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Occult Malignant Astrocytoma of Pons with Extracranial Metastasis to Bone Prior to Craniotomy *

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Summary. A 23-year-old man presented with signs of increased intracranial pressure. CAT scan, cisternogram, and angiogram on admission were reported to be normal. Lumbar puncture revealed elevated pressure and protein of 500 mg-%. CSF cytology revealed malignant tumor cells. A brain biopsy and decompression were carried out to reveal diffuse subarachnoid invasion by malignant tumor cells. Immunohistochemical studies using anti-glial fibrillary acidic protein serum revealed tumor cells to be positive for GFA protein. A lumbosacral CAT scan 9 days after surgery revealed numerous sclerotic densities involving bony pelvis, sacrum, T-12 vertebra and left femoral head. No definite primary site of tumor was found antemortem in the brain or any other organ. Autopsy demonstrated diffuse subarachnoid spread of malignant tumor in brain and spinal cord. Malignant astrocytoma was found in the midline pons projecting into the 4th ventricle. The histology of the neoplasm was identical in all sites including bone. No other tumor was found at autopsy. The vascular invasion by the tumor cells in the pons and distant bony metastasis in this case suggest hematogenous spread. A review of the lumbar X-ray taken 6 weeks prior to admission and the presence of well-established bony lesions within 10 days of craniotomy suggest that this is a rare case of extraneural metastasis of glioma occurring prior to surgery. The midline location of clinically occult pontine glioma and the presence of bony metastasis created difficulty in the diagnosis but immunohistochemical studies proved to be crucial in establishing correct diagnosis antemortem.

Key words: Malignant astrocytoma – Extracranial metastasis – Glial fibrillary acidic protein – Immunohistochemistry

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The occurrence of extraneural metastasis from malignant glioma is now common knowledge. Although it is extremely rare, distant extracranial metastasis of intracranial neoplasms in the absence of previous surgery has also been recognized and is reported to comprise as many as 10% of cases of remote metastases (Anzil 1970). This is to report a case of an occult astrocytoma of pons with wide-spread bony metastasis prior to craniotomy. Because of midline location of small primary focus in pons and absence of objective findings including CAT scan created difficulty in reaching a correct diagnosis. Even brain biopsy was not conclusive for a primary neoplasm on routine histological study. However, application of immunohistochemical methods using antiserum to glial fibrillary acidic (GFA) protein, a protein specific for astrocytes, proved crucial in arriving at a correct diagnosis prior to autopsy.

Case Report

The patient was a 23-year-old white male in good health until December 1979 when he was admitted to hospital with occipital headache, nausea, vomitting, diplopia, bilateral papilledema, nystagmus, brisk reflexes, and positive Babinski signs. Admission work-up included negative EEG, brain scan, and skull films. CAT scan showed no significant abnormality with questionable prominence in the 4th ventricular floor. Metrizamide cisternogram was negative, although spinal fluid showed high opening pressure (greater than 400 mm) and a low glucose (38 mg-%). CSF cytology revealed malignant tumor cells. Four vessel angiography, spine films, and myelogram were negative. The brain biopsy revealed diffuse subarachnoid infiltration by undifferentiated malignant tumor cells. Immunohistochemical studies using anti-GFA protein serum, however, revealed positive immune reaction in the cytoplasm and processes of tumor cells, thus indicating glial nature of the tumor cells (Fig. 1A–C). Total body scan and X-rays of pelvis 9 days after craniotomy revealed numerous sclerotic densities involving bony pelvis, sacrum, T-12 vertebra, and left femoral head (Fig. 2A–D). CAT scan of brain in March 1980 showed diffuse subarachnoid infiltration but no definite primary site of the tumor was determined antemortem in the brain or any other organ. Treatment included lumbar spine radiation, chemotherapy (BCNU), brain radiation, Diamox, and Decadron. The patient did well for a while, ambulating with a walker, alert and oriented, then became intermittently

