Multicentric Gliomas
Report of a Patient with a Thalamic Astrocytoma Associated with a Rare Primary Neurohypophyseal Tumor

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Multiple intracranial primary tumors of variable origin have been reviewed by Courville,6 Carl,4 and Madonick et al.14 These reviewers have described various combinations of gliomas occurring simultaneously, and the occasional association of gliomas with meningiomas, acoustic tumors, and neurofibromas of cranial nerves.

Batzdorf and Malamud2 have classified the group of multiple gliomas as: a) multiple tumors, apparently occurring as a result of dissemination by an established route, points of continuity being revealed by careful microscopic study; and b) multicentric tumors, existing as widely separated lesions in different areas of the brain, when no acceptable explanation was available for multiplicity. The latter category represents the true group of multicentric primary tumors. The present report deals with a patient in whom the clinical findings suggested that a pinealoma had spread to the hypothalamus or basal cisterns producing the classical signs of Parinaud’s syndrome and diabetes insipidus. However, autopsy demonstrated the presence of two separated tumors, one in the posterior part of the 3rd ventricle and another in the posterior part of the hypophysis. Upon careful histopathological examination, these lesions appear to be true multicentric tumors of unusual combination. It was not possible to find a report of a similar case in the literature, although McPhedran and Tom13 described pituitary adenomas and gliomas existing coincidentally.

Following histological study, the case reported here appears to be one of a glioma arising from the pars nervosa of the neurohypophysis differing from others described previously. Primary tumors originating in the pars nervosa or the neurohypophysis have been regarded as extremely rare neoplasms of the central nervous system. Although the literature contains reports of these tumors,17,23 the nature of these lesions has been contested.21 Moreover, Courville7 has stated that in his experience with over 60,000 autopsies, he has not observed such growth.* Kernohan and Sayre11 have questioned whether the few that have been described actually arose from the neurohypophysis. Well-documented cases, however, have described the infundibular part of the neurohypophysis as the site of unusual primary tumors (infundibuloma of Globus, granular-cell myoblastoma of Harland) and as a locus of secondary invading gliomas arising from structures of the 3rd ventricle in the chiasmic region.1

The present report, therefore, seems justifiable by the rarity of combination encountered and by the arresting microscopic features of the neurohypophyseal lesion.

Report of a Case

Summary. Diabetes insipidus for 1 year in a 30-year-old man. Diplopia and Parinaud’s syndrome for 3 weeks. Ventriculography and angiography disclosed a tumor in the posterior portion of the 3rd ventricle. Torkildsen’s shunt was done and radiation therapy was given. Death after a few months. Autopsy: astrocytoma of left thalamic region associated with a rare tumor of the pars nervosa.

History. A 30-year-old white patient was well until 1 year before admission, when he was found to have diabetes insipidus. Studies made elsewhere for a possible suprasellar lesion included examination of visual fields, roentgenograms of the skull and lumbar pneumoencephalography, all of which were reported to be normal. The cerebrospinal protein was slightly elevated. Administration of posterior pituitary extract intranasally controlled the excessive thirst and frequent urination. Three weeks before admission, the gradual onset of diplopia and frequent episodes of supraorbital headaches prompted his entry into the Long Beach Veterans Administration Hospital.

Examination. Upon his admission on Dec. 26, 1962, the patient was alert, well-oriented and cooperative. He displayed diplopia on horizontal gaze and paralysis of upward gaze. Visual acuity and fields were normal. The pupils were dilated and fixed to light and in accommodation. The left pupil was slightly larger than the right. There was no papilledema. Motor strength was normal in all extremities. Deep tendon reflexes were equal and normal. Coordination and sensory findings were normal. The skin was pale, dry and smooth. The hair was normally distributed on pubis and axillas, but was scanty on the trunk.

Lumbar spinal pressure was 110 mm. H2O. The cerebrospinal fluid was clear and colorless, containing 130 mg. per cent of protein. However, no cells were found. Pituitary gonadotropins in samples of urine were 1180 ml. in 24 hours.

