Primary neuroblastoma of the central nervous system with spontaneous extracranial metastases

Case report

ANTONIO S. HENRIQUEZ, M.D., DAVID M. ROBERTSON, M.D., AND W. JOHN S. MARSHALL, M.D., CH.B.
Departments of Pathology and Surgery, Queen's University, and Kingston General Hospital, Kingston, Ontario, Canada

A case of spontaneous extracranial metastases from a cerebral neuroblastoma in the absence of prior surgery is reported. The tumor was discovered incidently through biopsy of an enlarged retro-auricular lymph node in an apparently well 7-year-old boy who had not previously received surgery or radiotherapy. The patient died 15 months later. Autopsy excluded neuroblastoma of the adrenal glands or the sympathetic chains.

KEY WORDS
neuroblastoma, cerebral spontaneous extracranial metastatic neuro-ectodermal tumors

Neuroblastomas of the central nervous system are rare. Metastases outside the neuraxis from primary neuro-ectodermal tumors are very uncommon, particularly when metastatic dissemination occurs spontaneously in the absence of previous surgery. We report a case of a primary neuroblastoma of the central nervous system with spontaneous metastases outside the neuraxis.

Case Report

Two months prior to admission, a barber drew the father's attention to a mass behind the left ear of an apparently healthy 7-year-old boy. Six weeks later the mass became somewhat painful; during the week prior to admission the child complained of headaches and had vomited. There was no relevant family or past history except that an 8-year-old distant cousin had died of a brain tumor of unknown type.

Examination. On admission enlarged tender immobile lymph nodes were found in the left posterior auricular region and posterior triangle but no other lymphadenopathy; the liver and spleen were not enlarged. The head was unusually large, a feature said by the parents to have been present since infancy. On the following day, lymph node biopsy showed infiltration by neuroblastoma, and neurological and neurosurgical opinions were sought. At this time bilateral chronic papilledema was found but there were no focal neurological signs. Skull films showed enlargement of the skull with separation of sutures and demineralization of the sella turcica. X-ray studies of the chest and long bones showed no other lesions.

Operation. A ventriculogram revealed a
Metastatic primary neuroblastoma of CNS

large space-occupying mass in the posterior half of the left hemisphere and extending across the midline. A left posterior parietal craniotomy and biopsy of the mass were performed.

Postoperative Course. Recovery was uneventful, and the boy was discharged 5 days later. Cobalt therapy (3000 R) to the neck and head resulted in striking regression of the lymphadenopathy and the papilledema during the ensuing several weeks.

Three months after discharge from hospital the boy developed thoracic and lumbar back pain and sciatica. Spine films showed no bone lesions, but myelography demonstrated multiple subarachnoid filling defects. The cerebrospinal fluid contained malignant cells. Further cobalt therapy and cyclophosphohexamide produced alleviation of the symptoms. After a further 6 months, headache, vomiting, and severe back pain developed. By then the patient was blind with optic atrophy, bilateral facial paralysis, weakness and areflexia of the right limbs, drowsiness, and finally coma. He died 15 months after the initial investigation.

Biopsy Studies. The biopsy specimen from the retro-auricular lymph node was a rounded grayish-white firm piece of tissue measuring $2 \times 1.5 \times 1$ cm. Microscopically (Fig. 1) the lymph node was largely replaced by tumor, consisting mainly of small neuroblastic cells with spherical, relatively uniform nuclei containing finely distributed chromatin and with scanty cytoplasm having processes that mingled randomly between cells and, in areas, forming closely meshing "neuropil" of relatively low cellularity. These processes in part stained with the Bodian impregnation, indicating they were axons. Some large elements similar to mature ganglion cells were also seen. Mitoses were frequent. The tumor was diagnosed as a metastatic neuroblastoma.

