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CASE REPORT

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Sudden Unexpected Death Due to a Brainstem Glioma in an Adult

ABSTRACT: Sudden death due to undiagnosed central nervous system tumors is an uncommon, but well-described occurrence. Most of the tumors in these circumstances are supratentorial and occur in a wide spectrum of ages. Brainstem tumors are more rare and occur predominantly in the pediatric and adolescent populations. We present the case of a 48-year-old man who died suddenly and unexpectedly of a brainstem glioma. This case is unusual because of his age and the paucity of antecedent symptoms.

KEYWORDS: forensic science, forensic pathology, brainstem neoplasm, glial cell tumors, sudden death

The brainstem consists of the midbrain, pons, and medulla and contains many critical structures, including the cardiorespiratory center, within a compact area. Brainstem gliomas are neoplasms of neuroglia—particularly astrocytes and oligodendrocytes. They are most commonly seen in the pediatric population, with only occasional cases reported in adult individuals.

Sudden unexpected death from a cerebral neoplasm is an uncommon but well-described occurrence (1). The sudden death may be structural in origin, related to acute hemorrhage in the tumor or due to blood-brain barrier disruption with edema, leading to mass effects, including herniation (2). These structural changes are easily observed at autopsy and are convincing evidence as to the cause of sudden death. In some instances, the cause of the sudden death may be functional in origin, and the tumor may precipitate a fatal seizure or invade critical homeostatic regions of the brain. A growing, untreated tumor in the brainstem would be likely to cause symptoms and eventual death.

Sudden unexpected death from a brainstem glioma in an adult is an exceedingly rare event, predominantly because these lesions are rare in adults, but also because of the large number of symptoms with which they typically present. Often, the tumors are identified and treatment is initiated prior to death.

The following case presentation of a sudden unexpected death in a 48-year-old man from a brainstem glioma is unusual because of his age and the paucity of symptoms related to the tumor. This is followed by a discussion of brainstem gliomas in adults, including a review of the literature.

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Case Report

A previously healthy 48-year-old Caucasian male had a history of chronic alcoholism, without known medical complications or symptoms. He was last seen alive at 11:30 p.m. on the day before he died, at which time he complained of a headache. He went to sleep and was found dead on the bathroom floor of his residence the next morning. There was no sign of foul play. An autopsy was performed.

The body was that of a 179-cm, 85-kg adult white man who appeared to be the reported age of 48. External examination was unremarkable. Internal examination revealed a 470-g, normally configured heart with minimal coronary artery atherosclerosis and only slight concentric left ventricular hypertrophy. The lungs were mildly edematous (505 g left, 510 g right). The 2700-g liver had yellowish discoloration. The1310-g brain was fixed in formalin before detailed examination. Histologic exam of retained, nonneurologic tissue was unremarkable, except for the presence of mild steatotic change of the liver and mild pulmonary edema. Toxicologic exam was negative for alcohol and common drugs of abuse.

On neuropathologic exam, the external brain was unremarkable. Transverse sections through the pons revealed it to be remarkably firm and irregular with multiple irregularly shaped nodules measuring up to 0.5 cm, affecting both the basis pontis and the tegmentum. There were no areas of softening or hemorrhage. There was no evidence of cerebrospinal fluid outflow obstruction, and the cerebral aqueduct and the fourth ventricle were of normal size. The medulla and cerebellum were unremarkable. Coronal sections of the cerebral hemispheres were unremarkable. The ventricles were of normal size and there was no evidence of hydrocephalus. No stigmata of chronic ethanolism were identified.

Microscopic examination of the brainstem showed a diffusely infiltrating glial tumor that was most evident in the pons (Fig. 1) and the adjacent cerebellar white matter. The tumor had moderately increased cellularity and was composed of astrocytes with enlarged, mildly pleomorphic, angulated, variably elongated and circular nuclei (Fig. 2). Nucleoli were inconspicuous and mitotic

