**Sudden Death due to Primary Intracranial Neoplasms. A Forensic Autopsy Study**

**THEODORE VOUGIOUKLAKIS**, **ANTIGONY MITSELOU** and **NIKI J. AGNANTIS**

Departments of **1**Forensic Pathology and **2**Pathology, Medical School, University of Ioannina, Ioannina, Greece

**Abstract.** Although most fatal tumors are diagnosed well before a patient’s death, occasionally forensic pathologists encounter cases in which the presence of a primary tumor of the central nervous system had not been suspected prior to death. A search for cases of sudden death due to intracranial tumors from a total of 1985 autopsies from the archives of the Department of Forensic Pathology, University of Ioannina, Greece, in the period 1998-2005, was undertaken. Two such cases in which a medico-legal autopsy had disclosed brain tumors were found. The first case was a 34-year-old man who had been found unconscious in bed, and died a few hours after hospitalization. His autopsy had revealed a 7-cm glioblastoma at the level of the third ventricle. The second case involved a 67-year-old man presenting with brain tumor, diagnosed 1.5 months previously. The patient had died after 16 hours of hospitalization. A 4-cm astrocytoma of the left temporal lobe had been found at autopsy. In both cases, the tumors may, directly or indirectly, have been the underlying cause of death. The importance of a thorough neuropathological examination in all cases of sudden death, in which no extracerebral cause had been found, is emphasized.

Sudden death from an undiagnosed primary intracranial neoplasm is an exceptionally rare event, with reported frequencies in the range of 0.02% to 2.1% in medico-legal autopsy series (1-6) (Table I). Lindboe et al., however, pointed out that many of the individuals in these series had had long-term clinical symptoms of an intracranial process and, therefore, their deaths could not be regarded as unexpected; in fact, only a small minority of the patients had actually been found dead or died instantaneously (7). Mortality due to brain neoplasm is particularly high in young adults aged 20 to 39 years, representing the third leading cancer-related death in the past two decades (6).

As a result of increasingly widespread access to modern and sensitive imaging technology, such as computed tomography (CT) and magnetic resonance imaging, sudden death due to undiagnosed intracranial neoplasms probably accounts for fewer cases in forensic autopsy series (6, 7). In this article, two patients, whose sudden demise could be directly attributed to the effects of a previously augmented intracranial pressure due to acute and severe hemorrhage of a brain tumor, comprising a glioblastoma grade WHO-IV and an astrocytoma grade WHO-III respectively, are presented. The presence of astrocytic tumors is not surprising since they are the most common type of brain tumors, accounting for more than 38% of all primary central nervous systems (CNS) lesions, and are generally fatal (6). The mechanisms of death included seizures, acute hemorrhage and herniation due to mass effect (8-11).

**Materials and Methods**

A retrospective review of 1,985 autopsies, carried out at the Department of Forensic Pathology, University of Ioannina, Ioannina, Greece, in the period 1998-2005 (through September, 2005), was performed to identify out-patient fatalities due to primary brain tumors, which presented as sudden death. During this period, there had been two cases (accounting for 0.1% of all cases). In both cases, paraffin sections of the respective tumors were available and were re-evaluated according to the latest World Health Organization (WHO) (11) classification of tumors of the CNS as glioblastoma grade IV and astrocytoma grade III. The two cases fulfill the criteria of sudden death as death occurring in an asymptomatic person, with a maximum time-interval of 24 hours after the onset of symptoms.

**Case 1**

A 34-year-old man had been found unconscious in bed, in the military unit where he worked. He was rushed to the emergency department of the University Hospital. The patient appeared acutely ill, unresponsive with fixed dilated pupils and had the minimum Glasgow coma scale score of 3; he was ventilated and admitted to the intensive care unit.
The CT scan of the brain showed edema, dilatation of the lateral ventricles, hydrocephalia and the existence of a hemorrhagic mass at the third ventricle. After 1 day in a coma, the patient died. Approximately 2 months before his death, the patient had consulted a doctor in the neurological department of a hospital complaining of headache and neck pain. A diagnosis of tension headache had been made and the possibility of brain tumor appears not to have been considered. One week before his hospitalization, he had suffered loss of consciousness.