The diagnosis considered initially was Parinaud’s

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* Dr. Courville stated: “I have examined only suspicious lesions, not routinely this region of every brain of the 60–70 per cent of all brains removed.”
syndrome caused by pinealoma with seeding to the infundibulum, together with diabetes insipidus. Right carotid arteriography for the venous phase was performed, since the radiographs with air and positive contrast studies demonstrated a mass on the roof of the posterior part of the 3rd ventricle with a narrow aqueduct (Fig. 1A).

Operation. Radiation therapy was advised, and since the aqueduct was stenotic and displaced, a ventriculocisternal shunt was done on Jan. 10, 1963 as a preventive measure of impending ventricular occlusion.

Postoperative Course. The patient received a total roentgen-ray dose of 4444 r to the area of the tumor through 4 ports with 300 rads 4 mm. Cu HVL. During this period the patient’s condition gradually deteriorated. His serum electrolytes were kept under adequate balance. Pituitary extract was given both intranasally and parenterally. Although the shunt remained unobstructed, the protein in the cerebrospinal fluid continued to climb up to 400 mg. per cent and patient expired rather suddenly on March 29, 1963.

Autopsy. Gross Description. A complete autopsy was performed by Dr. Guillan of the Pathology Department. The brain weighed 1330 gm. and was edematous. The shunt was patent. Coronal sections of the brain demonstrated ventricles of normal size. The 3rd ventricle was not displaced and a mid-line mass arising from the left thalamus occupied most of the posterior portion of the 3rd ventricle. The mass was almost indistinguishable grossly from the surrounding normal parenchyma and was limited medially by a normal ependymal layer. The infundibulum and pituitary stalk appeared normal. The pituitary gland was surrounded by grossly adherent connective tissue attached to a sella turcica of normal size. The gland removed en masse measured 1.8 by 1.2 by 1 cm.

Microscopical Description. Thalamic Lesion. The thalamic tumor was found to be composed of an increased number of well-differentiated and mature astrocytes (Fig. 2), with only slight increase on blood vessels. The endothelium of these vessels showed no proliferation. The ependyma of the 3rd ventricle was not infiltrated by the tumor. Diagnosis: Grade I astrocytoma of the thalamus.

Pituitary Gland. Multiple sections were stained with hematoxylin and eosin, Wilder’s reticulin stain, Bodian and Holzer’s stains for nerve fibers, and van Gieson’s stain for connective tissue. A low-power view revealed the pars nervosa to be completely replaced by a mass of abnormal proliferative tissue measuring approximately 0.9 by 0.4 by 0.3 cm. The neoplastic mass of the posterior lobe was well demarcated from the other lobes (Fig. 3). The tumor consisted of a hyperplastic group of spindle or fusiform cells with elongated nuclei. There were areas where a cellular pleomorphism was observed and occasional large forms were present. These cells demonstrated hyperchromatic, eccentric nuclei and abundant hyaline cytoplasm exhibiting early malignant propensities as a first stage of increased biological activity (Fig. 4). No mitotic figures were observed. Their appearance was quite similar to the astrocytic elements seen in astrocytomas and glioblastomas of the cerebral hemispheres. The nuclei of the other cellular elements presented abundant granules of chromatin. The cytoplasmic processes were bipolar or multipolar, some of them extending to walls of vessels. Cellular proliferations formed, at times, whorl-like masses that reached the fibrous capsule. The pars nervosa was entirely replaced by the neoplastic tissue (Fig. 5). Without metallic impregnation, it was difficult to identify remaining normal cellular elements; but some forms seen had the appearance of abnormal pituicytes.

The stroma was formed by abundant capillaries which crossed throughout the neoplastic tissue and by what appeared to be strands of connective tissue which joined the fibrous capsule at the periphery. A framework was thus formed for the cellular elements. There were a few groups of plasma-cell elements, many of them within the stroma and others in the capillaries. Only occasional lymphocytes were seen. Deposits of hemosiderin and a few pigment-laden phagocytes were observed in the capsule. There was abundant reticulin, especially in areas near the fibrous capsule. Only an occasional nerve fiber, which had a swollen and beaded appearance, was

![Fig. 1. Thalamic tumor. (A) Positive contrast ventriculography demonstrates a large mass in the posterior part of the 3rd ventricle. The aqueduct of Sylvius is narrowed by the mass. Some contrast material has passed into the 4th ventricle. (B) The posterior part of the internal cerebral vein (arrow) is displaced downward. This displacement suggested a tumor arising from the thalamic region (pulvinar) rather than originating from the pineal area.](image-url)
Fig. 2. *Thalamic tumor*. Microscopic appearance of the tumor shown in Fig. 1. It is composed of mature fibrillary astrocytes that extend toward the ependymal layer of the 3rd ventricle. Hematoxylin and eosin stain, ×200.