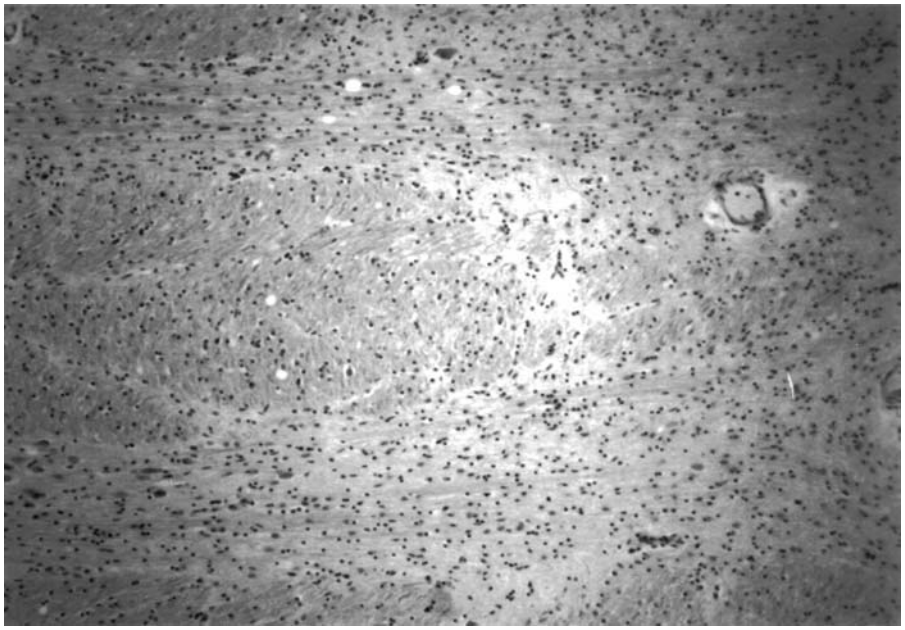

FIG. 1—*Low-power photomicrograph of the astrocytoma (horizontally-oriented and midline) infiltrating the basis pontis and surrounding the corticospinal tracts.*

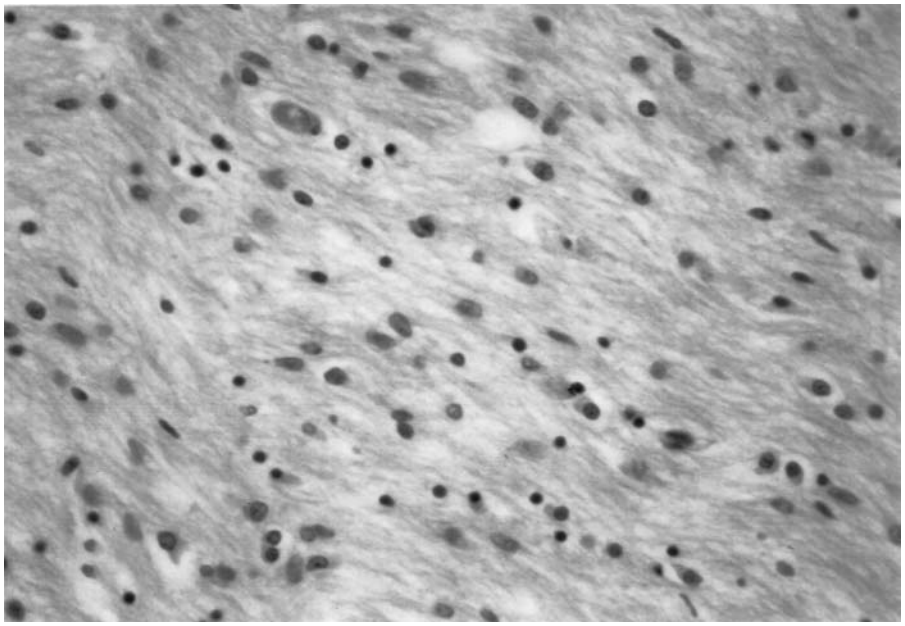

FIG. 2—*High-power photomicrograph of the astrocytoma showing a moderate degree of cellularity and mildly pleomorphic nuclei.*

figures were absent. The cytoplasm was appreciated only in occasional cells. There were no distinct borders of the tumor. No microcysts or Rosenthal fibers were seen. The tumor cells were haphazardly organized and infiltrated along and expanded the transverse fiber bundles in the basis pontis and extended into the cerebellar white matter. The tumor infiltrated cranial nerve nuclei and the dentate nuclei, but did not invade the cerebellar foliae. The tumor widely infiltrated the tegmentum of the pons and extended to a much lesser degree into the subependymal region of the medulla, but did not extend into the midbrain. There was no vascular hyperplasia or evidence of necrosis. In addition to highlighting reactive astrocytes, a glial fibrillary acidic protein (GFAP) immunostain demonstrated the astrocytic nature of many of the tumor cells. A Ki-67 stain for cell proliferation, as well as a myelin stain, were noncontributory.