A forensic autopsy was conducted the day after the patient’s death. Apart from artifacts of resuscitation, no significant injury was found. Internally, the heart was of normal size and configuration with no evidence of anomaly, while the lungs showed mild to moderate congestion and pulmonary edema. With the exception of the brain, the remaining organs were apparently healthy, with no evidence of macroscopic pathology. The brain weighed 1620 g and showed diffusely cerebral edema and swelling. A hemorrhagic mass, of maximum diameter of 6.9 cm, was present at the third ventricle, at the level of the foramen of Monro. On coronal sections of the brain, the cerebral hemispheres demonstrated widespread, marked flattening of the gyri and marked dilation of the lateral ventricles. The spherical mass was accompanied by massive fresh hemorrhage, measuring, in total, 6.9 x 5.2 x 3.4 cm. A cut surface revealed a friable mass, whitish in color, with extensive areas of necrosis and hemorrhage. Microscopically, the tumor was composed of small-cell astrocytes, with areas of poorly-differentiated pleomorphic astrocytic cells with nuclear atypia (Figure 1). Incipient microvascular proliferation was also present. Immunohistochemical staining was performed with antibodies against glial fibrillary acidic protein (GFAP), synaptophysin, p53 protein and the proliferation-associated antigen Ki-67 (MIB1). The tumor cells were GFAP-positive and synaptophysin-negative. The Ki-67/MIB1-labeling index (LI) was 6.7%. The percentage of the nuclei with accumulation of p53 protein was 5.2%. The final diagnosis was glioblastoma corresponding to WHO grade IV.

Case 2

A 67-year-old man had been admitted to the emergency room with unresponsive, fixed, dilated pupils, a temperature of 36.5°C, blood pressure of 110/40 mmHg, heart rate of 60 bpm and a respiratory rate of 8 bpm. He had absent papillary light, corneal and gag reflexes and had a Glasgow coma scale of 4. A head CT scan showed a mass in the left temporal lobe, accompanied by hemorrhage and cerebral edema. The patient died after 16 hours, following withdrawal of medical and mechanical life support. Reportedly, the patient had consulted a physician due to headache and occasional vomiting. A CT scan had revealed a tumor in the left parietal lobe, with no other specifications. Some weeks later, the man had been found unconscious in front of his house.

An autopsy was performed immediately after death. Internally, the heart was of normal configuration with no evidence of anomaly, was slightly hypertrophic and coronary atherosclerosis grade II/III was observed. The lungs showed mild to moderate congestion and pulmonary edema and few foci of condensation at the lower lobes. The brain weighed 1580 g and showed diffuse cerebral edema and cerebellar tonsillar herniation. Horizontal sections revealed a 4 x 4 x 5-cm, firm, variegated tan-brown mass, with areas of hemorrhage and necrosis, arising from the left temporal lobe. The tumor extended well into the third lateral ventricle, compressing the lumen and infiltrating deeply into structures.

The microscopic evaluation of the mass showed diffuse replacement of the cerebral tissue by neoplastic cells with the presence of small and large astrocytes, in some areas dispersed and in others arranged in small or larger groups; nuclear atypia and marked mitotic activity were present. The tumor was accompanied with foci of hemorrhage and necrosis. Immunohistochemical evaluation indicated positive staining from GFAP. The Ki-67/MIB1 LI was 4.9% and accumulation of p53 protein was 3.7 %. The final diagnosis was anaplastic astrocytoma corresponding to WHO grade III.

Table I. Undiagnosed central nervous system tumor studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Years</th>
<th>Autopsies</th>
<th>CNS tumor deaths %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington et al. (1)</td>
<td>Kern County, California, USA</td>
<td>1950 - 1955</td>
<td>3543</td>
<td>0.42</td>
</tr>
<tr>
<td>Schreiber and Warsok (2)</td>
<td>Erturt, Germany</td>
<td>1953 - 1976</td>
<td>54946</td>
<td>2.7</td>
</tr>
<tr>
<td>Di Maio and Di Maio (4)</td>
<td>Brooklyn, New York, USA</td>
<td>1960 - 1970</td>
<td>17404</td>
<td>0.16</td>
</tr>
<tr>
<td>Di Maio et al. (3)</td>
<td>Dallas County, Texas, USA</td>
<td>1970 - 1977</td>
<td>10995</td>
<td>0.17</td>
</tr>
<tr>
<td>Tiszlavicz (5)</td>
<td>Szeged, Hungary</td>
<td>1960 - 1990</td>
<td>37504</td>
<td>1.2</td>
</tr>
<tr>
<td>Eberhart et al. (6)</td>
<td>Maryland, USA</td>
<td>1980 - 1999</td>
<td>54873</td>
<td>0.02 - 0.05</td>
</tr>
<tr>
<td>This study</td>
<td>Ioannina, Greece</td>
<td>1998 - 2005</td>
<td>1985</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Discussion

