Decreasing Incidence of Sudden Death Due to Undiagnosed Primary Central Nervous System Tumors

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Context.—Although most fatal brain tumors are diagnosed well before a patient's death, occasionally medical examiners and coroners encounter cases in which the presence of a primary tumor of the central nervous system (CNS) was not suspected prior to death. Analysis of such cases can shed light on specific pitfalls hindering the diagnosis of brain tumors. In addition, by analyzing the incidence of these cases in a large autopsy series, one can draw conclusions about the evolving effectiveness of medical diagnosis.

Objective.—To determine the incidence of deaths due to undiagnosed primary CNS tumors in the era of advanced neuroimaging techniques.

Design.—Records from forensic autopsies performed during a 20-year period (1980–1999) at the Office of the Chief Medical Examiner of the State of Maryland were reviewed for the period January 1980 to December 1999 (inclusive), and all primary CNS tumor cases were identified. Autopsy findings, medical records, and histories taken by investigators at the time of death were reviewed to identify primary undiagnosed primary intracranial neoplasms.

We present 76 cases of primary CNS tumors identified at autopsy between January 1980 and December 1999 (inclusive) at the Office of the Chief Medical Examiner of the State of Maryland (Table 1). We concentrate on particular on 11 cases in which the tumor was the cause of death or contributed significantly to the patient's death, but was not identified prior to the patient's demise.

The last large series reviewing sudden death due to undiagnosed primary CNS neoplasms was published by DiMaio and colleagues 20 years ago. With the emergence of advanced neuroimaging and other improved diagnostic techniques, we thought it timely to reexamine cases of CNS tumors that eluded antemortem diagnosis but caused unexpected death. These cases highlight the continuing problem of death due to brain tumors that are undiagnosed or misdiagnosed because of vague symptoms, coexisting conditions, or poor access to health care.

METHODS

Neuropathology records of the Office of the Chief Medical Examiner of the State of Maryland were reviewed for the period January 1980 to December 1999 (inclusive), and all primary CNS tumor cases were identified. Autopsy findings, medical records, and histories taken by investigators at the time of death were reviewed to identify primary undiagnosed CNS tumors causing the individual's death. Cases in which the cause of death was known to be unrelated to neoplasia (trauma, drug overdose, cardiovascular disease, etc) were excluded. Also excluded were cases in which the tumor was only an incidental finding, such as a small meningioma unrelated to the individual's demise. Finally, we excluded cases in which medical records or other evidence demonstrated that the tumor had been identified previously. As in earlier studies, cases in which a tumor was thought to cause death directly by precipitating a motor vehicle accident were included. In many instances, sufficient data were not available to determine if an antemortem diagnosis had been made or if the
REPORT OF CASES

Case 1
A 20-year-old woman was found dead in the bed of her college dormitory room at 4:30 PM. She was last seen alive at 1 AM on the same day. Her past medical history was unremarkable, except for a heart murmur.

General autopsy was unremarkable, with no abnormalities identified in the heart. The brain weighed 1600 g and showed a cortical mass lesion in the left superior frontal gyrus, 4 cm behind the frontal pole. This lesion, which measured 4.0 \times 2.5 \text{ cm} at the surface of the brain, was soft and surrounded by edema. Cingulate herniation was not observed. At the base, there was questionable herniation of the left temporal lobe uncus. On coronal sections, the bulk of the lesion was located in the left frontal white matter with infiltration of the adjacent cerebral cortex. Neither hemorrhage nor necrosis was observed, and the ventricular system was normal. The brain stem, cerebellum, and hippocampal formations were normal. Microscopic examination revealed a grade II astrocytoma with infiltration of the cerebral cortex (Figure, E).

In conclusion, this woman died as a consequence of a left frontal lobe astrocytoma, but the mechanism of death was uncertain. Possibilities included uncal herniation and death due to infiltration of the cerebral cortex by the tumor.