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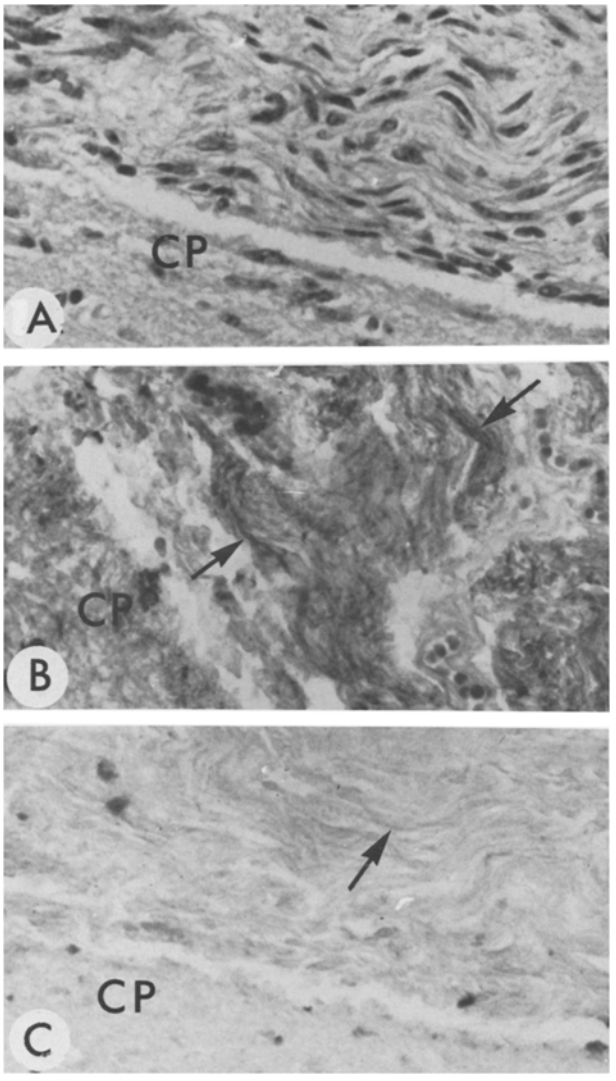

Fig. 1. A Photomicrograph of malignant astrocytoma in the subarachnoid space of cerebrum. Note elongated cells with wavy pattern simulating a neoplasm of mesenchymal origin. *CP* cortical plate. HE, ×420. **B** Photomicrograph of the same focus as in **A** after peroxidase-antiperoxidase immunohistochemical reaction with anti-GFA protein serum. Note strong immunoprecipitate (*arrows*) in tumor cells. *CP* cortical plate. ×330. **C** Control for above with preimmunization serum in place of anti-GFA protein serum. ×330

confused, weaker, non-ambulatory, and had increasing difficulty in swallowing. He died on April 25, 1980, after episodes of high fever, chills, deteriorating mental status, and papilledema.

Autopsy Findings

The brain weighed 1,330 g. There was diffuse cerebral edema with thickening of arachnoid membrane with focal accentuation of pale gray discoloration. The subarachnoid space over cerebrum and cerebellum contained scattered pale grey firm tissue. The spinal cord at all levels also showed similar firm tissue focally obscuring the underlying landmarks. Multiple coronal sections of the brain revealed the septum pellucidum slightly contorted at the level of mammillary bodies and displayed grayish brown discoloration with thickening of subependymal tissue. The firm pale gray tissue in the subarachnoid space did not invade the underlying cerebral cortex. There was a protuberance of a firm, pale gray tissue into the 4th ventricle at the level of the 8th cranial nerve nucleus of the pons (Fig. 3). The tumor measured 0.6 × 0.5 × 1.0 cm and was present at the midline of the floor of the 4th ventricle. It invaded the underlying tegmentum and also appeared to involve the subependymal tissue of the 4th ventricle and extended into a mass on the roof of the 4th ventricle (Fig. 3).

Histopathology

At autopsy, almost the entire subarachnoid space of the brain and the spinal cord was compacted with sheaths of malignant tumor cells with identical histology as the biopsy specimen (Fig. 1A). The tumor cells had a scanty to moderate amount of ill-defined cytoplasm. The nuclei were oval or fusiform and were hyperchromatic and pleomorphic. The neoplastic cells were arranged in clusters around blood vessels or thrown into wavy pattern (Fig. 4). The neoplasm extended into the 4th ventricle and in the subependymal plate. On higher magnification, involvement of blood vessels by the tumor cells was much more evident. Concentric layers of tumor cells completely obliterated the lumen of many capillaries in the tegmentum of the pons (Fig. 4). Representative sections from metastatic bone lesions showed identical histology with positive GFA protein reaction in the cytoplasm and processes.

Discussion

The unique features in this case are (1) absence of previous surgery or irradiation, (2) demonstration of direct vascular invasion by tumor cells in the primary focus, and (3) the use of immunohistochemical method to establish correct identification of tumor cells.

