THE DISSEMINATION OF GLIOMA BY EXTENSION AT A DISTANCE

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The manner of growth and dissemination of gliomata constitutes an important study, yet actual information concerning this subject, as such, is scant. The general impression is that these tumors are infiltrative, that they grow more or less symmetrically, and that in certain types, such as the medullo-blastoma, dissemination occurs by "seeding." The fact that dissemination may occur otherwise than by metastasis was shown in a brain harboring a pinealoma which recently came under observation. This tumor had spread directly from its original position in the pineal recess to the subependymal layer of the lateral ventricles. The unusual way in which this tumor had spread by extension at a distance stimulated an investigation of this method of dissemination. The case is reported together with other similar cases found in the literature in order to define as far as possible the dissemination of glioma by extension at a distance.

REPORT OF CASE

M. F. (University of Pennsylvania Hosp. No. 29690), a boy aged eighteen, was admitted to the service of Dr. A. Stengel in the University Hospital on May 22, 1934. He was subsequently studied on the service of Dr. W. G. Spiller and Dr. C. H. Frazier.

The patient was well until two years prior to admission, when he developed polydypsia and polyuria. These symptoms continued until he entered the hospital. One year prior to entrance marked the beginning of mental retardation along with hypersomnia, easy fatigability, and impaired memory for recent events.

The pupils were fixed and dilated, especially the right, and there was limitation of upward associated ocular movements. The left external rectus and superior oblique muscles were partially paralyzed. The fundi showed hazy disc margins of good color. The visual acuity was 6/15 for O.D. and 6/22 for O.S. Visual fields showed irregular defects in the upper left quadrant and lower right quadrant on both sides. There was general asthenia in all extremities, with decreased but equal tendon reflexes. The body hair was distinctly female in distribution. The basal metabolic rate was —32 per cent and —24 per cent. Roentgenograms of the skull showed definite evidence of increased intracranial pressure and
a calcified pineal body which was displaced downward and backward. The spinal fluid pressure was 180 and 200 mm. of water. The patient gradually deteriorated and died.

**Autopsy:** The post-mortem examination was performed by Dr. Bernard J. Alpers. The brain weighed 1530 grams. Its external surface presented nothing unusual. In the pineal recess was a large, hard, white mass which filled the entire space.

The brain was cut in coronal sections. This revealed, beneath the ependyma of both lateral ventricles, a granular tissue which undermined the ependymal lining, giving the latter a verrucose appearance. This was due to the pushing up of the ependyma into folds by the tumor tissue beneath it. The greatest area of subependymal infiltration was at the inferior angle of the anterior horns. The tissue infiltrated the adjacent white matter but was quite clearly demarcated from the latter. This granular tissue extended posteriorly, beginning at the base of the fornix, and from here dipped down into the floor of the third ventricle, where it invaded the tuber cinereum, the hypothalamus, and prechiasmal region. The infundibulum was much enlarged due to the adjacent invasion of the diencephalic floor by the tumor tissue. From the diencephalon the tumor extended posteriorly into the

![Fig. 1. Drawing of Coronal Section through the Pineal Tumor, Showing Extension of the Cells About the Aqueduct of Sylvius and the Subependymal Layer of Both Lateral Ventrices](image)

mesencephalon, where it involved the periventricular gray matter and the tegmental structure for a distance of a centimeter. The adjacent pulvinar of the thalamus was invaded but the red nucleus was spared.

From the mesencephalon the tumor could be traced to the hard, white, firm mass in the pineal recess, with which it was directly connected. With this exception the mass in the pineal recess was sharply demarcated, and did not invade the roof of the mesencephalon.

There was marked hydrocephalus of the lateral and third ventricles. The iter and the fourth ventricles were not dilated. The portion of the iter of Sylvius surrounded by the granular tumor tissue was partially but not completely occluded.

