

## Neuropathology Education

# Separate CNS lesions involving the brainstem and spinal cord in a 47-year-old man

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### CLINICAL HISTORY

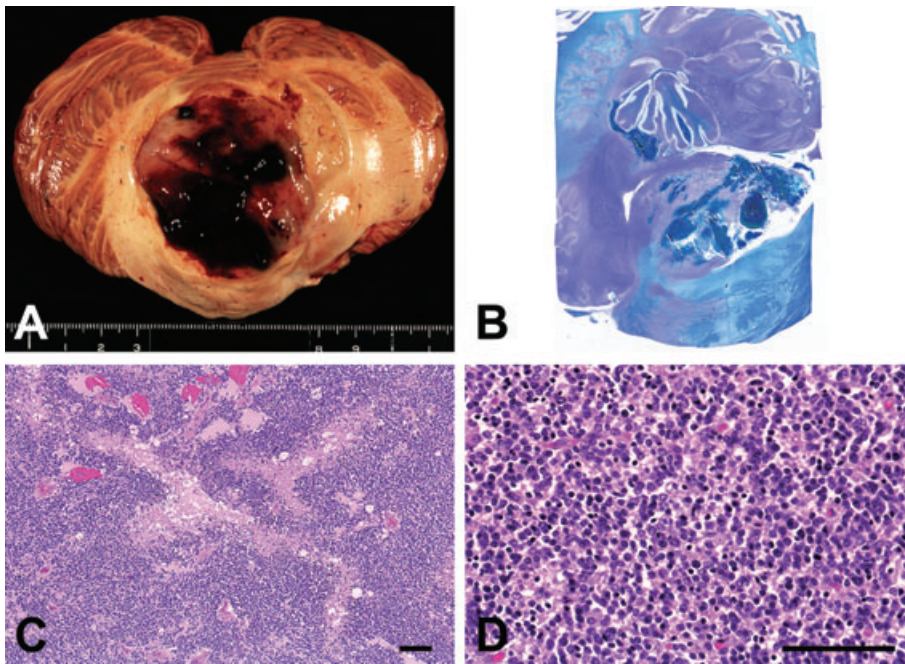
In the spring of 1997, a 43-year-old man developed dysesthesia in his left foot, and by the autumn, he had difficulty in descending stairs. In January 1998, the patient developed sensory disturbance and easy fatigue in the left leg. On the basis of an MRI examination, an AVM in the spinal cord was suspected, but a subsequent angiographic study failed to detect any feeder vessel. In May, an exploratory laminectomy of the Th7 through Th10 levels was performed, but no lesions including an AVM or AV fistula were detected in the spinal cord. The sensory disturbance in the leg persisted, and then in February 1999, the patient noted a sharp pain in the affected leg, followed by slowly progressive muscular weakness. In April, the patient was admitted to our hospital. Multiple sclerosis (MS) was suspected, but steroid pulse therapy was ineffective. In November, the clinical symptoms worsened and extended to both legs, and urinary incontinence also appeared. Spinal MRI showed the presence of two MS plaque-like lesions with T2-weighted image high intensity in the Th9–10 and Th12–L1 segments (Fig. 1). Between December 1999 and June 2001, the patient was admitted repeatedly, and was given medication including steroid therapy; however, there was no apparent effect on the spinal lesions. In July 2001, interferon was administered for the spinal lesion. In August, the patient developed clouding of consciousness and frequent vomiting. Brain MRI disclosed a T2-weighted image high-intensity lesion in the pontine parenchyma, adjacent to the fourth ventricle. Because the findings were initially interpreted as occurrence of an MS lesion in the brainstem, the patient received steroid pulse therapy. In September, he developed urinary tract infection and septi-

cemia, which resulted in disseminated intravascular coagulation and multiple organ failure. In November, brain MRI showed that the brainstem lesion had tumor-like features, such as massive expansion to the left cerebellopontine angle and heterogeneous enhancement with gadolinium. Due to growth of the lesion, the brain developed non-communicating hydrocephalus. The patient died of abrupt respiratory arrest in the same month. He had no family history of a genetic disease.