Fig. 3. *Tumor of pars nervosa*. (A) Low-power view of tumor (arrows) originating in posterior lobe of pituitary gland. Some remnants of the anterior and middle lobes are present. Hematoxylin and eosin stain, ×16. (B) High-power view showing the tumor (T), anterior (A) and middle (M) pituitary lobes. Hematoxylin and eosin stain, ×110.
seen within the stroma. Most of the peripheral stroma showed abundant collagen. Occasional psammomatosus bodies were also seen at the periphery of the mass, probably caused by arachnoidal proliferation of the pia-arachnoid membranes.

Comment. The chief features of this case are the unusual occurrence of the clinical findings produced by the rare association of two different intracranial tumors that certainly represent multiple foci. Moreover, this combination seems to be without parallel in the literature. The patient died because of the astrocytoma in the left thalamus and not from the tumor of the pars nervosa.

Clinical Manifestations of the Thalamic Tumor

Tytus has described 8 signs exhibited by patients with either gliomas of the posterior part of the 3rd ventricle or primary pinealomas: 1) papilledema or optic atrophy, 2) loss of upward gaze, 3) loss of pupillary light reflex, 4) palsy of 3rd nerve, 5) palsy of other cranial nerves, 6) pyramidal-tract signs, 7) cerebellar signs, and 8) mental changes, usually occurring as somnolence. Of these, he concluded that the 3 latter signs constituted the chief means of distinguishing clinically between the 2 types of tumor since they were found more commonly in patients with tumors of the posterior part of the 3rd ventricle.

The initial clinical findings observed in the patient reported here suggested that he presented signs of a pinealoma, since these tumors are known occasionally to result in secondary implants in the chiasmatic region, pituitary body, walls and floor of the 3rd ventricle and infundibulum. Carotid angiography, however, suggested the presence of multiple tumors rather than secondary implants. The downward displacement of the internal cerebral vein seemed to indicate the presence of a tumor growing in the pulvinar or posterior part of the 3rd ventricle rather than in the pineal gland (Fig. 1B). A mass arising in the pineal region or quadrigeminal plate would tend rather to shift this vein in an upward direction. When clinical signs of somnolence, cerebellar invasion and pyramidal-tract disruption appeared in the patient, it appeared more likely that glioma rather than pinealoma existed. Although gliomatous extension to the infundibular regions could explain the presence of diabetes insipidus, it was necessary to consider multi-
centric neoplasms in the diagnosis, one of which invaded the mechanisms regulating the anti-
diuretic hormone. Autopsy disclosed an astro-
cytoma which was confined to the region of the pulvinar and thus had no connection with the proliferation of neoplastic tissue in the pars nervosa of the pituitary gland.

Etiological relationships between these two tumors appear to be unlikely. Conceivably, the astrocytoma might have stimulated the growth in the neurohypophyseal gland as a reactive gliosis which subsequently underwent progressive neoplastic transformation. Storch\textsuperscript{34} was the first to offer the hypothesis that gliomas might induce neoplastic change in the adjacent glial tissue. This concept was held by Councilman\textsuperscript{8} who considered that the stimulus from the neoplastic elements might be chemical in nature and might be capable of inducing relatively distant foci of neoplasia apparently via tissue fluids, the blood stream, or cerebrospinal fluid. On the other hand, Scherer\textsuperscript{13} and Willis\textsuperscript{27} expressed the opinion that progressive neoplastic changes might occur simultaneously in different sites in the brain as the result of a wide variety of stimuli, either biochemical or hormonal.\textsuperscript{22} This concept conforms more with current opinion, and the coexistence of two circumscribed but separated tumors in the case reported here is explained more rationally by simultaneous development of neoplasia in different primary foci.

