Vincristine Sulphate in the Treatment of Skeletal Metastases from Cerebellar Medulloblastoma

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The most common site for metastatic deposits from a cerebellar medulloblastoma is the spinal subarachnoid space; distant spread of this malignant tumor usually takes place via the cerebrospinal fluid pathways. Extracranial metastases may occur after surgery, but metastases outside the central nervous system are extremely rare. There are a number of reports of confirmed extracranial metastases of medulloblastoma.1,2,4-7,13,14,16,39,20,22,23,27

Weiss24 formulated four criteria to aid in the establishment of a definite relationship between the primary growth and the secondary deposits:
1. The proven presence of a single histologically characteristic tumor of the central nervous system,
2. A clinical history which demonstrated that this tumor accounted for the initial symptoms,
3. A complete necropsy to exclude the presence of another primary site,
4. Identical morphology of primary lesion and metastases with due allowances for difference of anaplasia.

We are describing two additional cases of skeletal metastases that meet these criteria. The two patients have received cytotoxic drug therapy and are still living. Lassman et al.9-12 have noted that many of the malignant intracranial gliomas of childhood may improve and the patients live longer when treated with vincristine sulphate (Oncovin*). These two cases of medulloblastoma became radio-resistant, developed bony metastases, and then responded to treatment with this drug.

Case Reports

Case 1. This girl was 7 years old when an extensive solid cerebellar tumor was partially excised on October 9, 1963. The histology proved it to be a medulloblastoma. The operation was followed by high voltage x-ray therapy. After the treatment had been completed, incoordination of movement was still present on the right side.

Nine months later, in July, 1964, the patient was readmitted; 4 months previously she had developed infectious hepatitis with headaches and severe ataxia. Two days before admission her headaches became much worse and she started to vomit. On the day of admission her speech had become slurred and she had lost the use of her right hand.

Examination. Although papilledema was not present, the patient had nystagmus on looking to the right, marked ataxia in all four limbs, and weakness in the right arm. Ventriculography showed evidence of recurrence of the posterior fossa tumor. She was given a second course of high voltage therapy; she improved and was discharged after 7 weeks in hospital.

However, within 6 weeks of discharge, she had to be readmitted due to increasing pain in the back, shoulders, and hips, loss of weight, and general malaise. A ventriculoatrial shunt was performed to relieve the internal hydrocephalus; the plain x-ray film taken to check the position of the atrial catheter also revealed evidence of skeletal secondary deposits in the right scapula and humerus (Fig. 1). A skeletal survey was done, and this showed further evidence of osteolysis and osteosclerosis in the spine, pelvis, and femora (Fig. 2), resembling the metastases of neuroblastoma. A thorough clinical and x-ray search for such a tumor was made in the abdomen, pelvis, and thorax, but none was found. Intravenous pyelogram was normal.

Ten days after discovery of the metastases, a course of intravenous vincristine
sulphate was started (0.05 mg/kg per week). Within 48 hours of the first injection of the drug, the bone pains had almost disappeared and her condition rapidly improved. Five months later a repeat skeletal survey showed progressive sclerosis of the previous osteolytic deposits (Fig. 3).

Pathology. The cerebellar tumor, biopsied in September, 1963, showed a cellular tumor formed of primitive and generally undifferentiated cells with hyperchromatic nuclei, scanty cytoplasm, and a moderate number of mitotic figures. In a few areas spongioblastic differentiation was discernable but definite neuroblastic differentiation or rosette formation was not found. The histological appearance was compatible with the diagnosis of medulloblastoma (Fig. 4).

Case 2. This 10 year old boy was first seen when 5 years old when in February, 1961, total removal of a histologically verified medulloblastoma of the fourth ventricle was attempted. The patient received almost immediate high voltage therapy. He made a good recovery except for left optic atrophy which caused poor vision in that eye.

For approximately 4½ years after high voltage therapy he did well, but he was readmitted on July 20, 1966, suffering from headaches, vomiting, and the presence of a soft fluctuating swelling on the forehead. Over the three days prior to admission his walking had deteriorated, he became ataxic, and on examination there was bilateral optic atrophy, horizontal nystagmus to the left, and weakness of the left foot. Recurrence of the posterior fossa tumor was suspected but ventriculography showed an extensive space-occupying lesion in both frontal lobes extending as far back as the thalami. The

Fig. 1. Case 1. This chest film was taken to check the position of the atrial catheter of the Holter valve and incidentally showed new bone formation and sclerosis in the right scapula and metaphysis of the right humerus (October 10, 1966).

Fig. 2. Case 1. Lateral view of dorsal spine (upper) and anteroposterior view of pelvis (lower) showing patchy areas of osteolysis and osteosclerosis before treatment with vincristine sulphate (October 20, 1966).
very long and the patient was readmitted on November 15, 1966, with severe generalized pains in the back and lower limbs. Plain x-ray films showed multiple skeletal metastases in the spine, pelvis, and upper ends of both femora (Fig. 5). The renal shadows on a plain x-ray film of the abdomen were normal. A bone biopsy was performed and showed medulloblastoma.

