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MICROGLIOMATOSIS PRESENTING AS SUSTAINED HYPERVENTILATION*

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Microgliomatosis as a neoplastic proliferation of microglial cells of the central nervous system was first described in 1948 by Russell et al[1]. The problem of morphologic criteria for the diagnosis of microgliomatosis was later defined and discussed by several authors [2-6]. Adams and Jackson[2] noted the rarity of this type of tumor and related primary cerebral tumors of reticular tissue. This neoplasm has been seen in all ages, but most reported cases are in middle-aged adults. It is rare in children, although it has been described in an infant as young as 2 months[5]. Microgliomatosis is one of the most malignant tumors of the brain, with an average survival time from the onset of symptoms to death being 3 months in one study[3], and 3 to 5 months in another[5]. The clinical presentation of microgliomatosis is usually that of an intracranial space-occupying lesion [3,4]. The present report describes a case of microgliomatosis in a 7-year-old boy in which presenting symptoms, in the absence of clinically detectable intracranial tumor, were episodes of hyperventilation and respiratory alkalosis.

Case Report

A 7-year-old boy was admitted to Hacettepe Children's Hospital with the chief complaint of noisy breathing of 20 days' duration. No history of foreign body aspiration was obtained.

Family history revealed that he was the 8th child of healthy, unrelated parents. Seven earlier pregnancies had ended with stillbirths at term. This eighth child had been delivered by Caesarian section and had been in good health until twenty days prior to admission.

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Physical examination disclosed deep and frequent respiration (42-62 per minute) with subcostal retraction. No wheezing or additional respiratory sounds were detected. Hands and feet were cold with slight cyanosis. Normal blood pressure and tachycardia were observed. The remainder of the physical examination was normal.

Neurological examination revealed a mentally alert child with right-sided weakness including the face. Pupils were equal and reacted well to light. Mild, right-sided ptosis with normal eye ground bilaterally was observed. Deep tendon reflexes were hyperactive bilaterally.

Laboratory examination showed CO_2 content 8.62 to 14.75 mEq/l, hyperchloremia (113 and 109 mEq/l), pH of the blood 7.52 and 7.45, cerebro-spinal fluid protein 55 mg/dl, sugar 109 mg/dl. The blood levels of Na, K, Ca, P, creatinine, uric acid, lactic acid and total protein were all within normal limits. Routine blood counts, urinalysis, amino acids of the blood and urine were also normal.

Initial x-ray of the skull, chest and abdomen as well as IVP were normal. Left carotid arteriography, ventriculography, and pneumoencephalography (PEG) were within normal limits. Electroencephalography revealed diffuse dysrhythmia which was more pronounced on the left side.

The patient's neurological condition worsened progressively with convulsions, ataxia and inability to walk. Despite treatment with intravenous fluids, antibiotics and anti-convulsive drugs (phenobarbital, diphenylhydantoin), his intermittent respiratory difficulties increased, on one occasion leading to apnea. Bronchoscopy was performed but revealed no obstruction. On another occasion chest x-ray examination showed atelectasia of the left lung following PEG manipulation, which later disappeared spontaneously. He died of respiratory failure two months after admission.

Necropsy findings. A complete post mortem examination revealed no visceral lesions except for edema, congestion, atelectasis, and terminal bronchopneumonia. Pathological findings were limited to the brain, which weighed 1,365 g (normal for this age 1,263 g). The leptomeninges were slightly opaque along the sulci on the cerebral convexity; the gyri were flattened with narrowed sulci. Slight uncal and cerebral herniations were found. The pons appeared to be slightly prominent and enlarged. In coronal sections no ventricular enlargement or tumors were seen. Multiple, disseminated and ill-defined areas of greyish pink discoloration measuring 0.1 to 1.5 cm were seen in the head of the nucleus caudatus, in the putamen, thalamus, cerebral peduncles and pons, with a tendency to subependymal location. A spongy area of 1 cm in diameter was noted in the white matter adjacent to the head of the nucleus caudatus. The medulla and cerebellum appeared unremarkable.