Case 2
Three weeks prior to death, a 36-year-old male wallpaper hanger developed a feeling of pressure, heaviness, and numbness in his right leg. He later developed low back pain, which radiated up to the back of the neck. He developed severe headaches associated with diplopia and blurred vision in the left eye. Balance was also impaired. A computed tomographic scan of the brain was conducted at a local emergency room and was unremarkable. The patient was then referred for neurosurgical consultation.

Upon clinical examination, the patient could not rotate his head to the left. He had questionable weakness of the right triceps muscle. The patient walked with a normal gait, and there was no tenderness on percussion of the lumbar spine. Hyperreflexia was noted in the lower extremities, with sustained ankle clonus on the right and bilateral Babinski signs. Sensation was normal in both lower extremities. The patient was scheduled for magnetic resonance imaging of the entire spine, but died prior to the imaging.

At autopsy, the brain weighed 1600 g. Gross inspection of the brain revealed no abnormalities. The spinal cord showed no external abnormality, but horizontal sections revealed softening and loss of anatomical landmarks in the lower segments of the thoracic region. No abnormality was noted in the cervical or lumbosacral cord. Microscopic sections confirmed the presence of an anaplastic astrocytoma centered in the thoracic and lumbar spinal cord, extending into the cervical cord and medulla (Figure, D). Death most likely resulted from tumor infiltration into the brainstem.

Case 3
A 42-year-old woman was found unresponsive in bed. Prior to her death, she apparently had not been feeling well due to stress. She had also complained about stomach and chest pains.

At autopsy, the general examination was unremarkable and revealed no evidence of trauma. The brain weighed 1330 g, and macroscopic examination revealed marked grooving of both temporal lobe unci. The cerebellar tonsils were not herniated or grooved. On coronal sections, the cerebral hemispheres demonstrated widespread, marked flattening of the gyri and marked dilation of the lateral ventricles. A spherical mass with a maximal diameter of 1.5 cm was present within the anterior third ventricle at the level of the foramen of Monro. In the midbrain, the aqueduct of Sylvius was slitlike. Microscopic sections from the third ventricle mass were diagnostic of a colloid cyst. In this case, death can be attributed to obstructive hydrocephalus and increased intracranial pressure.

Case 4
Two days prior to death, a 24-year-old, mentally handicapped, pregnant woman, who resided in a foster home, fell in the bathtub and hit her head. She went to a local emergency room, where she was examined and sent home with a diagnosis of neck strain. On the following day, she returned to the emergency room complaining of a headache and vomiting and was admitted to the obstetrics floor. One day after admission, she suffered cardiovascular arrest and could not be resuscitated. The baby, who was in the third trimester of gestation, was delivered by cesarean section.

General autopsy was remarkable for evidence of a recent cesarean section. The brain weighed 1210 g and showed a large tumor measuring 4 \times 3 \text{ cm} in the left pontocerebellar angle. The tumor had a soft consistency and appeared cystic in one of its extremes; it indented the inferior surface of the left cerebellar hemisphere and displaced the medulla toward the contralateral side. The left cerebellar tonsil was displaced backward, and the right cerebellar tonsil was herniated and closely apposed to the medulla. Coronal sectioning of the brain revealed mild enlargement of the lateral and third ventricles and the aqueduct of Sylvius. Microscopic examination revealed a schwannoma (Figure, F). Death in this individual can be explained by tonsillar herniation, and distortion and compression of the medulla by the tumor.

Case 5
A 39-year-old man was found unresponsive on the bathroom floor by his landlord and was pronounced dead at the scene by paramedics. The decedent was last seen alive several days prior to his death, and his sister stated that he had recently been complaining of back pain.