On December 2, 1966, he was started on a course of vincristine sulphate, 0.05 mg/kg per week. A few days after the first injection his bone pains disappeared. His subsequent improvement was so marked that he was able to start part-time school in April, 1967, with full-time attendance by May, 1967.

The only clinical abnormality now present is poor vision on the right side due to optic atrophy. On March 10, 1967, another skeletal survey showed some re-ossification of the osteolytic areas and increase of the osteosclerosis (Fig. 6).

patient was given a further course of high voltage therapy; almost complete recovery followed.

Examination. Improvement did not last

Fig. 3. Case 1. Lateral view of dorsal spine (upper) and anteroposterior view of pelvis (lower) showing increase of the bone sclerosis after treatment with vincristine sulphate (October 10, 1967).

Fig. 4. Case 1. Photomicrograph of cerebellar biopsy, 1963. The tumor is largely formed of primitive and undifferentiated cells with hyperchromatic nuclei and scanty cytoplasm, with a moderate number of mitotic figures. In some areas, there are numerous spindle-shaped cells showing spongioblastic differentiation. The appearances are consistent with those of medulloblastoma, H. & E. ×120.
Fig. 5. Case 2. Anteroposterior views of the lumbar spine (left) and pelvis (right) showing multiple areas of osteolysis and bone sclerosis before treatment with vincristine sulphate (November 16, 1966).

Fig. 6. Case 2. Anteroposterior views of the lumbar spine (left) and pelvis (right) showing extension and increase in the density of the osteosclerotic areas after treatment with vincristine sulphate (March 10, 1967).
Pathology. Histological examination of the cerebellar tumor removed in February, 1961 (Fig. 7 left), showed a mass of densely packed, primitive, and undifferentiated cells with a small amount of cytoplasm and hyperchromatic nuclei. Mitotic figures were numerous. In many areas the cells had no definite arrangement but in some parts groups of cells lay between strands of collagen and reticulin where invasion of the meninges had occurred. There was no reticulin among the tumor cells except related to meningeal spread. Definite differentiation into either neuronal or spongioblastic cells could not be verified; rosettes were not seen. The appearance was compatible with that of an undifferentiated medulloblastoma.

Neoplastic cells similar to those found in the original cerebellar biopsy were present within the bone cavities of the November, 1966, biopsy below and internal to the iliac crest cartilage. They were consistent with the diagnosis of metastatic deposits from a medulloblastoma. As in the original cerebellar biopsy, there was no reticulin found among the cells forming the metastatic tumor clumps. (Fig. 7 right).

Discussion

None of the patients reported with skeletal metastases from medulloblastoma were living when diagnosed and therefore, it is of interest to describe two rare instances of bony metastasis diagnosed in life which also responded to therapy with vincristine sulphate.

We wish to emphasize the significance of bone pains in cases of medulloblastoma since they may be due to skeletal metastases. Pain of this type has often been interpreted as being due to nerve root compression associated with secondary deposits in the spinal

Fig. 7. Case 2. Left: Photomicrograph of cerebellar biopsy, 1961. The tumor is formed of primitive cells with hyperchromatic nuclei and scanty cytoplasm. Mitotic figures are present. There is no definite arrangement of the cells or evidence of differentiation. In this and similar areas reticulin was confined to the blood vessels but where leptomeningeal invasion had occurred reticulin was found intimately related to small groups of tumor cells. The appearances are consistent with those of an undifferentiated medulloblastoma. Right: Photomicrograph of iliac crest biopsy, 1966. Primitive and undifferentiated neoplastic cells similar to those of the cerebellar biopsy are seen within bone spaces and are consistent with metastatic deposits from a medulloblastoma. H. & E., ×120.
subarachnoid space. Characteristically, the pain of osseous metastases is diffuse, associated with tenderness in the affected region, and not affected by coughing, sneezing, or straining. As would be expected, there is deterioration in the general health of the patient, with loss of weight, appetite, and energy. As we have shown, all these changes in our cases have been very favorably modified by the cytotoxic drug therapy.

Certain features have been common to almost all the reported cases of extracranial metastases from medulloblastoma. These include: the following: a history of at least one operation at the primary site; radiotherapy; the detection of secondary lesions after diagnosis of the primary lesion; and a high incidence of the skeleton as the metastatic site most commonly involved. There have been no recorded cases of metastasis to the lungs although pulmonary metastases have been reported from other intracranial tumors. Many other viscera have been invaded including liver, kidney, suprarenals, ovaries, skin, and lymph nodes.