Microscopic findings. Surprisingly, multiple sections from the cerebral cortex, the head of the nucleus caudatus, cerebral peduncles, pons and medulla revealed an

extensively infiltrating tumor with similar microscopic patterns and malignancy, not only in the grossly noted areas, but also in the areas which appeared unaffected to the naked eye. Sections of tumor were highly cellular with a tendency to characteristic pericapillary arrangement and infiltration of the surrounding brain tissue (Figures 1 and 2). The meninges were also focally infiltrated by the tumor (Figure 3). The survival of neurons in the infiltrated areas was also seen (Figure 4). The tumor cells contained small amounts of cytoplasm and had mainly round or oval nuclei, although some showed twisted or lobed nuclei. Occasional mitotic figures were seen. The nuclei were mostly rich in chromatin; however, a few appeared to be vesiculated. Areas adjacent to the tumor showed zones of infarction with capillaries, numerous gitter cells and astrocytic reaction. Sections of cerebellum and spinal cord showed no tumor infiltration.

Special stains. A number of special stains were made in addition to the routine hematoxylin and eosin, including phosphotungstic acid hematoxylin for glial fibers, methyl green-pyronine (Unna-Pappenheim) for plasma cells, silver staining for reticulin fibrils and modified microglia stain for paraffin sections[7]. These special stains revealed metallophilia (impregnation with silver carbonate for microglia) of some of the tumor cells and the presence of plasma cells within the tumor. No glial or reticulin fibrils arising from the tumor cells were seen.

Discussion

The tumor presented showed malignant neoplastic proliferation of primitive cells in Virchow-Robin spaces with a suggestion of differentiation to microglia, reticulum cells, and plasma cells. In general it had the characteristics of neoplasia originating from the reticulo-endothelial system (RES) of the brain. Among the primary tumors of the RES of the brain (reticulosis) the neoplasm presented corresponds to the criteria for the diagnosis of microgliomatosis[1-6]. It is surprising that such tumors of the RES of the brain are rare in children whereas malignant tumors of the RES of other parts of the body are among the most frequent childhood tumors. That our patient died within three months of the onset of the symptoms corresponds to the high degree of malignancy reported in previous cases[1-5]. Onset symptoms were respiratory difficulties and repeated episodes of hyperventilation, which persisted throughout the course of illness, on one occasion leading to apnea and on another to atelectasia with immediate spontaneous recovery. Clinically and pathologically no pulmonary, cardiac or other system abnormalities were found. Neurologic examinations, direct x-rays, arteriogram, and ventriculogram studies revealed no increased intracranial pressure or space occuying lesions. The only significant findings were respiratory alkalosis with lowered CO_2 content, hyperchloremia and high blood pH. These findings suggested central neurogenic hyperventilation.

