METASTASIZING CEREBELLAR TUMORS
THE DIFFICULTY IN DISTINGUISHING BETWEEN MEDULLOBLASTOMA AND NEUROBLASTOMA

ROBERT P. BARDEN, M.D., AND FREDERIC H. LEWEY, M.D.

Department of Radiology and the Pathological Laboratory of the Neurosurgical Service, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

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It is now 20 years since one of the first reports in the literature of cerebellar neoplasm with tumors in distant bones was presented from this clinic. In the ensuing years, evaluation of many of the clinical and radiologic problems attending cerebellar medulloblastoma has been pursued based on experiences with patients passing through our neurosurgical clinic. As a result, additional information has become available which warrants re-examination of the concept that medulloblastoma may occasionally metastasize to extraneural structures.

Although it is generally agreed that these tumors remain localized to the central nervous system, sporadic case reports of skeletal and visceral dissemination, in addition to the one mentioned above, have appeared in the literature. When all of these are critically appraised, it appears that the group of the “medulloblastoma” is not so unequivocally defined as it was originally thought to be. The term “medulloblast” was coined by Bailey and Cushing to designate a hypothetical immature, bipotential cell which may develop into neuroblasts or glioblasts. This concept implied the possibility that in some of these tumors, neuroblasts prevailed, in others, glial elements. A similar thought was expressed in the opinion of two opposing schools of thought as to the origin of the type cell of these tumors. Penfield and his co-workers suggest that a group of embryonal cells commonly found in the anterior medullary velum give rise to the formation of the medulloblastoma, whereas Stevenson and Echlin, and others derive them from the marginal layer of embryonal granular cells in the cerebellar cortex which gradually disappear in the third year of life. These authors prefer the name granulocytoma to medulloblastoma. Be this as it may, the consensus of opinion today is that there exists a common tumor of childhood of a particular type, located primarily in the cerebellar vermis, though later extending into the hemisphere. This tumor is extremely radio-sensitive in the beginning, without being completely destroyed by any present method of radiation. With repeated irradiation, it becomes increasingly insensitive, and eventually, lethal, after a course of from 1½ to 3 years. There seems to be no doubt that the tumor represents clinically, pathologically, and radiologically a well defined disease entity independent of the name given to it.

The ambiguous nature of the characteristic cell of this tumor, on the other hand, raises the question as to whether some of these neoplasms may not be part of the group of so-called sympathicoblastomas. This means neuro-
blastosmas of the sympathetic nervous system, and would open the possibility that a primary tumor in the adrenals, the sympathetic chain, or anywhere else in the body in a sympathetic ganglion could metastasize into the brain and the bones. On the other hand such tumors might originate in various organs independently of one another or take their origin from sympathetic or other immature nerve cells in the brain and metastasize from there, although no precedent is known for this sequence of events.

It seems, therefore, important to review the subject of disseminating cerebellar tumors, using as a basis for discussion 1 of our early cases and 2 others recently observed.

CASE REPORTS

*Case 1.* A white female, aged 32, was admitted to the service of Dr. Frazier at the University Hospital on Nov. 1, 1919, her chief complaint being staggering gait. The symptoms and signs, which indicated cerebellar dysfunction and increased intracranial pressure, began about July of that year.

A 1st stage suboccipital craniectomy was performed several days after admission. Subdural tension was extreme, but on account of the poor condition of the patient, the 2nd stage was delayed for 2 weeks. At that time, the tension had subsided somewhat, and the only abnormality encountered was a somewhat enlarged right cerebellar hemisphere. Fifty mg. of radium were inserted into the cerebellar hemisphere and left there for 18 hours. Two weeks later, the patient was discharged in fair condition. Pathologic study of a small amount of tissue removed proved it to be edematous cerebellar tissue.

In January, 1921, another operation was necessary, and this revealed a large, soft, friable, grayish-red tumor covering the left cerebellar hemisphere. As much of this as possible was removed, and 50 mg. of radium were applied for 11 hours. Subsequently, the patient received 5 radium applications. The pathologic diagnosis at that time was "glioma (medulloblastoma)." Five months after discharge, she returned for more radium applications. She did not seem so well as previous to the operation. However, she had neither headache nor pain. For approximately ½ year, the condition remained about the same, and then there developed pain over the sacrum and shooting pains in the legs.