At autopsy, the general examination was unremarkable and revealed no evidence of trauma. The brain weighed 1620 g, and macroscopic examination revealed congested leptomeninges covering the cerebral hemispheres. A 2 \times 2-\text{cm} defect with extruding hemorrhage was noted in the left frontal pole. Left cingulate and uncial herniations were observed. On coronal sections, the cerebral hemispheres were asymmetrical with deviation of midline structures from left toward right. A massive fresh hemorrhage measuring 5.0 \times 5.0 \times 2.5 \text{ cm} was noted in the left frontal white matter; it was surrounded by significant edema and focal necrosis, and extended into the subarachnoid space of the frontal pole. The hemorrhage also extended into the genu of the corpus callosum and the head of the left cau-
Table 1. Primary Central Nervous System Neoplasms Identified in 54 873 Coroners’ Autopsies (1980–1999)*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex/Race</th>
<th>Site</th>
<th>Tumor</th>
<th>Cause of Death</th>
<th>Antemortem Diagnosis</th>
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* W indicates white; B, black; A, Asian; Y, yes; U, undetermined; N, no.
† An incidental meningioma was also identified in this patient.


date nucleus. As a consequence of mass effect, central herniation was observed, in addition to the left cingulate and left uncual herniations, and the left lateral ventricle was partially collapsed. Microscopic sections revealed a glioblastoma multiforme. Massive hemorrhage into the glioblastoma, brain edema, and herniation explain the death of this patient.

**Case 6**

A 29-year-old woman was found unresponsive in the bathroom at 6:45 AM. On the previous night at 11 PM, she complained of a headache and vomited. Her past medical history was significant for migraine headaches treated with amitriptyline hydrochloride.

General autopsy was unremarkable. The brain weighed 1380 g and showed diffusely swollen cerebral hemispheres with marked flattening of the gyri throughout the convexities. At the base, the temporal lobe unci and hypothalamus were prominent, but definite herniation was not observed. The cerebellar tonsils were also prominent, without definite herniation. On coronal sections, the ventricular system was enlarged. A spherical mass, measuring 2.5 cm in diameter, was attached to the left side of the septum pellucidum at the level of the foramina of Monro (Figure, A). This spherical mass partially occupied the third and left lateral ventricles. Microscopic examination revealed a colloid cyst. The cause of death can be attributed to obstructive hydrocephalus and increased intracranial pressure secondary to intraventricular tumor.

**Case 7**

A 35-year-old man was found unresponsive at home and pronounced dead on the scene. He had recently complained of headache and neck pain. His past medical history was unremarkable except for a history of intravenous drug abuse.

At autopsy, external examination revealed needle tracks on the arms. There was no evidence of trauma. Toxicology tests for drugs and alcohol were negative. The brain weighed 1600 g and showed edema of the right cerebral hemisphere. There was right cingulate herniation, but no uncual or tonsillar herniation. On coronal sections, the right cerebral hemisphere showed a large mass lesion, which measured 5 × 4 cm in cross-section, involving the basal ganglia and internal capsule (Figure, A). This lesion was hemorrhagic and surrounded by edematous tissue with greenish discoloration. As a consequence of mass effect, the right lateral ventricle was completely collapsed, and
the midline structures, including the third ventricle, were
displaced from right to left. Microscopic examination re-
vealed a glioblastoma multiforme. Mass effect from the
tumor and increased intracranial pressure can explain the
sudden death in this case.

Case 8

A 29-year-old Indonesian woman was found dead on
the bathroom floor of the home where she had worked as
a nanny for the past 7 years. She had recently complained
of headaches and suffered episodes of vomiting. Her past
medical history was unremarkable.

General autopsy was remarkable for acute pancreatitis.
Coronal sections of the brain revealed a large frontopari-
etal mass. This mass, which had a volume of at least 250
mL, occupied most of the white matter of the left cerebral
hemisphere and extended across the corpus callosum into
the right hemisphere. The mass obliterated the corpus cal-
sosum and frontal horns of the lateral ventricles. The lat-
eral ventricles were slightly dilated, but there was no di-
lation or elongation of the third ventricle or displacement
of adjacent hypothalamic structures. Microscopic exami-
nation revealed a glioblastoma multiforme (Figure, C). In
this case, the best explanation for sudden death is the mass
effect of the tumor. However, the possibility of a seizure
cannot be completely ruled out.

Case 9

A 39-year-old man was found unresponsive in bed. He
had a history of seizure disorder and behavioral changes,
which were attributed to severe head injuries sustained 10
years prior to death. He was being treated with antiepi-
leptic medication.