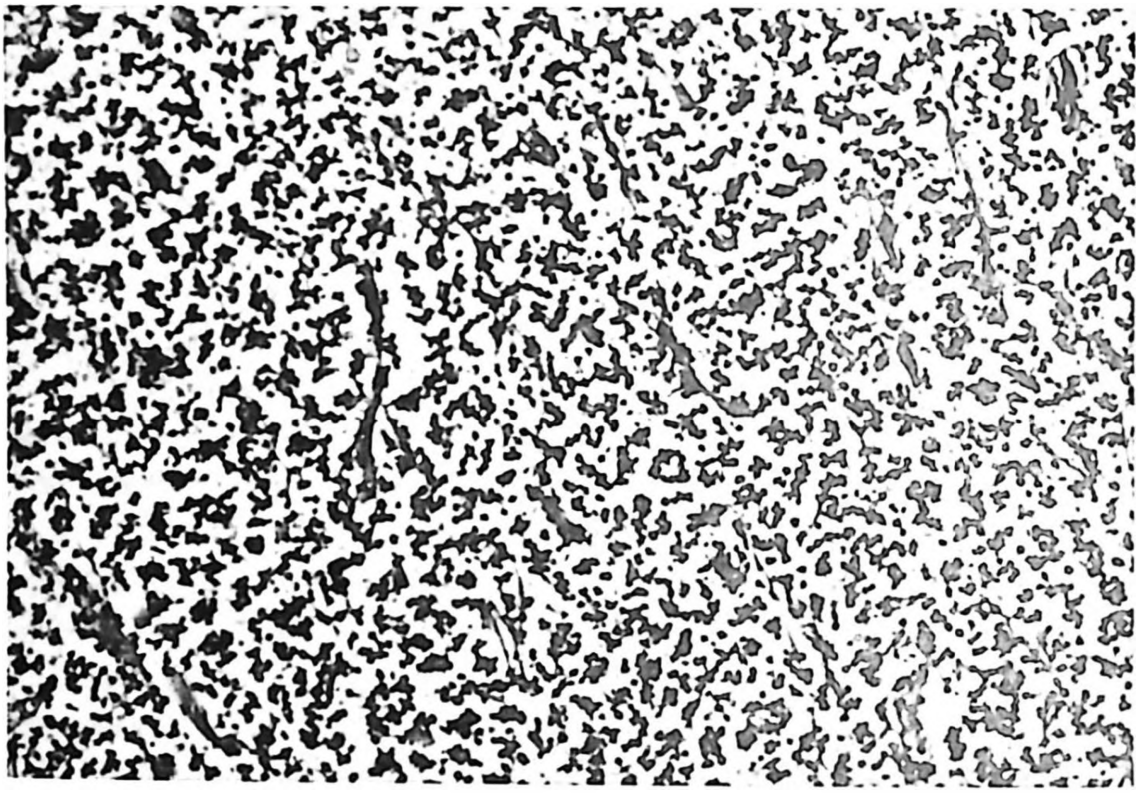

Figure 1
Dense cellular area of tumor.
(H and E stain x 320)

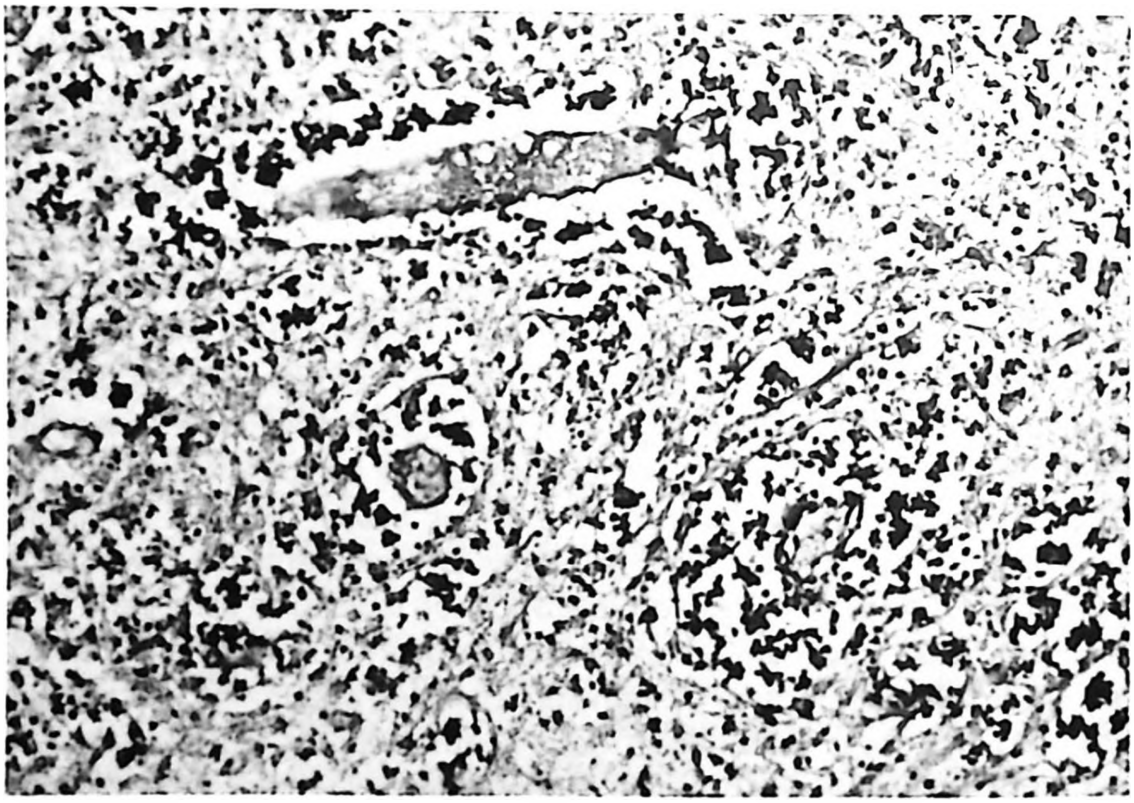

Figure 2
Periphery of the tumor showing characteristic perivascular arrangement.
(H and E stain x 75)