![Fig. 1. Metastasis in the retro-auricular lymph node. Left: In the inferior half there is extensive involvement by fairly well-differentiated tumor tissue, while the marginal sinus (top left) and sinusoids appear filled with more immature cells. A relatively well-preserved zone of lymphatic tissue lies between these two areas. Hematoxylin-phloxin-saffron, ×100. Right: Higher power photomicrograph of the lymph node metastases, showing clusters of primitive neuroblasts and fibrillar bundles of their processes. Hematoxylin-phloxine-saffron, ×600.](image)

J. Neurosurg. / Volume 38 / February, 1973 227
Blocks of brain tissue were processed for both light and electron microscopy. By light microscopy the tumor had the same basic morphology as that in the cervical node. In occasional areas there were a few fairly well-differentiated ganglion cells with Nissl substance. Poorly defined rosettes were also present. A few cells with PTAH positive processes were also found, suggesting a glial component. The Fontana-Masson stains failed to reveal evidence of neurosecretory granules.

Tissue preservation for electron microscopy was poor. The small neuroblastic tumor cells consisted of oval cell bodies with long processes that were frequently arranged in parallel bundles. The nuclei of these cells were relatively large and contained prominent irregular nucleoli. The scanty perikarya contained a few mitochondria and well-defined rough endoplasmic reticulum. Occasionally fine filaments were also seen in the cytoplasm. The large ganglion cells presented abundant cytoplasm with prominent endoplasmic reticulum often consisting of long narrow parallel cisternae. Ribosomes were numerous both free and associated with membranes. In some instances, filaments and structures similar to neurotubules were also found. Electron-dense secretory granules described previously in a cerebral neuroblastoma by one of us and dense core vesicles as observed by Rubinstein and Herman were absent. No glial cells were found.

**Autopsy.** Extracranial tumor deposits were found only in the posterior and mid-supraclavicular cervical lymph nodes bilaterally (Fig. 2) and the spinal canal. There was diffuse moderate-to-severe hypoplasia of the vertebral and sternal bone marrow but no evidence of tumor involvement. Both lungs were congested and microscopically affected by interstitial pneumonia. The right and left adrenal glands weighed 5.3 and 6.8 gm respectively and presented no tumor masses or tissue necrosis. The sympathetic chain was dissected throughout its length in both sides; it was free of tumor, and in the cervical region was entirely separate from the lymph node metastases.

The brain weighed 2550 gm and was extremely swollen, with the left hemisphere somewhat larger than the right. There was an irregularly shaped hemorrhagic and partially necrotic area about 9 cm in diameter in the left parietal lobe which was firmly attached to the suprajacent dura mater. Coronal sections disclosed a large, apparently well-circumscribed and finely granular whitish-grey firm tumor mass with extensive areas of hemorrhage and necrosis and containing numerous calcified foci (Fig. 3). The mass lay in the white matter of the left cerebral hemisphere and extended from the posterior half of the frontal lobe to the parieto-occipital junction; superiorly it reached and destroyed the cortex of the parietal lobe; inferiorly the tumor extended to the level of the corpus callosum and produced considerable downward displacement, distortion and compression of the subjacent basal ganglia and lateral ventricles. Medially it extended through the corpus callosum to the right hemisphere infiltrating the white matter of the parietal and more caudal portions of the frontal lobe. The ventricular cavities were compressed and the left lateral ventricle con-
Metastatic primary neuroblastoma of CNS

Fig. 3. Posterior aspect of a coronal section of the brain showing extensive tumor involvement of the left frontoparietal region with extension to the right hemisphere producing severe compression and deformity of the ventricular cavities and the basal ganglia.

There was invasion of the walls of the fourth ventricle especially along its roof and around the caudal orifice of the Sylvian aqueduct. The meninges were heavily involved at all levels. The pineal gland was surrounded by abundant tumor tissue but its capsule and parenchyma were intact. The longitudinal sinus was filled with tumor.

There was no evidence of invasion of the epidural space or bones of the skull and vertebrae. The spinal cord was totally encased by tumor, which infiltrated the spinal nerve roots, but did not penetrate the dura (Fig. 4). Gross examination of the cerebellum, brain stem and spinal cord revealed no neoplastic tissue within those structures.