**Microscopic Examination:** The tumor in the pineal recess invaded the quadrigeminal plate and completely surrounded the proximal end of the iter. The ependymal lining of the iter was in part intact, showing only partial occlusion of the aqueduct of Sylvius. The tumor was cellular, with a moderate amount of loose stroma. The predominating cell was large, containing nuclei which were either oval, round, or indented. Each nucleus had a rather large nucleolus, which was centrally placed. The cytoplasm of the cell was granular and not very abundant. Occasionally a multinucleated cell was found. Interspersed in groups among these large cells were small, round, dark-stained cells which resembled lympho-
cytes. Mitoses were not frequent. The tissue was vascular, and the walls of many of the blood vessels showed cellular proliferation. Small deposits of calcium were frequently seen.

The tumor tissue beneath the ependymal lining of the ventricles presented somewhat the same picture. The stroma was scanty and loosely arranged. The large, irregularly shaped cells were more abundant but with the same general characteristics as those of the primary tumor. There were many more multinucleated cells, and mitoses were more frequent. The vessels showed a greater tendency to round-cell infiltration and thickening of the walls. The tumor tissue was in parts confined to the subependymal region; in others it invaded the periventricular gray matter.

The histologic diagnosis was pinealoma, based upon the character of the individual tumor cells and not upon cellular arrangement. In none of the sections examined was there any suggestion of a cellular pattern found in the pineal gland. The tumor cells, however, resembled those seen in a mature gland. The important fact is that the cells of the distant growth beneath the ependyma resembled in every way those of the primary tumor, except that the former gave evidence of greater activity.

FIG. 2. DRAWING OF CORONAL SECTION THROUGH THE ANTERIOR HORN OF THE LATERAL VENTRICLES, SHOWING TUMOR EXTENSION IN THE SUBEPENDYMAL LAYER AND THE WAVY APPEARANCE OF THE WALLS OF BOTH LATERAL VENTRICLES

This case demonstrates an unusual form of dissemination by extension at a distance. The tumor, a pinealoma, spread from the pineal recess into the quadrigeminal plate, about the aqueduct of Sylvius, and thence forward into the subependymal layer of the lateral and third ventricles. The connection between the primary growth and the subependymal region of the lateral ventricles was seen both grossly and microscopically.

CASES FROM LITERATURE

The literature was searched for further examples of this unusual type of dissemination. Cerebral tumors which had projected into the ventricles and cerebellar tumors which had projected into the spinal canal, both by virtue of their size, were not considered examples of this process. Those cases where the pathological descriptions clearly stated that there was direct extension of the tumor tissue to distant parts were considered as representing this type of dissemination. They will be presented under their various classifications.
**Pinealoma:** Two examples in which a pinealoma had extended to distant parts in a manner similar to that described above are reported by Horrax and Bailey (1). In one (Case 3) the tumor tissue had spread from the primary growth, over the cerebellum and brain stem or, as the authors state, had infiltrated the meninges over these structures. The type of dissemination is somewhat different from the example just given in that the tumor tissue over the cerebellum and brain stem was beneath the pia instead of the ependyma. The method of dissemination, however, is by extension at a distance. In the second case (Case 5), following the description of the lesion, the pathologist stated that two large, soft, semi-gelatinous tags spread forward from the tumor into the third ventricle, one downward into the infundibulum, the other through the foramen of Monro into the right lateral ventricle. In this specimen it will be noted that the extension was over the ependyma.

![Fig. 3. Low-power and high-power photomicrographs of tumor in the pineal recess, showing the typical collections of large and small cells. The small cells predominate. Toluidin blue stain.](image)

A recent report by Friedman and Plaut (2) of a pinealocytoma with meningeal and neural metastases describes a most interesting type of dissemination. At first this was thought to correspond to the form of dissemination under discussion. Careful analysis showed, however, that the authors had not established a communication between the primary lesion and the tumor tissue present in the meninges and nerves. For this reason the case has not been included in this study.

Though other examples must exist, the majority of pathological descriptions show that the growth remains confined to the pineal recess except when the tumor extends by reason of its size.

