CASE REPORT

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Sudden Death Due to Primary Diffuse Leptomeningeal Gliomatosis

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ABSTRACT: Tumors of the central nervous system are an unusual cause of sudden death. This report describes the sudden death of a presumed healthy 28-year-old woman from primary diffuse leptomeningeal gliomatosis. She presented to an emergency room with headache and vomiting, subsequently became unresponsive and was pronounced dead 14 h later. Autopsy revealed a diffuse extensive infiltrate of well-differentiated astrocytoma in the leptomeninges of the brain and spinal cord without an underlying parenchymal tumor. Primary diffuse leptomeningeal gliomatosis is a rare tumor that arises within the leptomeninges from small neuroglial heterotopic rests that undergo neoplastic transformation. Grossly, this tumor can mimic leptomeningeal carcinomatosis, pachymeningitis, tuberculosis, sarcoidosis, and fungal infections. However, the histologic features of primary diffuse leptomeningeal gliomatosis should allow it to be readily distinguished from grossly similar conditions. The mechanism of death in this case is most likely tumor obstruction of cerebrospinal fluid outflow resulting in the usual complications seen with increased intracranial pressure. Although this tumor is aggressive and is associated with a rapidly progressive fatal course, it has not been previously associated with sudden death.

KEYWORDS: forensic sciences, forensic pathology, sudden death, primary leptomeningeal gliomatosis, astrocytoma, autopsy

Autopsy reveals the cause of many sudden natural deaths in adults. The most common etiology of these deaths is cardiovascular disease (1). Certain disorders of the central nervous system such as ruptured cerebral aneurysms, hypertensive hemorrhages, and meningitis are not uncommon causes of sudden death (2). It is unusual, however, for primary tumors of the brain and spinal cord to result in sudden death; the few cases that are reported are most often primary intraparenchymal gliomas (1). We report a case where sudden death was caused by a rare form of primary leptomeningeal gliomatosis. Ten similar autopsy-confirmed cases of this condition have been described (3–12). Of the ten cases, seven cases were well-differentiated astrocytomas. The remaining cases were glioblastoma multiforme (6), oligodendroglioma (10), and primitive neuroectodermal tumor (7). Regardless of the histologic type, primary leptomeningeal gliomatosis is very aggressive. Patients experience a rapid clinical decline and death usually two months to two years after becoming symptomatic (4,8). To the best of our knowledge, this is the first case where primary leptomeningeal gliomatosis caused sudden unexpected death.

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Case Report

A 28-year-old woman presented to an emergency room with a two-day history of headache and vomiting. She denied visual disturbances, prior trauma, or seizures. She was able to answer questions clearly and appropriately. No papilledema or nuchal rigidity was noted and neurological examination showed no motor or sensory deficits. Routine laboratory tests were normal and she was given intravenous hydration. The vomiting persisted and she became unresponsive. A computed tomography scan showed slightly dilated ventricles (Fig. 1). She went into cardiorespiratory arrest and was pronounced dead 14 h after presentation.

At autopsy, the only significant findings were within the brain and spinal cord. The fresh brain weighed 1350 g. The brain and spinal cord were sectioned after fixation in 10% buffered formalin. Slight diffuse symmetrical cortical edema with bilateral uncal herniation was present. The leptomeninges over the cerebral convexities were thin and translucent. Over the base of the brain, especially in the region of the circle of Willis and the inferior brainstem, the leptomeninges were opaque, white, thickened, nodular, and firm (Fig. 2*A*). The leptomeninges over the cerebellar vermis had a similar appearance. Nodular opaque leptomeninges also surrounded cranial nerve roots of the right pons and medulla, the right cerebellomedullary cistern, the optic chiasm and both internal carotid arteries. The basilar and posterior cerebral arteries were surrounded by lesser amounts of this material. The cerebral vessels were not occluded. Careful inspection of the cerebrum, cerebellum, and brainstem showed no evidence of an intraparenchymal neoplasm. The cerebral ventricles were slightly dilated. The aqueduct was patent. In the spinal cord, the anterior leptomeninges showed confluent white nodular thickening that surrounded the anterior spinal artery (Fig. 2*B*). A 3.0 × 3.0 × 1.0 cm fusiform hard white nodule surrounded the conus medullaris and extended over a nerve root (Fig. 2*C*). Multiple smaller nodules, each less than 1.0 cm, surrounded nerve roots of the cauda equina (Fig. 2*C*). There was no evidence of an intramedullary neoplasm.