General autopsy was unremarkable. The brain weighed
1620 g, and gross examination revealed extensive softening
of the left superior and middle frontal gyri. There was
no herniation of the temporal lobe unci or cerebellar tonsils.
On coronal sections, the left frontal lobe exhibited a
3-cm cavity lesion filled with necrotic and gelatinous
material. In addition, softening and hemorrhagic discol-
oration of gray and white matter surrounded the lesion.
Slight deviation of the midline from left to right was ob-
served in the frontal lobes. The ventricular system was
partially collapsed, but there was no deviation of the se-
ptum pellucidum or third ventricle. Microscopic sections
revealed a malignant glioma. Although the brain of this
individual had evidence of mass effect, that is, left to right
shift and collapse of the ventricular system, the most like-
ly explanation for his death is seizure.

Case 10

A 78-year-old man was the unrestrained driver and sole
occupant of an automobile that crossed the center line and
hit another vehicle head on.

At autopsy, general examination was remarkable for lac-
erations of the aorta and pulmonary artery, a fracture of
the sixth cervical vertebra, and multiple rib fractures. The
brain weighed 1360 g, and macroscopic examination re-
vealed mild cortical atrophy in the frontoparietal lobes.
At the base, a lesion measuring 5.5 × 4.0 cm was noted
in the region of the pituitary gland and inferior surface of
the frontal lobes. This lesion was brown, irregular in
shape, and had a consistency that varied from gelatinous
to firm. On coronal sections, the lesion projected into and
separated the anterior portion of the frontal lobes,
wrapped around the optic nerves and chiasm, but did not
infiltrate brain structures. Microscopic examination re-
vealed a pituitary adenoma. It seems likely that the tumor
played a direct role in this individual’s death, either caus-
ing a seizure or compromising his vision. It is possible,
however, that the accident and subsequent death were un-
related to the pituitary adenoma.

Case 11

A 45-year-old man died after his automobile left the
road at a high rate of speed and impacted a tree. His past
medical history was unremarkable.

General autopsy revealed multiple facial injuries. The
brain weighed 1690 g and the cerebral hemispheres were
diffusely swollen. There was no herniation of the temporal
lobe unci or cerebellar tonsils. On coronal sections, a mass
measuring 4 cm in diameter was observed in the right
frontal lobe white matter. This mass had a variegated ap-
pearance and contained regions of necrosis and hemorrhage.
The mass extended into the left hemisphere through the anterior corpus callosum and obliterated the
frontal horn of the right lateral ventricle. The right cir-
gulate gyrus demonstrated minimal herniation. Micro-
scopic examination revealed a glioblastoma multiforme.
While seizure is the most likely explanation for this acci-
dent, the possibility of an accident unrelated to the tumor
cannot be excluded.

COMMENT

We present 11 cases of sudden deaths due to undiag-
osed primary CNS tumors discovered at autopsy during
a period of 20 years (1980–1999). These 11 cases represent
0.02% of the 54,873 autopsies performed at the Office of
the Chief Medical Examiner of the State of Maryland dur-
ing this time period. In an additional 16 cases out of the
76 listed in Table 1, deaths may have been caused by un-
diagnosed primary CNS tumors, but the medical infor-
mation available was insufficient to determine if the tu-
mors were the cause of death or if an antemortem diag-
nosis had been made. Thus, the incidence of undiagnosed
brain tumors causing death in our study could potentially
be as high as 0.05% if all 16 of these additional “undeter-
dined” cases were included.

The last review of this subject, published 20 years ago
by DiMaio and colleagues,2 involved 10,995 consecutive
autopsies performed by the Dallas County Medical Ex-
aminer’s Office in Texas from January 1970 through De-
cember 1977. The authors found unsuspected primary in-
tracranial neoplasms caused death in 0.17% of their cases.2
Yet earlier studies of 17,404 autopsies at the Brooklyn Of-
cice of the Medical Examiner in New York and 3,543 au-
topsies at the Kern County Coroner’s Office in Bakersfield,
Calif, identified undiagnosed CNS neoplasms resulting in
death in 0.16% and 0.4% of cases, respectively.2,4