Intracranial tumors are said to account for 8% of non-traumatic intracerebral hemorrhage. About half of this may be the first manifestation and in a small proportion of these cases the patients die suddenly (12). In our experience, sudden death is rare and only two cases were identified in the files of the Department of Forensic Pathology from 1998 to 2005. In the literature, of the primary brain tumors glioblastoma multiforme (3) predominates; other tumors that have been reported to present in this way include anaplastic astrocytoma, oligodendroglioma, medulloblastoma, lymphoma, teratoma and pituitary adenoma (4). Astrocytomas are the most frequent malignant primary brain tumors in adults. Clinically, this group of tumors can be divided into four World Health Organization (WHO) grades. Pilocytic astrocytomas (WHO grade I) are generally slow growing and non-infiltrative pediatric tumors, which are rarely fatal. Grade II astrocytoma patients survive an average of over 5 years, but survival drops to 3 years for anaplastic carcinomas (grade III). Grade IV astrocytomas account for about half of all astrocytic tumors, with a median survival of less than a year (12).

Glioblastoma, defined as the most malignant astrocytic tumor, is a relatively frequent intracranial neoplasm, representing about 12-20% of all intracranial tumors and accounting for about 50-60% of all astrocytic gliomas. Generally, the peak incidence age range is between 45 and 75 years; while decidedly rare before 30, no age is exempt and cases may arise in childhood and even in the prenatal stage. The sex distribution shows a preponderance of males, ranging from 2:1 to 3:2 (13). The white matter of the brain is characteristically involved and the distribution of the tumor is wide. The frontal lobes are most often involved and, generally, the forepart of the brain is implicated far more frequently than the posterior; the occipital lobes are a rare site (14).

Histopathologically, glioblastomas are heterogeneous tumors, including small cells with minimal cytoplasm and round hyperchromatic nuclei, as well as large multinucleated cells. Tumor necrosis in glioblastoma appears as either foci of micronecrosis or broad necrotic zones, as in our cases, surrounded by a hypercellular zone consisting primarily of parenchymal infiltration, which is visible as a soft grey rim. The observation of a red and brown coloration from extensive hemorrhaging, which often elicits stroke-like symptoms, is common. In our cases, extensive fresh hemorrhage had been observed both within and surrounding the tumor. Another prominent characteristic of these tumors is the presence of thrombosed vessels surrounding and within the neoplasm (14, 15).
The concept of two distinct glioblastoma subtypes has been developed in recent years, combining clinical, morphological and genetic data (14, 16). Primary glioblastomas, arising de novo with no apparent low-grade precursor lesion, and in the majority of cases occurring in older patients, with a mean age of 55 years. Secondary glioblastomas develop through progression from low-grade or anaplastic precursor astrocytoma in patients typically younger than 45 years. In contrast to the primary tumors, most secondarily glioblastomas show significant accumulation of the p53 protein, but lack immunoreactivity for EGFR, and PTEN mutation is rare (16). In our case, significant immunostaining for the p53 protein, was observed. These data indicate that primary and secondary glioblastomas carry different genetic alterations.

WHO grade III astrocytomas are preferentially located in the cerebral hemispheres. The growth may be deep, involving such structures as the corpus callosum, septum pellucidum and basal ganglia. They occur in adult patients (peak incidence 45-60 years). Microscopically, anaplastic astrocytomas are characterized by signs of focal or diffuse anaplasia, such as increased cellularity, nuclear atypia and marked mitotic activity. The typical histological hallmarks of glioblastoma (microvascular proliferation and necrosis) are not yet present, but anaplastic astrocytomas tend to progress to secondary glioblastomas, as mentioned above (12, 14). On cytogenetic analysis, most anaplastic astrocytomas demonstrated deletions in chromosomes 6, 9p, 11p, 19q and 22q. When present, PTEN mutation indicates a poor prognosis. The TP53 tumor-suppressor gene mutation located at chromosome 17p13 is altered in anaplastic astrocytomas (17, 18).

Over recent years, improvements in imaging techniques, notably the introduction of CT and magnetic resonance imaging, have resulted in increased early detection of CNS neoplasms (6, 13). Furthermore, we observed a significantly lower incidence of death due to undiagnosed CNS tumors than reported in different studies (Table I).

In conclusion, autopsy of the brain is still definitive in determining the exact location, topography, mass effects and histology of brain tumors (19).

References


Received December 5, 2005
Revised February 15, 2006
Accepted February 20, 2006