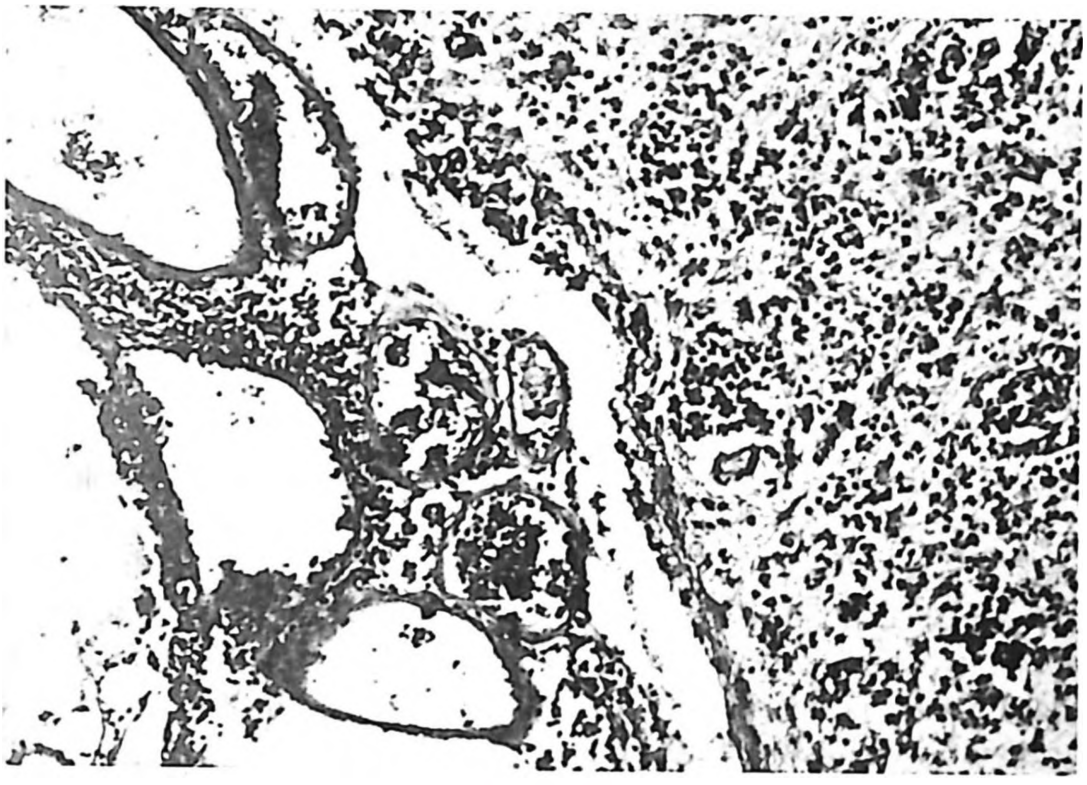

Figure 3
Tumor showing perivascular cuffing and focal infiltration of the leptomeninges. (H and E stain x 320)