**Oligodendroglioma:** The oligodendroglioma may disseminate by extension at a distance. Kwan and Alpers (3) in a clinico-pathological study of these tumors describe one (Case 2) which extended into the sylvian fissure and infiltrated the subarachnoid space in that region. This patient had been operated upon fourteen months before death. At that time a generous portion
of the tumor had been removed. The operative notes state that the lesion lay chiefly in the frontal lobe above the sylvian fissure and that the region of the sylvian fissure was not disturbed during the procedure. This latter fact makes it possible to exclude mechanical spread of the lesion at operation and to consider this an example of dissemination by extension at a distance.

Interesting, too, is the statement by the authors that the tumor cells observed in the subarachnoid space showed cytoplasmic processes similar to oligogliocytes, but the impregnations were more suggestive than conclusive. Whether this was due to the several courses of x-ray treatment the tumor received, or to the new environment into which the cells had grown, is difficult to say.

In a paper by Martin (4), a case is reported (Case 2) in which an oligodendroglioma lying adjacent to the body of the lateral ventricle had extended along the floor of the inferior horn up to its tip. This extension was 3 to 4 mm. wide. A similar extension was observed which spread from the primary tumor into the opposite lateral ventricle up to the tip of the anterior horn. This latter extension had a fine connection through the foramen of Monro. In the author's microscopic description, it is stated that in the thin extensions it appeared as though the growth had evidently skimmed along the ependyma.

Two additional examples are to be found in a paper by Greenfield and Robertson (5). These authors describe a cystic oligodendroglioma (Case 2) which communicated with the lateral ventricle. The tumor tissue had spread over the inferior surface of the anterior horn of the lateral ventricle as an irregularly thickened felt-like membrane. From here it had passed through the foramen of Monro and was seen as a slight opacity on the walls of the third ventricle. The second example in the same paper (Case 3) showed direct extension from the tumor, which lay in association with the third
ventricle and extended backward to the pineal recess and downward to the iter of Sylvius, into which a thin tongue of growth had protruded.

**Medulloblastoma:** When this study was started, it was thought that the medulloblastoma, because of its rapid growth, would give the best illustrations of dissemination by extension at a distance. Very shortly this theory was found incorrect. As is well known, when dissemination occurs in the medulloblastoma, it is seen as separate discrete nodules apart from the parent growth, and so far as could be learned, no direct connection has ever been established between these nodules and the primary lesion. It is not the purpose of this paper to enter into a discussion as to why this is so, but rather to point it out as a characteristic of this type of glioma.

The one illustration of dissemination by extension at a distance which may be included here is reported by Cairns and Russell (6). They describe a lesion which was located in the vermis of the cerebellum and had extended into the cerebellopontine angle. In this region it had formed a soft, white mass measuring 2.2 cm. x 1.4 cm. There were other features about the growth of the tumor, but this particular aspect conforms with that under discussion.

**Spongioblastoma:** No examples were to be found in which a spongioblastoma spread by extension into distant parts. Cairns and Russell (6), however, report a case (1) in which the diagnosis was glioma (unclassified), and the type of cell, as pointed out in their pathological comment, was a unipolar spongioblast with fibrillated cytoplasm. Nevertheless, as they so emphatically point out, the growth cannot be classified as a unipolar spongioblastoma because of the simpler and more primitive type of spongioblast than that occurring in this type of glioma. The case is included here, because of its close similarity to the spongioblastoma.

The primary lesion originated in the third ventricle. It extended into the leptomeninges over the floor of the third ventricle and encased the optic chiasm and adjacent internal carotid arteries. A layer of gray tumor tissue, up to 0.3 cm. deep, covered the cerebral peduncles and spread backward over the front of the pons and adjacent cerebellum. The posterior communicating and posterior cerebral arteries and the origins of the third and eighth cranial nerves on each side were obscured by a thin layer of tumor. The basilar and vertebral arteries were superficial to it. The arachnoid membrane which covered them was white and opaque. Here again the spread was beneath the pia.

**Ependymoma:** The difficulty in determining whether this type of tumor extends to distant parts is obvious. In spite of this fact, one example may be drawn from a paper by Barnes (7). A subcortical frontal lobe tumor (Case 1) had spread along a sulcus to reach the surface of the hemisphere. This particular feature of tumor growth again demonstrates dissemination by extension at a distance.