**Tumor of Pars Nervosa**

Both the histological appearance of the cellular collection in the pars nervosa of this patient, and the symptoms of diabetes insipidus which it produced, identify the lesion as a neoplasm. The cells of the tumor were permanently altered elements having the power of growth\textsuperscript{26} and appeared to have entirely replaced the normal structure of the pars nervosa. That the lesion might be the result of radiation therapy which this patient received can be disregarded for the following reasons: 1) the anterior and middle lobes were histologically normal, 2) the central nervous system, including the pars nervosa, is known to be resistant to doses of radiation even after *in-situ* radiation that produced destruction of the pituitary gland.\textsuperscript{18} The characteristic cellular components described here resembled either abnormal pituicytes or neoplastic astrocytes. These cellular structures characterize this neoplasm as belonging to the glioma group. The pituicyte has been considered a modified glia
cell and probably qualifies as a cellular derivative of the spongioblastic series. Theoretically, therefore, the pituitary is susceptible to neoplastic proliferation, although the reason why this tumor is not often observed is obscure.

We have found no report in the literature of a primary glioma, such as that described here, developing in the pars nervosa of the hypophysis. McLean suggested that primary tumors of the posterior lobe are practically unknown. Antoni suggested that those gliomas appearing to originate in the neurohypophysis were probably related to ependymal tumors. Such tumors probably originate from the floor of the 3rd ventricle, where true neuroglial tissue is present, and extend secondarily into the neurohypophysis.

In 1921 Sternberg described a minute tumor in the posterior lobe which he called a choristoma, and Priesel in 1922 reported 19 similar tumors located in the posterior lobe and hypophyseal stalk, which he called progonoblastoma, the largest of which measured 3 mm. in diameter. Harland described a large primary tumor in the neurohypophysis and found 2 others which showed all the characteristics of the so-called granular-cell myoblastoma. According to him, the histological descriptions of Sternberg's and Priesel's cases conform to the appearance of these latter tumors. Simonds and Brandes reported 8 cases of fairly circumscribed but unencapsulated cellular masses, measuring 0.35–1 mm. in diameter, found within the normal structure of the posterior lobe of the hypophysis. These authors thought that such lesions were probably not neoplasms, although they identified them with the cases of Priesel. The histological descriptions and photomicrographs of Simonds and Brandes' cases are quite similar to those of Harland's cases.

These observations of Priesel, Simonds and Brandes, and Harland appear to delineate the so-called granular-cell myoblastoma as a tumor entity which is found not uncommonly in the neurohypophysis. The histological appearance of these tumors, however, is quite different from that reported here. It must be concluded then that two kinds of tumors may develop in the posterior lobe: 1) the granular-cell myoblastoma and 2) the primary gliomas, the latter occurring more rarely.

The location and histological appearance of the tumors mentioned above support the concept of neural origin of both. Diabetes insipidus produced in the patient reported here resulted from obliteration by the tumor of mechanisms involved in the production of antidiuretic hormones. A current view of the syndrome of diabetes insipidus proposes that the antidiuretic hormone is synthesized in the neurons of the medial hypothalamus, transported down to the nerve fibers and stored in the terminals of the neurohypophysis from which it is released into the blood stream upon appropriate stimulation. Electron-microscopy studies by Palay have shown that the neurosecretory granules were confined to only the interior of the axons and terminals. For this reason, the concept of the neurohypophysis as a storehouse for these hormones is therefore very important to an understanding of the clinical manifestations of the hypophysal tumors described here. Any neoplastic or glial proliferation that would replace nerve fibers of this system would have the effect of a biological "section" of the hypothalamo-hypophysial tract. It has been demonstrated that the surgical section of the pituitary stalk is able to produce diabetes insipidus, probably because of the degenerative process of the nerve fibers. There was almost complete absence of these fibers in the tumors reported here.

Summary

A case of Parinaud's syndrome associated with diabetes insipidus is presented. This was caused by two tumors of multicentric origin, one located in the neurohypophysis and the other in the thalamus, extending into the posterior part of the 3rd ventricle.

The small tumor of the posterior lobe of the hypophysis shows histological characteristics of abnormal astrocytic glia. Similar lesions apparently have not been described previously, although primary tumors corresponding to the so-called granular-cell myoblastoma have been reported. It is probable that true primary gliomas in this region may not be too rare if a careful pathological examination of the hypophysis is always made at autopsy, especially in the presence of unexplainable diabetes insipidus.

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References

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