Microscopic sections from many regions of the neocortex, deep gray matter, brainstem, cerebellum, and spinal cord showed a fibrillar glial neoplasm confined to the leptomeninges and separated from the brain parenchyma by the thin fibrous layers of the pia mat-

ter (Fig. 3*A*). Several cranial and spinal nerves were also encased by the tumor. Multiple sections of the brain and spinal cord did not reveal an intraparenchymal focus of tumor. The neoplastic cells were mildly pleomorphic with small angulated hyperchromatic nuclei (Fig. 3*B*). Focally, more pleomorphic tumor cells (Fig. 3*C*) and occasional multinucleated cells were identified. In some regions, there were microcysts surrounded by densely packed tumor cells arranged in palisades. Rosenthal fibers were also noted in focal areas. Mitoses and necrosis were not present. A majority of the neoplastic cells were immunoreactive for glial fibrillary acidic protein (DAKO Corporation, Carpinteria, CA) (Fig. 3*D*). Ki-67 immunostain (DAKO) showed rare staining of the neoplastic cells, indicating a low proliferation index.

Based on the pathologic findings the diagnosis of primary diffuse leptomeningeal gliomatosis (well-differentiated astrocytoma, WHO Grade II) was made. The cause of death was certified as astrocytoma of the brain and spinal cord and the manner of death as natural.

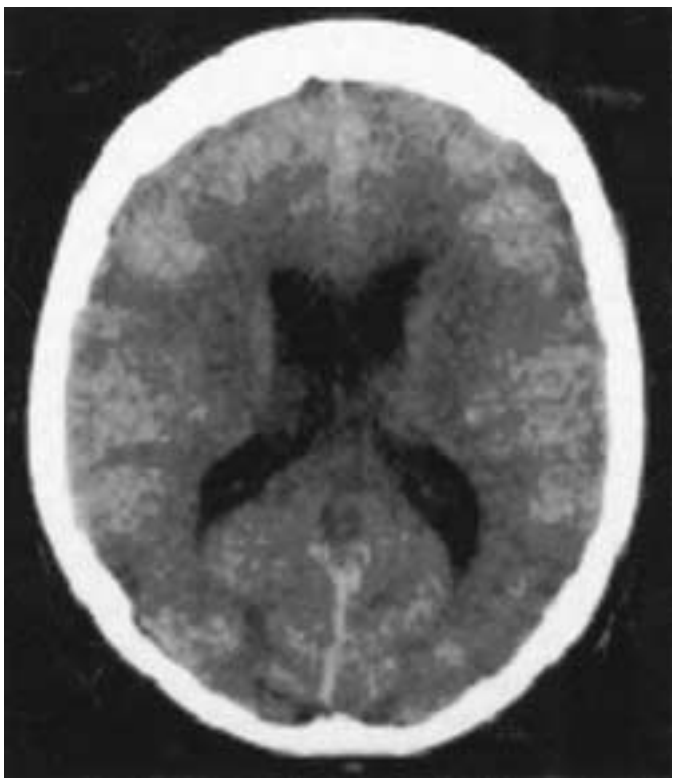

FIG. 1—*Computed tomography scan of primary diffuse leptomeningeal gliomatosis. The image exhibits slight ventricular dilatation but no other abnormalities are present.*

Discussion

Primary leptomeningeal gliomatosis is a rare tumor with two variants that are both thought to arise from the leptomeninges (9). The solitary variant is more common and presents as a single, localized mass (13). The diffuse type, as seen in this case, exhibits extensive tumor infiltration within the leptomeninges of the brain and spinal cord; the point of origin is often not identifiable (9). In contrast to primary leptomeningeal gliomatosis, secondary leptomeningeal gliomatosis is common and usually arises from an intracerebral or intraspinal primary parenchymal tumor that extends into the subarachnoid space (6). This form of spread occurs in up to 23% of patients with intraparenchymal gliomas (14). An autopsy is necessary to distinguish between primary and secondary leptomeningeal gliomatosis (15).