**Glioma (unclassified):** Probably the most striking illustration of tumor spread by extension at a distance is that reported by Viets (8). In his case the primary tumor originated in the right temporal lobe and basal ganglion. The lesion extended to the surface of the temporal lobe and thence as a slightly granular, grayish layer over the right temporo-sphenoidal lobe as far
as the optic chiasm. It then spread posteriorly along the inferior surface of
the brain to cover the right cerebellar hemisphere and a portion of the left
cerebral peduncle and thence over the pons, medulla, and spinal cord, "as
though a cup of molasses had been poured over it." In the cerebellum there
were several places which appeared to be infiltrated by the tumor.

Equally as extensive a process is found in the specimen described by
Councilman (9). The primary tumor was located in the pons, from which
it extended to the surface and infiltrated the leptomeninges over the pons and
along the entire length of the spinal cord. The author expressed it as resem-
bling a mass of plaster which had been poured over the spinal cord and pons.

Brannan (10) calls attention to a specimen in which a primary tumor of
the left optic thalamus spread to involve nearly all the surface of the base of
the brain. He traced the extension from the primary growth through the wall
of the third ventricle to the leptomeninges. He could find no evidence that
the tumor disseminated in the spinal fluid. It is his belief that the cellular
structure of these tumors changes when they enter a new environment.

**DISCUSSION AND SUMMARY**

This study shows that dissemination by extension at a distance does occur,
though is not a common finding. The process is not limited to one type of
glioma but nearly all types have produced examples. The pinealoma is repre-
sented by three cases, the oligodendroglioma by four, the medulloblastoma by
one, the ependymoma by one, the spongioblastoma by one, and the glioma
(unclassified) by four.

The characteristics of this type of dissemination may be described under
two headings. The first is the tendency of the growth to extend to the surface
of the brain and thence beneath the pia mater. The second method is the
extension of the tumor over or beneath the ependyma of the ventricles when
the lesion develops in close relation to the ventricular system.

Extension to the surface of the brain and thence beneath the pia is the
predominating mode of dissemination at a distance. This process is demon-
strated by the case of Kwan and Alpers, in which the extension was into the
sylvian fissure and overlying pia from a frontal lobe oligodendroglioma. Viet's
temporal lobe glioma spread to the base of the brain and thence over the pons,
medulla, and spinal cord beneath the pia mater. Similarly in Brannan's case,
a glioma of the optic thalamus, extended by way of the third ventricle to the
base of the brain and over its surface beneath the pia. A tumor described by
Cairns and Russell, arising in the vermis of the cerebellum, extended into the
cerebellopontine angle. The same authors describe a spongioblastoma which
originated in the third ventricle and burrowed its way to the base of the brain
to spread over its surface beneath the pia. The cases of Barnes and Council-
man, both gliomas of the pons with extension down the spinal cord, again
demonstrate this tendency. The last example is the pinealoma, reported by
Horrax and Bailey, which infiltrated the meninges over the cerebellum.

The second way by which these tumors spread by extension at a distance
is over or beneath the ependyma; this occurs in tumors which grow close to the
ventricle. The latter tendency is illustrated by the case reported in this paper,
in which there was extensive dissemination from the primary pinealoma directly to and throughout the entire subependymal layer of the lateral ventricles. The two cases of Greenfield and Robertson represent a less marked example of a similar process. The tumors described by Martin, an oligodendroglioma, and by Horrax and Bailey, a pinealoma, demonstrate the tendency to spread over the surface of the ependyma.

The studies thus far have not revealed just how dissemination by extension at a distance takes place. In the case reported it might be concluded that the tumor cells followed vessels and thus came to infiltrate the vascular subependymal layer of the lateral ventricles. Other than this, it may be said that the extensions are along paths of least resistance, and for the most part downward, so that gravity or the flow of spinal fluid may exert an influence upon the growth. When the extension reaches the subpial space, it seems to grow within it.

References