She did not return to the hospital, however, until October 1923, at which time there was severe pain in the back and shoulders, persistent edema of both legs, and emaciation. Whereas physical examination had previously given negative results except for the neurologic observations, the patient now appeared cachectic. There was a visible and palpable mass just above the left buttock over the sacro-iliac joint, and the back of the lumbosacral region was discolored. Rectal examination revealed extreme tenderness in both sacro-iliac joints. Roentgenograms of the pelvis showed evidence of an extensive growth involving both iliac bones, the right side of the sacrum, and probably the upper part of the right femur (Fig. 1). Roentgenograms of the lower part of the thoracic region and chest disclosed a large shadow to the right and in front of the spine and behind the heart which might have been a tumor originating in the sympathetic chain. Evidence of spinal involvement in this region was not present.

A cordotomy was performed at the 5th thoracic level to control her pain. Upon

*Previously reported by Pendergrass and Wilbur.*
discharge from the hospital there was little pain in the legs, although some pain was still present in the region of both hips. The patient died at home and postmortem examination could not be obtained.

Comment. The original histologic diagnosis of the tumor removed at operation in 1919 was "glioma (medulloblastoma)." These sections were reviewed in 1942 and the diagnosis was changed to neuroblastoma (Fig. 2). If this diagnosis were accepted it would remove 1 of the cases of so-called metastasizing medulloblastoma from the literature.

Fig. 1. Case 1. (From Arch. Neurol. Psychiat., Chicago, 1928, 19: p. 443.) "A metastatic growth involving both wings of the ilium and both femora, especially the right, and the right wing of the sacrum. Unfortunately, a large amount of gas tends to confuse the true areas of metastases, which can be easily differentiated in the original roentgenogram."

Case 2. A white male, aged 13 years, was admitted to the University Hospital on Dec. 28, 1938 with a history of severe headache for 3 weeks and intermittent vomiting for 2 weeks. There was also some blurring of vision and difficulty in walking. Examination showed left-sided incoordination, nystagmus, and evidence of increased intracranial pressure. Operation resulted in the removal of a large tumor from the left cerebellar hemisphere.

The tumor was originally called "medulloblastoma" with reservations. On recent detailed histological examination it was noted that the tumor cells were arranged in parallel rows separated from one another by reticulin fibers. Both cells and fibers coiled up in the shape of large whorls in some places and formed pseudorosettes in others. The reticulin fibers sprang from the blood vessels. The majority of the cells were of the larger variety. Their nucleus was irregularly shaped, bright,
its chromatin often assembled at opposite poles. Cytoplasm was scant. Most of the cells were apolar; some had one, occasionally long but usually short, prolongation. No mitoses were found (Fig. 3).

The patient received roentgen therapy during February and March 1939 with a total of 2000 r into the mid-portion of the brain. A 2nd course of therapy was given in July and August, 1939 with a total tumor dose of 2000 r. He remained well until November, 1941, when he began to complain of severe pain in the arms and legs and presented himself with a swelling of the left thigh and an enlargement in

the left groin. Although the initial explanation for the pain in the extremities was that the patient had seeding of the recurrent tumor along the spinal cord, roentgenograms of the left femur showed a large destructive lesion in the bone (Fig. 4). The diagnosis was then changed to osteomyelitis. An incision was made in the femur and pus, under pressure, was released.

The histologic diagnosis on the biopsy material was a malignant bone tumor and the consensus of opinion of several pathologists was that it might be classified as an Ewing's tumor. The bone was found to be invaded by strands of tumor cells. The
Fig. 3. Case 2. Cerebellar tumor (medulloblastoma or neuroblastoma). Left, Hematoxylin and eosin, ×300; right, Laidlaw. The cells are arranged in rows which are separated by reticulin fibers springing from the blood vessels. Both cell rows and reticulin fibers coil up to form large whorls which may simulate pseudorosettes. The cells of this tumor are more mature and better differentiated than those of Case 3. (Compare with Fig. 6.)