It is believed that primary leptomeningeal gliomatosis arises from small heterotopic neuroglial sites within the leptomeninges that undergo neoplastic transformation (13). Heterotopias in the leptomeninges are well described and these rests have been found in 1% of normal autopsies and in 25% of autopsies on patients with congenital neurological abnormalities (16). The most common heterotopia in the leptomeninges consists of a glial fibrillary matrix with astrocytes (15). Oligodendrocytes, ependymal cells, neurons, choroid plexus, small round primitive cells, and skeletal muscle have also been identified within heterotopic foci in the lep-

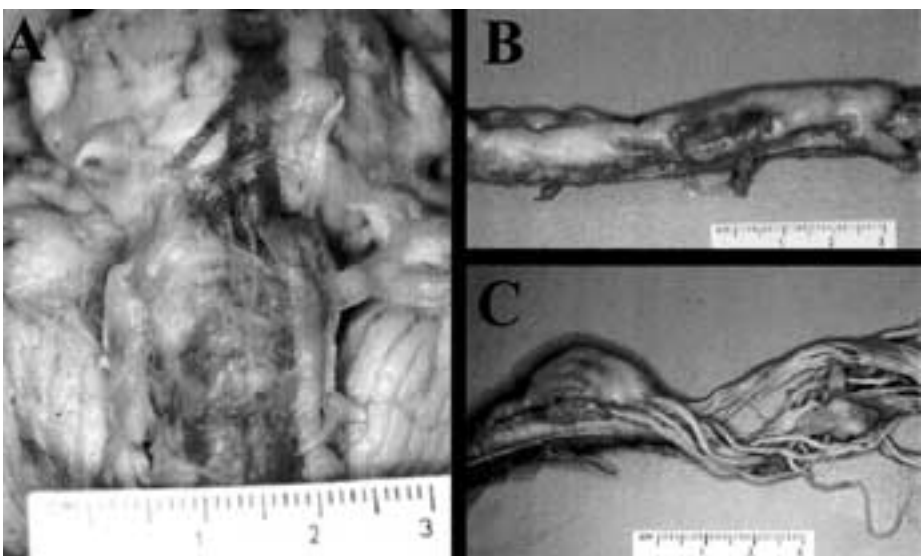

FIG. 2—*Gross appearance of primary diffuse leptomeningeal gliomatosis.* A: *Thickened and nodular leptomeninges cover the brainstem.* B: *The leptomeninges over the anterior portion of the spinal cord are thickened and nodular.* C: *A firm white tumor nodule surrounds the conus medullaris with smaller nodules of tumor within nerve roots of the cauda equina.*