Because of the unusual location of the primary lesion and the small size of the tumor the determination of the primary site was difficult in life. It is most likely that the patient already had a metastatic focus in the pelvis when he originally complained of lumbago 6 weeks prior to this admission. Review of the X-ray film taken at that time (Fig. 2A) as compared to the film taken on his admission (Fig. 2B) suggests the presence of such a focus. The lack of obvious primary focus on various examination and the presence of multiple metastatic bony lesions caused difficulty in differential diagnosis. The undifferentiated nature of the tumor cells in the subarachnoid space on frozen section and the general histological pattern of the tumor in addition to elongated nature of the tumor cells even suggested mesenchymal tumor. This is one of the diagnostic problems one often encounters when gliomas infiltrate into the subarachnoid space with marked desmoplastic reaction. It is here that the specific immunohistochemical identification of tumor cells can be of extreme help as was in this case. The immunohistochemistry using antiserum to GFA protein as a specific marker for astrocytes has become increasingly popular in recent years. Since 1975, we have used this method routinely on frozen section diagnosis of brain

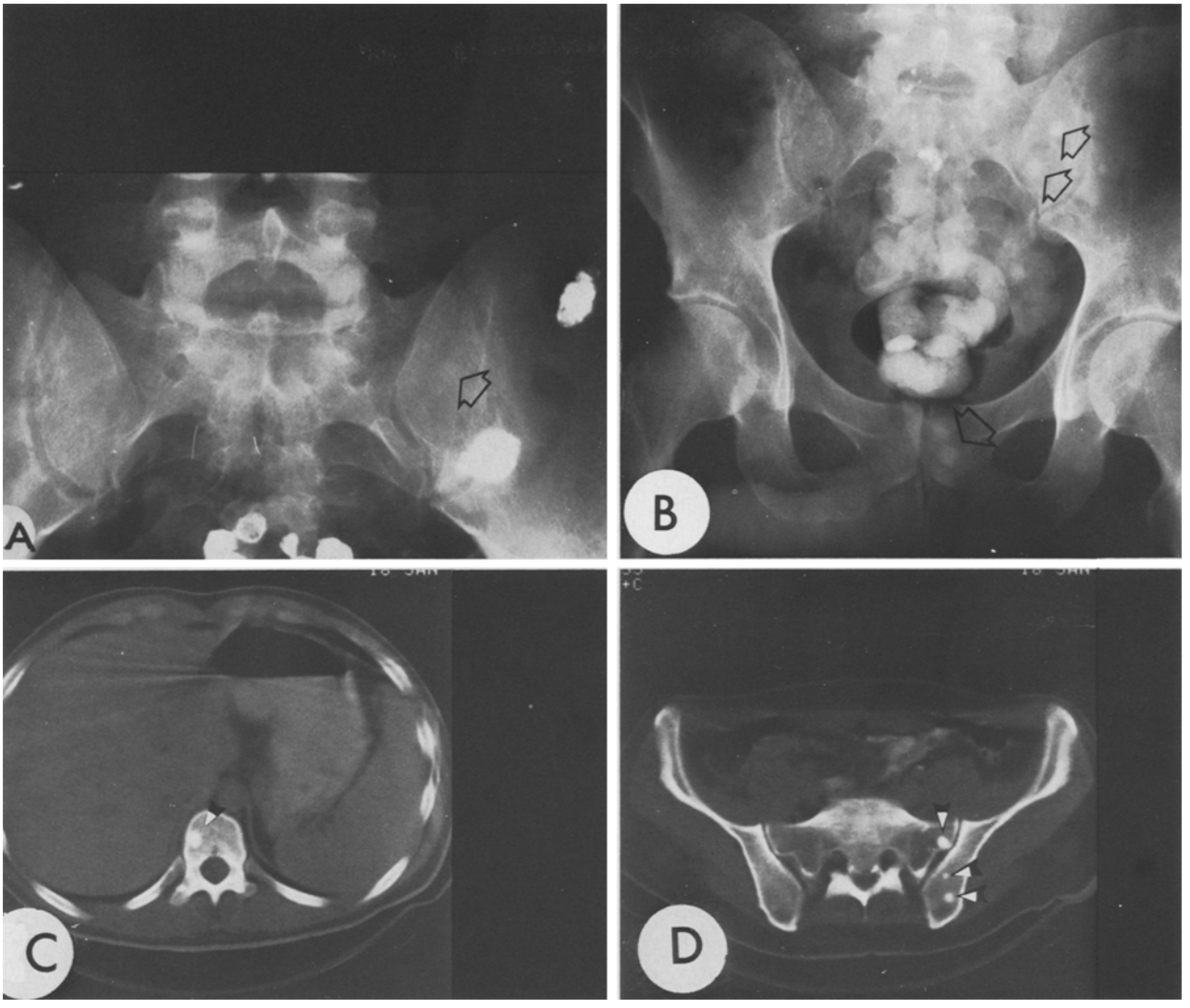

Fig. 2. A Plain X-ray film taken 6 weeks prior to admission. An open arrow points to obscure density which later proved to be a metastatic lesion as shown in **B**. **B** Plain X-ray film taken 9 days after craniotomy. Open arrows point to circular densities in the pelvic bones identified as metastatic foci. **C** and **D** Scan of vertebra and pelvis showing metastases (*arrow heads*)