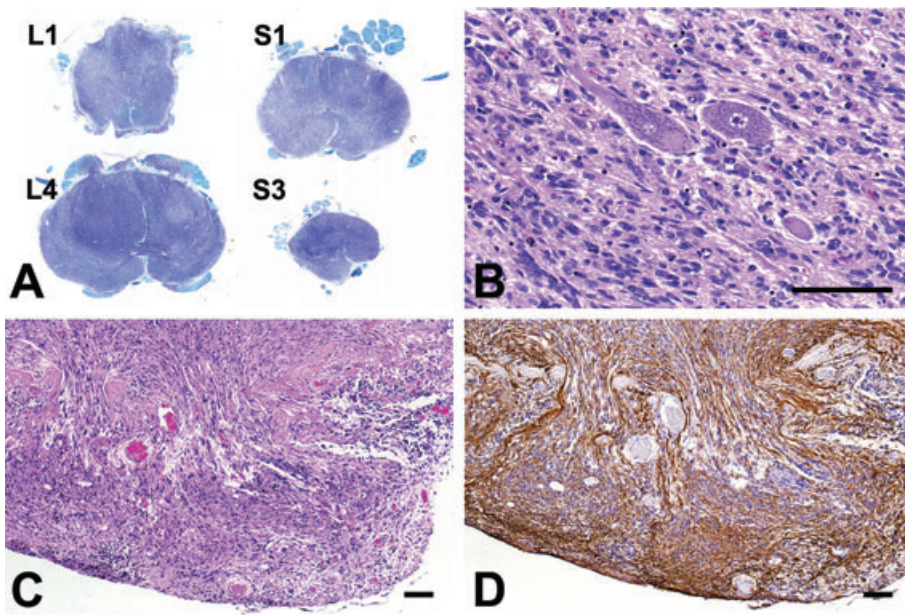


**Fig. 1** Spinal MRI of the Th9, showing the presence of a plaque-like lesion (arrow) with T2-weighted image high intensity in the spinal parenchyma.

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**Fig. 2** (A) Transverse section of the pons and cerebellum, showing the presence of a massive gelatinous tumor with fresh intratumoral hemorrhage, which occupies the entire fourth ventricle. (B) The brain tumor involves the pons, middle cerebellar peduncle and cerebellar vermis. (C,D) Histologically, the tumor shows high cellularity, frequent necroses and vascular proliferation, and is composed of small round or spindle-shaped cells. B, Klüver-Barrera stain; C and D, HE stain. Scale bars = 100  $\mu$ m.



**Fig. 3** (A) Transverse sections of the lumbar (L) and sacral (S) segments of the spinal cord, showing diffuse involvement by tumor cells, resulting in loss of spinal intrinsic structures. (B) In the spinal cord, the tumor is moderately cellular and is composed of spindle-shaped astrocytes with nuclear atypia, but lacks vascular proliferation or tumor necrosis. Note vivid anterior horn cells in the diffusely infiltrative lesion. (C,D) Tumor cells are also associated with the outlets of the spinal anterior nerve roots. A, Klüver-Barrera stain; B and C, HE stain; D, immunohistochemistry for GFAP. Scale bars = 100  $\mu$ m.

## PATHOLOGIC FINDINGS

The brain was swollen with bilateral uncal and tonsillar herniations, and weighed 1575 g. The cerebellum was especially swollen, and a grayish tumor (about 1 cm in diameter) was exposed at the left cerebellopontine angle. Horizontal sections of the brainstem and cerebellum showed the presence of a soft, large tumor that involved the cerebellar vermis, white matter of the left cerebellar hemisphere and left half of the pons, resulting in occupation of the fourth ventricle (Fig. 2A,B). The tumor was

occasionally associated with fresh, massive intratumoral hemorrhages. Histologically, the tumor showed vascular proliferation and frequent necrotic areas (Fig. 2C), and was composed of spindle-shaped or small round cells (Fig. 2D). Mitotic figures were frequent. Immunohistochemically, the tumor cells were occasionally positive for GFAP. Extension of the tumor was restricted to the lower level of the pons caudally and to the midbrain rostrally. There were some disseminated foci of undifferentiated tumor cells in the subarachnoid space around the brainstem.