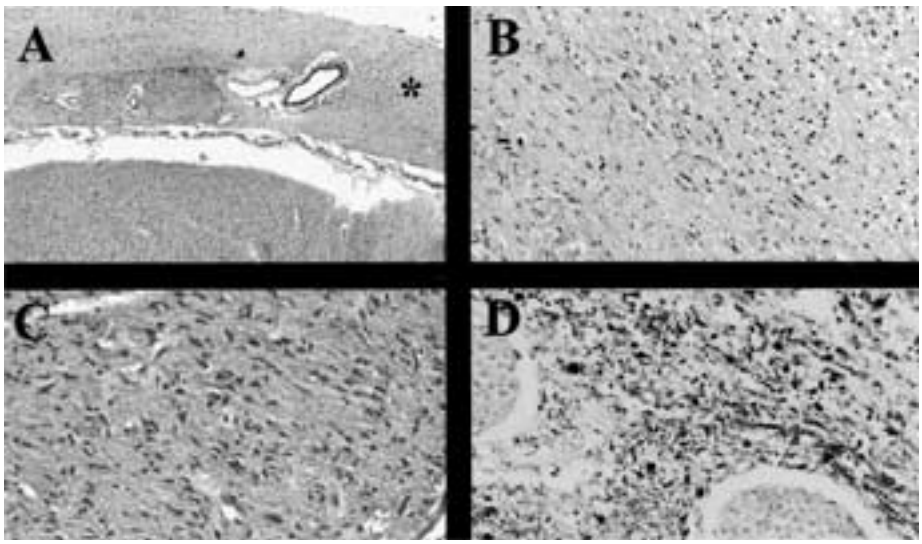

FIG. 3—A: *Low power microscopic section of the spinal cord exhibiting a fibrillar glial neoplasm (*) confined to the leptomeninges (hematoxylin-eosin; original magnification × 40). Thin fibrous tissue of the pia matter separates the tumor from the underlying parenchyma.* B: *The neoplastic cells exhibit astrocytic features with mildly pleomorphic angulated nuclei enmeshed in a fibrillar background (hematoxylin-eosin; original magnification × 160).* C: *Focal areas of the tumor have more pleomorphic astrocytic cells with hyperchromatic nuclei (hematoxylin-eosin; original magnification × 250).* D: *Glial fibrillary acidic protein immunostain demonstrates immunoreactive neoplastic cells that surround normal immunonegative nerves (original magnification × 250).*

tomeninges (16). The rests are found most commonly around the medulla, lumbosacral spinal cord, and cervical spinal cord (14). The diffuse variant of primary leptomeningeal gliomatosis is thought to spread from a single focus as opposed to being a multicentric neoplasm (9).

The most likely mechanism of death in the case we report is tumor obstruction of the cerebrospinal fluid outflow with increased intracranial pressure, herniation and compression of vital brainstem structures. This mechanism of acute decompensated hydrocephalus has also been postulated to explain sudden death caused by colloid cysts of the third ventricle (2).

The clinical signs and symptoms of primary diffuse leptomeningeal gliomatosis are relatively non-specific and relate primarily to increased intracranial pressure including mental status changes, headache, and visual difficulties (3). Papilledema may also be present (6). Computed tomography scans of the head and spinal cord often appear normal in patients with primary diffuse leptomeningeal gliomatosis (3). However, there may be mild to moderate ventricular enlargement, as seen in this case, or meningeal enhancement (3). Diffuse thickening of the leptomeninges can be seen by magnetic resonance imaging, which is the imaging method of choice if leptomeningeal gliomatosis is suspected (5).

Primary diffuse leptomeningeal gliomatosis usually causes thickened and opaque leptomeninges. However, the tumor can be nodular and can encase cranial and spinal nerves (6). Grossly, this condition can mimic metastatic leptomeningeal carcinomatosis, meningioma, pachymeningitis, sarcoidosis, tuberculosis, and fungal infections (9,17,18). However, as the histologic features are similar to that of the neoplastic cell of origin, usually well-differentiated astrocytoma, it can readily be distinguished from other conditions in the differential diagnosis list (3). No parenchymal focus of tumor should be identified after several microscopic sections of the brain and spinal cord are examined (3). Glial fibrillary acidic protein immunostain will highlight the neoplastic cells in the astrocytic variants of primary diffuse leptomeningeal gliomatosis (5).

In conclusion, we report a case of sudden death in a young woman due to a rare tumor, primary diffuse leptomeningeal gliomatosis. The lethal mechanism likely involved uncompensated hydrocephalus. In addition to acute vascular events and infectious processes, forensic pathologists should be aware of the possibility of unsuspected central nervous system neoplasms such as primary diffuse leptomeningeal gliomatosis as the cause of death in otherwise healthy adults. The histologic features of this neoplasm should allow it to be readily distinguished from commonly occurring and grossly similar central nervous system conditions such as meningitis and metastatic leptomeningeal carcinomatosis.

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