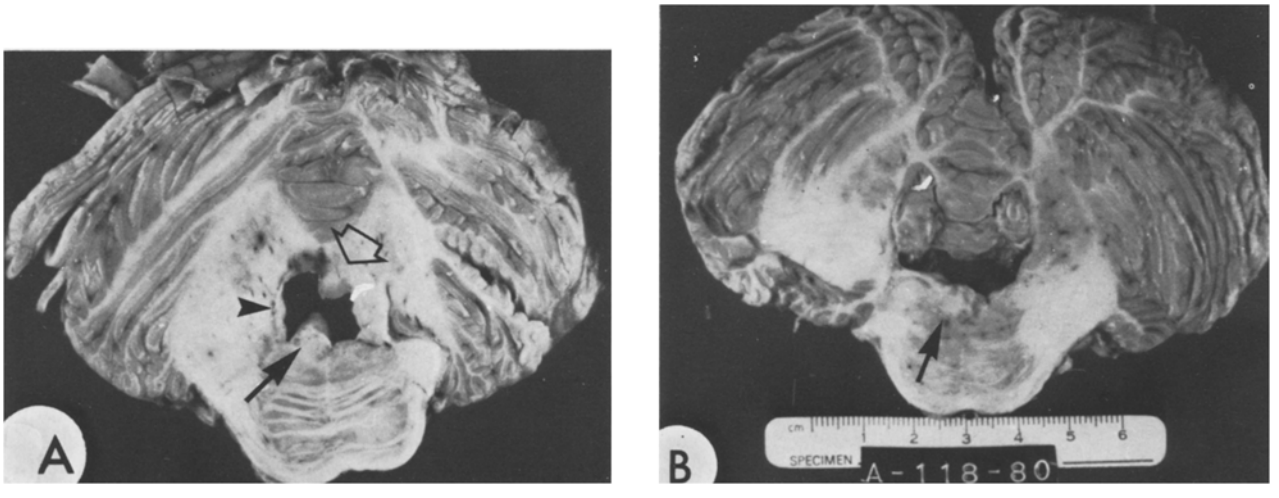

Fig. 3. A Gross photograph showing nodular mass (*arrow*) projecting into the 4th ventricle in pons. There is thickening of the subependymal tissue (*arrow head*) extending to another nodule (*open arrow*) on the roof of the 4th ventricle. **B** Gross photograph showing partly necrotic tumor in pons (*arrow*) with focal ulceration of the ependymal surface