The radiological appearances of the skeletal metastases are non-specific. They are usually a mixture of bone destruction and sclerosis. Solitary osteolytic lesions have been reported in the spine, pelvic, and shoulder girdles, but the metaphyses of long bones are the commonest sites involved. Roentgenographically, they must be differentiated from neuroblastoma, leukemia, Hodgkin’s disease, and Wilms’ tumor. Similar appearances have been reported from other intracranial tumors, particularly meningeal sarcoma, retinoblastoma, and glioblastoma multiforme. These diagnostic possibilities were considered and eliminated in the two cases we have described. Lamellar periosteal new bone formation, occasionally encountered in neuroblastoma or Ewings’ tumor has never been found in metastases from medulloblastoma. Despite the presence of increased intracranial tension and separation of suture lines in many cases of cerebellar medulloblastoma, there has been no case reported in which secondary deposits were present along the suture lines, an appearance pathognomonic of neuroblastoma. Metastases in the orbit were found in only one case.

The relationship between medulloblastomas and neuroblastomas has been discussed in detail by Willis and Rubinstein. Neuroblastomas metastasizing to the central nervous system have rarely been reported. Russell and Rubinstein describe a case in which a large presacral neuroblastoma metastasized to bone, an iliac lymph node, olfactory tract, lateral orbital gyrus, cerebellar vermis, spinal cord, and cauda equina. Primary tumors of the central nervous system that can with certainty be diagnosed as neuroblastomas are of extreme rarity. Russell and Rubinstein reported two children aged 5 months and 4 years with tumors considered to be neuroblastomas in the cerebrum, one of which had metastasized in the cerebrospinal pathways; Gyepes and d’Angio reported one case of neuroblastoma in the posterior fossa of a boy aged 8 years and 9 months, with bone metastases. It is possible that medulloblastomas described as originating in sites other than the cerebellum might well be neuroblastomas. However, Willis doubted whether primary neuroblastomas ever occurred within the central nervous system, and he strongly deprecated any attempts to lump together neuroblastomas and medulloblastomas just because they are malignant, poorly differentiated, cellular, neural growths.

Neuroblastomas not infrequently show some degree of neuronal differentiation, as may medulloblastomas, but in addition astrocytic differentiation in medulloblastomas may also occur. Although Zülch does not entirely concur with this view, we consider that astrocytic differentiation, as found in our Case 1, can be an important histopathological feature distinguishing between these two tumors. Preliminary electronmicroscopic studies of medulloblastomas have largely substantiated this view by demonstrating astrocytic fibril formation from tumor cells. The cellular origins and histopathology of medulloblastomas present many problems, and it is hoped that further information will be gained by tissue culture and electronmicroscopic studies; these techniques are at present being used in our laboratories. Although electronmicroscopy was not carried out on the biopsies from these two cases, paraffin sections were studied with particular reference to astrocytic and neuronal differentiation by the following tech-
niques: hematoxylin and eosin, Masson's trichrome method, Mallory's phosphotungstic acid-hematoxylin, cresyl fast violet, Azure B, and Glees' silver method for axons. Stains for reticulin were also used.

A primary sarcoma of the cerebellum might be considered as an alternative diagnosis. Rubenstein and Northfield, in a critical discussion of the "circumscribed arachnoidal cerebellar sarcoma," concluded that this may be a variant type of medulloblastoma associated with a local infiltration of the leptomeninges and accordingly with a production of reticulin at that site. The term "desmoplastic" was suggested by these authors for this form of medulloblastoma, and it was thought that the term "circumscribed arachnoidal cerebellar sarcoma" should be abandoned. Dexter and Howell concurred with this view, as did Schenk.

The tumor cells of our Case 2 were seen to invade the leptomeninges where they were surrounded by reticulin fibrils which were wholly absent in the deeper parts of the tumor away from the meninges. Reticulin was not found among the metastatic tumor cells in the bone biopsy. Although the relationship of sarcomas and medulloblastomas is still being debated and although absence of reticulin may not necessarily exclude a sarcomatous type of tumor, there is no apparent morphological relationship between the two cases reported here and primary cerebr al sarcomas. The problems of the different types of cerebral sarcomas have been described and reviewed by Kernohan and Uihlein. The difficulties involved in the differential diagnosis that may arise on occasion between the medulloblastomas and ependymoblastoma have been discussed by Crue, et al., who also pointed out that in the future such distinctions may be of more than academic interest with the likely advent of future advances in chemotherapy.

There is little reason to doubt that our two cases are true cerebellar medulloblastomas; we base this opinion on the anatomical site of the primary growth, the histology, and the clinical course. Apart from our two cases, we have not seen any reference to cases in which clinical improvement has been noted following discovery of bone metastases.

**Summary**

Two cases of cerebellar medulloblastoma with skeletal metastases have been described; in both, the osseous lesions responded to treatment with the cytotoxic drug vincristine sulphate ("Oncovin"). This rare type of metastasis seldom occurs except after surgery.

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**References**

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