenatal stage. A concept of two distinct glioblastoma subtypes has been developed in recent years, combining clinical, morphological, and genetic data. Primary glioblastomas (i.e., arising de novo with no apparent low-grade precursor lesion) account for the majority of cases in older patients with a mean age of 55 years. These tumors often show overexpression of the epidermal growth factor receptor (EGFR) involved in control of cell proliferation, but simultaneously only seldom bear alterations of the p53 tumor suppressor gene on chromosome 17p. On the other hand are secondary glioblastomas, developing through progression from low-grade or anaplastic precursor astrocytoma in patients typically younger than 45 years. Contrariwise to the primary tumors, most secondary glioblastomas show significant accumulation of p53 protein, but lack immunoreactivity for EGFR. After diagnosis of glioblastomas, the mean survival is only about 12 months [5, 6].

The clinical picture of any intracranial tumor is a function of its location rather than its histology [7]. The likelihood of clinical symptoms in patients with an intracranial mass rises with the rapidity of its growth, thus simultaneously keeping compensatory mechanisms from developing. Consequently, the more malignant the tumor, the more likely the occurrence of clinical symptoms and the greater the likelihood that the tumor will be detected. It is the slowly expanding benign tumor that threatens the patients, allowing a long time for compensatory mechanism to be eventually exhausted, thus leading to sudden unexpected death in a person without any obvious complaints prior to death. In this respect, it is no surprise that judging from the cases published in the literature, two thirds of all sudden deaths due to primary intracranial neoplasms are histologically benign (Table 1). Contrary to the notions made by other authors [8], in our analysis of the literature, only 12% of all cases of sudden unexpected death due to primary intracranial tumors were due to glioblastomas. This figure rises, when comprising all possible "malignant gliomas", i.e., the anaplastic variants (i.e., according to WHO grade III) of astrocytoma, oligodendroglioma, and ependymoma as well as gliosarcoma and "malignant glioma" not otherwise specified, to 24%—which is still lower than the 66% benign tumors.

The tumor in case no. 1 is remarkable in so far as large parts of the right hemisphere as well as neighboring parts of the left hemisphere were diffusely infiltrated and overrun by the tumor cells. Together with the low mitotic count and the extensive calcifications in some regions it seems safe to say that the tumor obviously has been growing rather slowly and indolently for a relatively long period of time. This would explain the fact that the patient reportedly did not suffer any symptoms because sufficient compensatory mechanism were already developed. The only few and focal anaplastic changes (i.e., necrosis and endothelial proliferations) on a background of a mostly monomorphic astrocytic tumor in this case indicate progression to glioblastoma from low-grade astrocytoma (secondary glioblastoma). This assumption is further strengthened by the patient's age of 33 years and lack of EGFR immunoreactivity. Although the comparatively low p53-labeling index in this case might not be considered typical, it does not exclude secondary glioblastoma since the percentage of secondary glioblastomas with labeling indices less than 5% (or even with no p53 immunoreactivity at all) has been reported as 30%, the average labeling index being 10.5±7.5% [9]. The morphological findings with signs of central dysregulation and fresh tongue biting marks indicate a rather rapid death in this 33-year-old woman due to epileptic seizure followed by central apnea and/or cardiac arrest. Histological studies of the hippocampus and the neocortex failed to detect any ischemic neurons. Since these take some hours to develop, the duration of agony most probably had not been too long.

A clear-cut assessment of the cause of death in case nos. 2 and 3, respectively, was strongly hampered by the lack of detailed descriptions of the finding situation of the deceased at the death scene inside the hospital. Accordingly, findings of potential medicolegal relevance (e.g., hints toward terminal seizures) were not reported. The same holds true for the only sparse acknowledgment of findings of possible relevance to the patient's death in the protocols of the clinical autopsies. In particular, the presence or lack of specific findings, such as fresh or old tongue biting marks, signs of central dysregulation (e.g.,

lung edema, dilatation of urinary bladder, and intestines), were not given by the pathologists performing the clinical autopsies.

In case no. 2, pronounced peritumoral edema most probably led to lethal marked brain edema; whether a terminal seizure had been present or not remains unclear due to lack of both any witnesses at the scene of death and detailed pathoanatomical descriptions. Despite the patient's age and the lack of histological low-grade parts, the p53-labeling index, the negative EGFR immunoreactivity, and the lack of clinical symptoms all make a diagnosis of secondary glioblastoma most probable.

In case no. 3, only thorough neuropathological examination, including extensive histological investigation of the lower brainstem, contributed to the elucidation of the man's actual cause of death. Most probably, the cause of death in this case was central dysregulation due to tumorous infiltrative destruction of vital centers in the lower brainstem [10] and/or decompensation of chronic occlusive hydrocephalus. It remains speculative, whether the "cardiac syncopes" in this patient could have been early signs of involvement of cardioregulative centers in the lower brainstem. Most astonishing in this case is the fact that obviously at no time during the whole clinical stay of 10 days, any intracranial lesions has been suspected or searched for since neurological signs or symptoms reportedly were not present. Age of the patient and lack of significant accumulation of p53 as well as the histological picture with no "low-grade areas" in case 3 all make a diagnosis of primary glioblastoma most probable, even when considering the lack of immunoreactivity for EGFR (which does not exclude primary glioblastoma, since 36.8% of primary glioblastomas show no EGFR overexpression as shown by immunohistochemistry [9]). The location in the cerebellum might had at least initially produced only vague symptoms.

When evaluating cases of sudden death due to undiagnosed glioblastoma reported in the literature, similar problems in defining the most probable causes of death, as put forward here, are encountered. Although modern diagnostic imaging techniques have revolutionized the diagnosis of brain tumors, autopsy of the brain is still the final word in determining exact location, topography, mass effects, and histology of glioblastomas [11]. The majority of authors that the final common pathway in most cases of sudden death due to undiagnosed glioblastoma is an increase in intracranial pressure due to local mass effect, compression of cerebrospinal fluid circulation, or hemorrhage from arrosion of vessels affected by the infiltrative nature of these tumors [2, 8, 11–16].

The investigation of sudden unexpected death is one of the most important and, simultaneously, one of the most challenging tasks for the forensic practitioner. In cases with suspected intracranial pathology [17, 18], the necessity of a multidisciplinary approach, including a full autopsy with detailed documentation even of negative findings that might be of relevance in later stages of the medicolegal investigation as well as neuropathological examinations, is once more illustrated by the cases presented here.

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