The above findings are diagnostic of a low-grade diffuse astrocytoma of the pons (brainstem glioma) (3,4). Remaining sections of the basal ganglia, hippocampus, and cerebral cortex were unremarkable.

Discussion

Brainstem gliomas have a peak age of onset between five and eight years of age, with nearly 80% occurring before the age of 20 (5). Many begin with an insidious onset of symptoms, the most

common being cranial nerve dysfunction and ataxia caused by cerebellar involvement or infiltration of the cerebellopontine tracts and edema (5). Another study showed the most frequent symptoms to be gait disturbance, followed by headache, nausea, and vomiting (6). Affected children have a median survival of only nine to twelve months (7).

Brainstem gliomas in the adult are distinctly uncommon, but there is a peak in frequency in the fourth decade (7). Tokuriki and others reported peaks in the first and fourth decades (6). Only 23 brainstem gliomas in adults were identified in an eight-year review of cases at the Memorial Sloan-Kettering Cancer Center (7). In their study, the median survival was 54 months, which is much longer than in children, possibly reflecting a less aggressive tumor in the adult population. Common symptoms were diplopia and headache. Thirteen patients had tumors localized to the pons, two to the tectum, and four to the cervicomedullary junction. The tumors had an indolent growth pattern, and some patients had mild symptoms of long duration. In many of these cases, the tumors were merely observed. Treatment in the form of radiotherapy was begun when there was a significant progression of neurologic symptoms.

In a study of histologically verified brainstem gliomas in 71 children and 30 adults, the peak incidence was the first decade in children and the third and fourth decades in adults (8). The mean duration of symptoms before admission was 9.7 months in adults and 3.6 months in children. The majority of gliomas in this study were Grade 2 astrocytomas, both in children (75%) and adults (57%). In adults, the most common symptoms were palatal palsy (67%), raised intracranial pressure (50%), and focal limb weakness (50%) (8).

Brainstem gliomas often lead to a diffuse symmetrical expansion of the preexisting brainstem structure. The tumor usually begins in the pons and over months to years spreads into contiguous brainstem structures, including the midbrain, medulla, and the cerebellum (2,5,9). Most of the tumors infiltrate between parenchymal elements rather than destroying them and may lead to obstructive hydrocephalus (5). Most of these tumors are astrocytomas.

The literature reveals a report of a 20-year-old woman dying suddenly of an undiagnosed medullary-pontine astrocytoma. However, she had symptoms of the neoplasm from the age of eleven months that included choking, coughing, shortness of breath, ataxia, poor motor coordination, nasopharyngeal incompetence, slow growth, etc., which were attributed to other conditions, and, hence, the tumor went undiagnosed until autopsy (10). In a series of 10,995 consecutive autopsies, DiMaio found 19 sudden unexpected deaths due to primary intracranial tumor (1). In five of these cases, there were no prior symptoms. In none of these cases was the tumor located in the brainstem.

In our case, the pontine parenchyma was grossly described as "firm," which is in keeping with the appearance of brainstem gliomas. The pontine parenchyma was additionally described as "nodular." The "nodules" were, in fact, the descending corticospinal tracts that were accentuated by the surrounding, infiltrating tumor.

This tumor infiltrated critical areas of the brainstem, including the region of the respiratory center that includes the nucleus of the solitary tract, the nucleus ambiguus, and the surrounding reticular formation (11). There was no evidence of sudden parenchymal expansion due to hemorrhage or edema and no evidence of sudden obstruction of cerebrospinal fluid outflow that would explain a sudden death. The decedent apparently tolerated the growing neoplasm well, as he had no visible or expressed symptoms until complaining of a headache shortly before he died. Alternatively, he may have simply denied or rationalized recognized symptoms in the context of his chronic ethanolism. Although no acutely devastating event such as hemorrhage, necrosis, or acute hydrocephalus was seen, the growing, expanding tumor likely exerted significant pressure on, or sufficiently disrupted, nearby vital structures to result in sudden death.

Conclusion

The brainstem contains many critical anatomic structures within a compact region, and a growing tumor in this area will likely produce a plethora of symptoms. This middle-aged gentleman, however, had a paucity of symptoms, which allowed the brainstem glioma to grow and infiltrate many structures of the brainstem, including areas near the regions purported to regulate the cardiorespiratory system. The brainstem glioma expanded to a degree that resulted in death. This case highlights the surprise finding of a brainstem glioma in a middle-aged man and the extent of its infiltration into critical brainstem structures without eliciting many symptoms before causing his sudden and unexpected death.

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