The cervical and upper thoracic segments of the spinal cord appeared normal; however, the lower thoracic, lumbar and sacral segments were markedly swollen, making spinal internal structures, such as the boundary between the gray and white matter, indistinguishable (Fig. 3A). Histologically, spindle-shaped tumor cells with nuclear atypia diffusely involved the lumbar and sacral segments with low to moderate cellularity (Fig. 3B). Mitotic figures were occasionally evident, but necrosis was absent and vascular proliferation was not prominent. In most of the spinal segments, tumor cells also invaded the anterior and posterior nerve roots (Fig. 3A,C). Immunohistochemically, the tumor cells were highly positive for GFAP (Fig. 3D). Tumor cell invasion was severe up to the T8 segment of the spinal cord, but showed gradual regression in density from this segment upwards, and became hardly detectable in the upper cervical segments (Fig. 4). In the spinal cord, there was also ascending tract degeneration secondary to tumor involvement; however, we were unable to detect any apparent MS lesions at any stage.

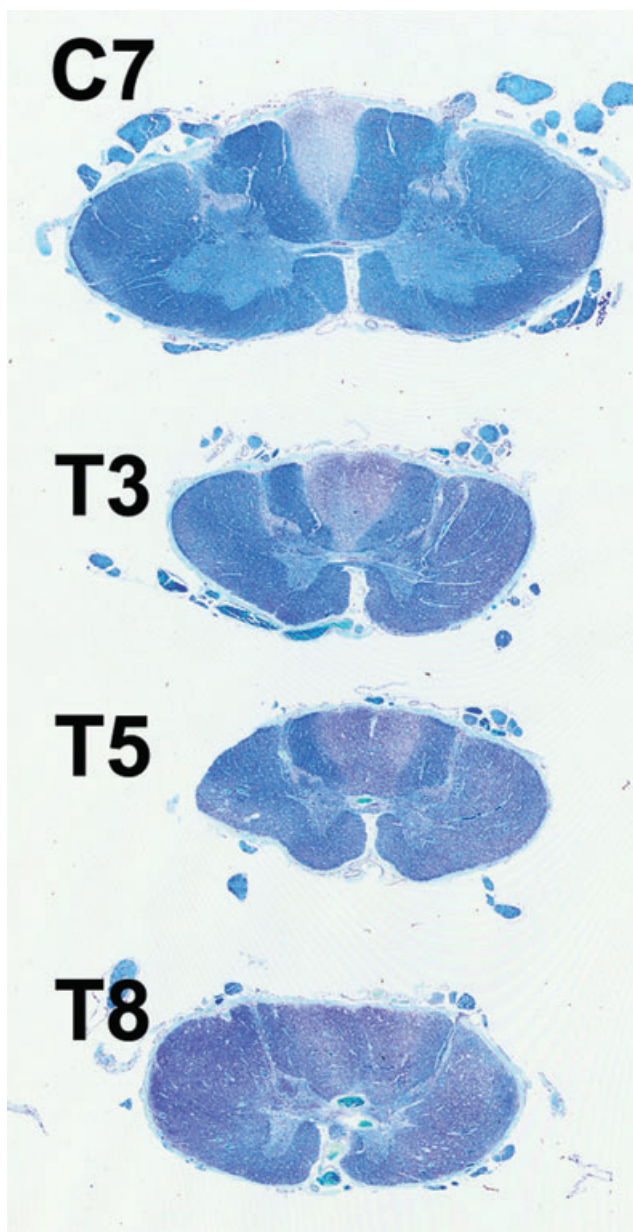
Examination of the visceral organs showed mild prostatitis and the presence of small hamartomas in the spleen. The kidneys showed segmental mesangiolytic lesions and microangiopathy, the latter of which showed double-contoured glomerular capillary walls and was suspected to be a drug-induced vascular change.

### DIAGNOSIS

Anaplastic astrocytoma of the spinal cord and glioblastoma of the brainstem/cerebellum.