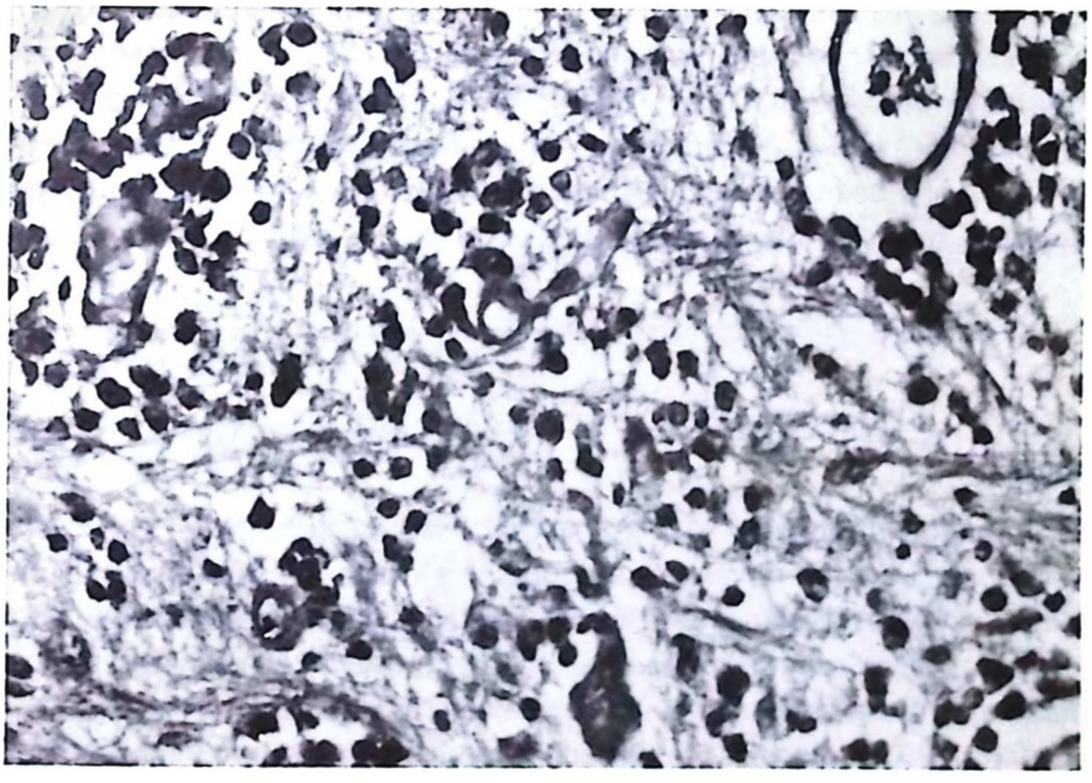

Figure 4
Survival of neurons in an area of tumor infiltration. (H and E stain x 320)

The respiratory abnormalities produced by fulminating meningitis, basilar artery thrombosis, pontile hemorrhage and encephalitis are well known. Disorders of respiration in brain tumors usually occur with the development of herniation which gives rise to increased intracranial pressure followed by brain stem compression, but these did not occur in this case. Sustained, regular, rapid, and fairly deep hyperpnea occurs in certain patients with dysfunction in the brain stem tegmentum. At autopsy, destructive lesions were found between the lower midbrain and the lower third of the pons, destroying the reticular formation up to the aqueduct and fourth ventricle[8-10].

With central neurogenic hyperventilation (CNH) the respiratory threshold is low, the blood gases reveal respiratory alkalosis with low arterial CO_2 pressure, elevated blood pH, and mild hypoxia (reflecting pulmonary congestion) unless the patient receives oxygen. In the case presented microgliomatosis was extensive. Since it infiltrated the upper pons and cerebral peduncle, the respiratory symptoms may have been produced by the tumor. Another interesting but unusual microscopic observation was the zones of infarction in the areas adjacent to the tumor, suggesting that vascular cuffing of the tumor cells may cause hypoxemia. This hypoxemia may also have played a role in the production of the respiratory symptoms.

We found one case report by Suzuki et al[11] in which CNH was associated with pontile astrocytoma in a five-year-old boy. The case presented here serves to emphasize two points. The first is that in some cases of brain tumor, increased intracranial pressure may not be present, and the tumor may not be demonstrable by arteriogram or air studies because of the diffuse infiltration which fails to alter the anatomy of the brain. The second point is that hyperventilation and respiratory alkalosis, although rare, may occur as associated symptoms.

Summary

A case of microgliomatosis in a 7-year-old boy is reported. In the absence of clinically demonstrable intracranial space-occupying lesion, presenting symptoms were episodes of hyperventilation and respiratory alkalosis. Complete autopsy showed no visceral lesion. The brain tumor was not visible to the naked eye, and the diagnosis was made only after microscopic examination. This was due to the diffuse and multifocal infiltrative character of the tumor. Microgliomatosis involving the upper pons and midbrain may have produced the dysfunction of the higher central regulation of respiration. To our knowledge, association of central neurogenic hyperventilation with microgliomatosis has not been previously described.

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