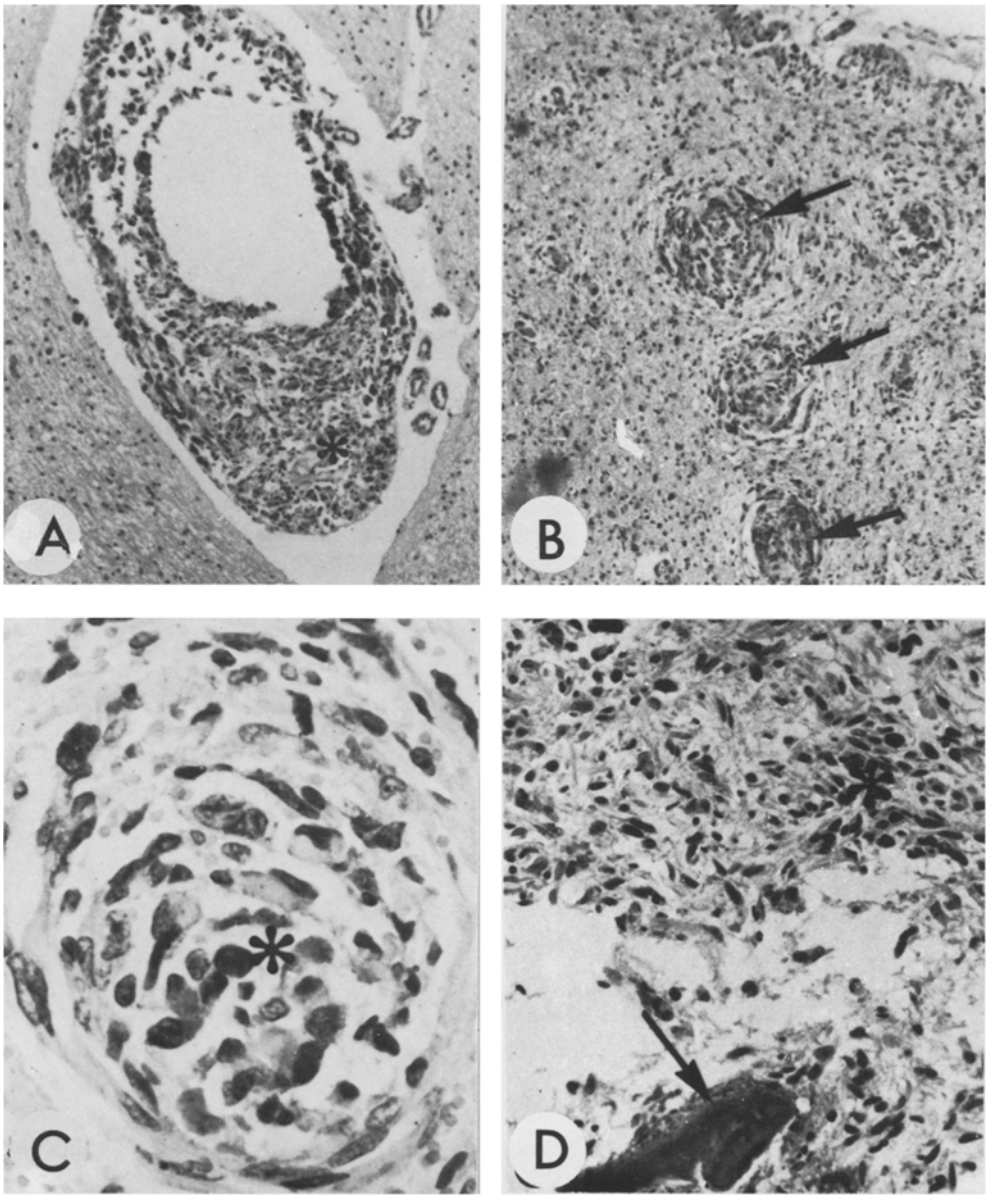

Fig. 4. A Photomicrograph showing massive subarachnoid spread of malignant astrocytoma (*) surrounding a blood vessel. HE, ×75. **B** Photomicrograph showing three nodular collections of malignant tumor cells (*arrows*) in and around small blood vessels in pons. HE, ×75. **C** Photomicrograph of malignant tumor cells (*) in the small blood vessel. HE, ×420. **D** Photomicrograph of metastatic lesion in vertebra. *Arrow* points to bony specule. HE, ×188

tumors (Choi et al. 1976). We have also used this method successfully in studies of ontogenesis of glial cells in developing human CNS (Choi and Lapham 1978, 1980). More recently the use of unlabeled antibody enzyme technique of Sternberger (1979) has become popular in the diagnosis of glial neoplasms (Duffy et al. 1977). This method allows retrospective study of gliomas and related tumors in paraffin-embedded specimen.

The literature on extraneural metastasis of intracranial tumor is extensive and excellent review articles have appeared in recent years (Glasauer and Yuan 1963; Smith et al. 1969; Jackson and Graham 1978; Liwnicz and Rubinstein 1979). The rarity of extracranial metastasis of primary glial neoplasms remains unexplained. The absence of cerebral lymphatics, occlusion of venous system by early tumor compression, and even the short span of postoperative life of patients with glioblastoma have been considered to be factors involved. It is also generally observed that within the central nervous system (CNS) vascular invasion by glioma cells is practically never found by

light microscopy. In this context, our case represents only the third case in which vascular invasion by glioma cells in the primary site was demonstrable in the absence of previous surgery. It is interesting to note that in the majority of cases of spontaneous metastasis of gliomas, bone has been a common site of metastases in addition to liver (Anzil 1970; Hulbanni and Goodman 1976).

This case clearly demonstrates that spontaneous metastasis of intracranial gliomas is indeed possible even in the absence of previous surgery and even with no clear cut localization of primary site. Therefore, those dealing with intracranial tumors should be on the alert as to the frequency of such a spread and the usual sites of metastases of these tumors. Certainly, the use of immunohistochemical methods and ultrastructural methods in the diagnosis of such tumors brought about one of the significant advances in recent years.

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