Fig. 4. Case 2. Roentgenograms of the left femur of a 13-year-old boy previously treated for cerebellar medulloblastoma. Irregular destruction of cortex and medullary cavity, periosteal new bone formation and a large soft tissue mass, all suggest a malignant bone tumor. The original diagnosis from biopsy specimen was Ewing's tumor.
type cell contained an irregularly shaped, elongated nucleus surrounded by a small amount of cytoplasm which tapered out on the two opposite ends of the nucleus. The prolongations formed a loose network. Occasionally, a few cells were arranged in rosette shape (Fig. 5).

Pain was temporarily relieved by further roentgen therapy, but the patient died in September, 1942. Postmortem examination was not obtained.

Comment. This patient exhibited the classical clinical picture and gross and microscopic pathology of medulloblastoma (Fig. 3). His postoperative course and response to radiation therapy was exactly as expected until the late complication occurred. It was unfortunate that no autopsy was obtained, but from the evidence of the biopsy of the femur (Fig. 5), it must be assumed that the patient either had two separate tumors of extremely similar histologic pattern, or that the medulloblastoma metastasized, or that both the cerebellar and the bone tumors were part of a metastasizing neuroblastoma (vide discussion).

Case 3. A white male of 14 years was admitted to the University Hospital in May, 1945 because of severe headache, dizziness and loss of equilibrium. In June, 1945, a small midline cerebellar tumor was removed and the pathologic diagnosis was a highly differentiated medulloblastoma.

The tumor showed a definite pattern. The background was formed by a loose
arrangement of small, round, almost bare nuclei with a few short prolongations. Some of the nuclei were dark and round like lymphocytes, others larger, more irregular in outline, with only a few chromatin dots. Many nuclei were carrot-shaped. The amount of cytoplasm increased with the size of the nucleus and surrounded the nucleus without prolongations or ended in one, occasionally bifurcating, prolongation. This diffuse background was permeated by strands of cells in fish-school

arrangement. These cells were considerably larger, their nuclei multiform and bright though with a tendency to elongation, often on one end only. They were tighter packed than the background cells, sometimes in rows but not interconnecting with one another. No reticulin or collagen had been laid down (Fig. 6).

During August, 1945, roentgen therapy was administered to the head with a total of 5,000 r delivered to the midportion of the brain. Another course was given in March, 1946, with the same dose to the brain and additional treatment to the spinal canal. In July, 1946, the patient began to suffer from pain in the arms and legs which was unusually severe.

Following the 3rd admission in July, 1946, roentgenograms of the skeleton showed widespread destruction of bone (Fig. 7), and a biopsy of a lesion in the right humerus was interpreted as showing neuroblastoma. Histological examination disclosed that
the bone was completely replaced by connective tissue containing large fibroblasts. The tumor cells were arranged in rosette shape. Most of the type cells were monopolar, some bipolar. Their nuclei were multiform, polygonal, oblong, often pear-shaped or triangular. The cytoplasm was confined to the prolongation or surrounded the nucleus in a small rim. The cells resembled those commonly described as neuroblasts (Fig. 8).

Roentgen study of the urinary tract, abdomen, and chest showed no visible disease. The patient's bone pain was controlled by roentgen therapy. He left the hospital on Aug. 11, 1946, much improved but his condition deteriorated rapidly and he died a month later. No postmortem examination was obtained.

Comment. Here, again, a distinction between medulloblastoma and neuroblastoma could not be made on the sections from the original tumor, but the eventual outcome and later biopsy from the bone suggested the true nature of the disease.

DISCUSSION

If one turns to the classical original description of medulloblastoma from the pen of Harvey Cushing, it is found that while most of the tumors he described occurred in children under 12 years of age, there were a few in older individuals in the 2nd and 3rd decades of life. Not only was the natural
history and prognosis more unpredictable in these few, but the position of the cerebellar tumors also differed from that in the younger group of patients. Although reluctant to eliminate these cases from his new classification, Cushing recognized their dissimilarity and suggested the possibility that some of them might be part of the group of neuroblastomas. Considerable argument has ensued since about this problem, and the opposing view-

![Image of bone tumor (neuroblastoma)](https://example.com/image)

**Fig. 8. Case 3. Bone tumor (neuroblastoma). Hematoxylin and eosin, ×440.** Nest of tumor cells in completely destroyed bone whose tissue is replaced by connective tissue. Large fibroblasts are seen in this tissue. The tumor cells show rosette formation. The type cell is monopolar or bipolar. The multiform nuclei are surrounded by scant cytoplasm which may be confined to the prolongation. (Compare with Fig. 6.)

points of Penfield\(^{11}\) and Stevenson\(^{15}\) have been quoted to illustrate the uncertainty of the subject.