### DISCUSSION

By the mid-stage of the clinical course, the present patient had slowly progressive symptoms involving the spinal cord, and was thought to have MS. In the late stage, a brainstem lesion also appeared as an overlapping lesion. This was initially thought to be an MS lesion, but its rapidly and massively expanding nature suggested that it was a brain tumor. Autopsy revealed that both the brainstem and spinal cord lesions were gliomas, and that no MS lesions or other neuropathologic conditions could have caused the clinical manifestations in this patient. The lack of apparent continuity between the two tumor lesions and their different histology suggest that the patient had developed multicentric gliomas in the CNS. The brainstem-cerebellar lesion was a glioblastoma composed mainly of undifferentiated tumor cells. Fresh intratumoral hemorrhages might have led to an abrupt increase of intracranial pressure in the posterior fossa, resulting in sudden death of the patient due to respiratory arrest. The spinal cord lesion was diagnosed as an anaplastic astrocytoma; however, the slow



**Fig. 4** Transverse sections of the cervical (C) and thoracic (T) segments of the spinal cord. Tumor cell invasion shows a gradual regression in density from the T8 segment upwards, and becomes sparse in the C7 segment. Secondary degeneration is obvious in the posterior column and spinocerebellar tracts. Klüver-Barrera stain.

clinical course as well as the lack of tumor necrosis or marked vascular proliferation suggested that the tumor had relatively low malignancy and might have had a diffusely infiltrating nature.

It has been reported that lesions of MS are occasionally indistinguishable from malignant brain tumor, especially when neuroradiological studies demonstrate a single, large white matter lesion with a mass effect.<sup>1,2</sup> For accurate diag-

nosis, brain biopsy is recommended and histopathological guidelines have been proposed.<sup>3</sup> On the other hand, it is relatively rare for brain tumors to be neuroradiographically misdiagnosed as MS lesions. Rogers *et al.* reported five patients with cerebral astrocytomas, in whom neuroimaging demonstrated diffuse abnormal density of the bilateral cerebral hemispheres and a minimal focal mass effect, which was mistaken for a non-neoplastic MS lesion.<sup>4</sup> Autopsy revealed that such misdiagnosis can easily occur in patients with diffusely infiltrating cerebral astrocytomas. It is conceivable that this was also the case in the present patient, because, as discussed above, the spinal cord tumor might have behaved as a low-grade astrocytoma during the course of his illness, although at autopsy the final diagnosis was of anaplastic astrocytoma.

It has also been reported that a few patients show concurrent MS and intracranial glioma.<sup>5,6</sup> Most of these patients develop gliomas several years after MS has been diagnosed. It is not clear whether MS lesions actually lead to the development of gliomas or whether the two conditions occur coincidentally. The present case may not represent this rare condition, because the spinal cord parenchyma showed a monotonous histology due to tumor cell invasion, and had no glial scar lesions. During the patient's clinical course, steroid therapies had no obvious effects on the manifestations or neuroradiological findings.

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#### REFERENCES

1. Mujic A, Liddell J, Hunn A *et al.* Non-neoplastic demyelinating process mimicking a disseminated malignant brain tumor. *J Clin Neurosci* 2002; **9**: 313–317.
2. Wurm G, Parsaei B, Silye R *et al.* Distinct supratentorial lesions mimicking cerebral gliomas. *Acta Neurochir* 2004; **146**: 19–26.
3. Sugita Y, Terasaki M, Shigemori M *et al.* Acute focal demyelinating disease simulating brain tumors: histopathologic guidelines for an accurate diagnosis. *Neuropathology* 2001; **21**: 25–31.
4. Rogers LR, Weinstein MA, Estes ML *et al.* Diffuse bilateral cerebral astrocytomas with atypical neuroimaging studies. *J Neurosurg* 1994; **81**: 817–821.
5. Khan OA, Bauserman SC, Rothman MI *et al.* Concurrency of multiple sclerosis and brain tumor: clinical considerations. *Neurology* 1997; **48**: 1330–1333.
6. Shuangshoti S, Hjardeemaal GM, Ahmad Y *et al.* Concurrency of multiple sclerosis and intracranial glioma. Report of a case and review of the literature. *Clin Neuropathol* 2003; **22**: 304–308.