We observed a significantly lower incidence of deaths
due to undiagnosed CNS tumors compared to earlier
studies (Table 2). Although the series were collected from
different locations, the autopsies in all 4 studies were per-
formed at medical examiners’ offices, and the methodol-
gies used were similar; that is, deaths due to previously
undiagnosed primary CNS neoplasms were identified on
retrospective review. Earlier studies included cases in
which the tumor was thought to cause death by precipi-
tating a motor vehicle accident or drowning. We therefore
also included all such cases in our review to maintain a
homogeneous methodology. The populations involved in the 3 most recent studies are all large and predominantly urban, and variations in demographics are unlikely to account for the observed differences. Rather, we believe that the advent of advanced imaging techniques, such as magnetic resonance imaging and computed tomographic scanning, has resulted in fewer cases of CNS neoplasia escaping medical attention. In keeping with this hypothesis, the apparent increase in CNS cancer rates during the last 15 years is now thought to reflect a temporary phenomenon due to improved technology and earlier detection.5,6

As advanced imaging techniques were less commonly available in the 1980s than in the 1990s, we thought a significant decrease in undetected tumors in the second decade of our study would support a role for imaging in improved detection. In fact, the number of undiagnosed CNS tumors decreased slightly over the course of our study, with 6 of the 11 cases we present occurring in the 1980s and 5 occurring in the 1990s. However, this change is too small to support or refute our hypothesis that improved imaging has played a role in the decreased incidence.

The largest group of neoplasms in our series consisted of 7 glial lesions of varying grade: 1 grade II diffuse astrocytoma, 1 grade III anaplastic astrocytoma, 1 malignant glioma not otherwise specified, and 4 grade IV glioblastoma multiforme. The preponderance of this group is not surprising; astrocytic lesions are the most common type of brain tumor, accounting for more than 38% of all primary CNS lesions, and they are generally fatal.1 Two colloid cysts, 1 schwannoma, and 1 pituitary adenoma made up the remaining 4 cases. The mechanisms of death included seizures, acute hemorrhage, and herniation due to mass effect. Recent case reports and reviews of the literature have highlighted similar scenarios.7–10

Seven of the patients did not seek medical attention prior to their deaths. Four of these 7 patients were symptomatic, but the short duration of symptoms, poor access to health care, or other factors may have prevented them from seeing a doctor. The remaining 4 patients were under the care of a physician. In these cases, vague or misleading symptoms and the presence of concurrent medical conditions likely obscured the correct diagnosis. One patient (case 2) died prior to having his scheduled diagnostic procedure (spinal magnetic resonance imaging). Three other patients were treated initially for neck strain (case 4), migraine headache (case 6), and seizures presumed to be secondary to past trauma (case 9). Similar scenarios have been reported previously. For example, Aronica and colleagues recently described the case of an adolescent boy being treated with sumatriptan succinate for migraines, who died suddenly due to a colloid cyst of the third ventricle.11 Indeed, sudden death due to colloid cysts is a well-described phenomenon; more than 40 cases have been reported in the literature to date.11–18

The case involving the pregnant woman (case 4) raises the issue of hormone-driven tumor growth causing acute medical complications. A pregnant woman presenting with vomiting and headache usually creates suspicion for eclampsia, but it is also important to consider the possibility of a hormone-responsive tumor in these cases. Dramatic increase in the size of meningiomas expressing receptors for progesterone and other hormones in pregnant women is a well-documented phenomenon.19,20 The data concerning hormone responsiveness in schwannomas is less clear-cut. However, a subset of these tumors were found to express hormone receptors in several studies,21,22 and preliminary experiments using tumors implanted in nude mice support the concept that hormones can modulate schwannoma growth.23

In summary, our data support a decline in the percentage of sudden deaths due to undiagnosed brain tumors. This decrease is most likely due to improved detection methods, such as computed tomography and magnetic resonance imaging, and may reflect improved access to health care. However, even with these improvements, a baseline number of patients still die due to unsuspected or undiagnosed brain tumors. These cases highlight the importance of considering a primary CNS neoplasm in patients with vague symptoms or in patients not responding to therapy.

References