Our own experience indicates that there may be two types of medulloblastoma. The one is commonest in childhood and very malignant. Histologically, a diffuse arrangement of immature cells is prevalent in it. The other variant is more frequent in adults. It may be less malignant, with the patient surviving an unexpectedly long time.\(^{6,12,14}\) Whorl and strand formations with reticulin septa are slightly more prevalent histologically in this group.\(^{7}\) Widespread metastases to the rest of the body may develop, as illustrated by the 3 cases presented above. It is hoped, in a later essay, to present a basis for histologic differentiation between these two types of anaplastic cerebellar
tumors, so that with more accurate prognosis, a more selective therapy can be utilized.

If one considers the possibility that some of the cerebellar tumors in the older age group are neuroblastomas rather than medulloblastomas, the inconsistencies in the clinical course of these patients become explained. The natural history of abdominal neuroblastoma in patients over 12 years of age discloses the same two-fold potentiality. It is known that some of these tumors mature after radiation therapy, or even without any treatment, and become benign neurocytomas. Conversely, some of these patients present extensive metastases to the bones and viscera when they are first seen, and succumb rapidly. The protean manifestations of neuroblastoma in this age group are not widely appreciated and an understanding of them may help in evaluating some of the peculiarities of the cerebellar tumors under discussion.

Furthermore, it is possible that the cerebellar tumor for which a patient requires hospitalization is a metastasis from an occult primary tumor outside the central nervous system. Since it is conceivable that this situation may be present in any given case with the clinical and histological picture of medulloblastoma, it would seem essential that the pre-operative evaluation of the patient include a search for a primary tumor elsewhere than the brain, and particularly an intravenous urogram and roentgen survey of the skeleton and chest. If, as a result of these studies, the probability is that the cerebellar tumor is metastatic, a more conservative neurosurgical procedure may be indicated.

In addition to the difficulties of distinguishing between some cases of medulloblastoma and neuroblastoma, it should be pointed out that a similar confusion exists between neuroblastoma and Ewing’s tumor. Here, too, the clinical, radiological and pathological features of the two diseases may be so similar as to render differentiation between them extremely difficult.

Although thorough radiation therapy contributes a great deal to the management of the typical case of medulloblastoma, it becomes of even greater importance in the group of atypical cases considered in this paper. While roentgen therapy is of value in palliation of most medulloblastomas, it may arrest the disease permanently in older patients with primary cerebellar tumors derived from neuroblasts, by influencing maturation of the cells in the same manner as in the abdominal neuroblastomas. Once metastases to the skeleton and chest have occurred, however, radiation therapy may relieve symptoms temporarily, but will not effect a cure.

CONCLUSION

1. Cerebellar tumors that are associated with similar tumors beyond the central nervous system are rare, but do occur.
2. Although presenting the histological picture of medulloblastoma, it is possible that they are in reality neuroblastomas.
3. Patients with clinical evidence of a cerebellar tumor, particularly
those in the 2nd and 3rd decades of life, should be subjected to pre-operative roentgenograms of the chest, skeleton and urinary tracts, to determine the presence of metastases or an occult primary tumor outside the central nervous system.

4. The difficulty of distinguishing some cases of cerebellar medulloblastoma from neuroblastoma by clinical, radiological or pathological methods parallels the situation in regard to neuroblastoma and Ewing’s tumor.

5. Unexpectedly long survival of a patient with a cerebellar tumor resembling medulloblastoma, after thorough roentgen therapy, suggests that the tumor may have been a neuroblastoma which has undergone maturation and become arrested in growth.

REFERENCES