Microscopically, the cerebral tumor appeared for the most part composed of clumps of neuroblastic cells with scanty cytoplasm and round or oval relatively uniform nuclei and containing finely distributed chromatin, separated by a finely fibrillar matrix of neural processes (Fig. 5 upper left). This undifferentiated pattern was accompanied by foci of necrosis and calcification as well as marked vascular proliferation. Occasionally the cells tended to aggregate about small blood vessels, thus giving the appearance of pseudorosettes; there was also true rosette formation (Fig. 5 lower left), the centers of which were occupied by filamentous expansions of cytoplasm. The larger cells had fairly abundant eosinophilic cytoplasm containing eccentrically situated large, round or ovoid nuclei with small single or multiple nucleoli. The processes were stained by Bodian (Fig. 5 lower right) but no myelin sheaths could be demonstrated. Irregularly arranged Nissl granules were found only in the large neuroblasts with distinct neurites. Mitotic figures and giant multinucleated forms were rare. There was slight evidence of glial proliferation as demonstrated with PTAH stain within the tumor. It is uncertain whether the cells were true neoplastic elements or simply represented reactive astrocytes. In the meninges, and in the perivascular regions of the intracerebral parts of the tumor there was a prominent reticulin and fibrous stroma. The meningeal infiltrates, particularly around the spinal cord, were generally well-differentiated, containing numerous ganglion cells, abundant neuropil, and few neuroblastic cells.

Fig. 4. Transverse sections of the cervical, thoracic, and lumbar spinal cord and cauda equina showing massive tumor involvement of the meninges surrounding a normal cord.
Discussion

Almost 100 cases of neuroectodermal intracranial tumors with histological proof of extracranial metastases have been published, but in most of these the metastatic tumor first appeared after intracranial surgery. Glioblastomas and medulloblastomas make up the bulk of these reports, and other glial types are less commonly implicated.

Table 1 summarizes those cases we located in which there appear to have been spontaneous metastases of neuroectodermal tumors in the absence of surgical intervention. The cases reported by Rubinstein, Bogdanovich, and Anzill are well documented. Two of the three cases of spontaneous metastases from medulloblastomas lack histological proof of the nature of the metastases.
Metastatic primary neuroblastoma of CNS

TABLE 1

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Age</th>
<th>Sex</th>
<th>Location of Site of Diagnosis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gropp (1955)</td>
<td>48 M</td>
<td>lt. parietal</td>
<td>heart: subendocardial nodule, r. ventricle</td>
<td>glioblastoma multiforme, metastasis questionable</td>
</tr>
<tr>
<td>Zülch (1956)</td>
<td>8 M</td>
<td>cerebellum</td>
<td>spine, sacrum</td>
<td>medulloblastoma, no histologic proof</td>
</tr>
<tr>
<td>Zülch (1956)</td>
<td>12 F</td>
<td>cerebellum</td>
<td>skin of thigh</td>
<td>medulloblastoma, no histologic proof</td>
</tr>
<tr>
<td>Grieppentrog and Pauly (1957)</td>
<td>8 wks F</td>
<td>cerebellum</td>
<td>infraclavicular teratoma containing medulloblastoma</td>
<td>medulloblastoma, probably teratoma</td>
</tr>
<tr>
<td>Bogdanovich (1958)</td>
<td>61 F</td>
<td>rt. frontal</td>
<td>lungs</td>
<td>spongioblastoma multiforme</td>
</tr>
<tr>
<td>Rubinstein (1967)</td>
<td>37 M</td>
<td>lt. frontoparietal</td>
<td>vertebral marrow and lymph nodes</td>
<td>poorly differentiated astrocytoma, treated with radiotherapy</td>
</tr>
<tr>
<td>Anzil (1970)</td>
<td>54 F</td>
<td>lt. frontoparietotemporal</td>
<td>spine, liver</td>
<td>glioblastoma multiforme, treated with radiotherapy</td>
</tr>
</tbody>
</table>

tases, and in the third\(^3\) the diagnosis may be open to question. No reports of spontaneous metastases from an intracerebral neuroblastoma were found.

Since in our case there was extensive involvement of cranial and spinal nerves, the most probable route of spread would seem to be by way of the perineural spaces and their interconnections with the regional lymphatics. Alternatively, involvement of the superior longitudinal sinus may have played a role.

References


Address reprint requests to: David M. Robertson, M.D., F.R.C.P. (C), Professor of Pathology, Queen's University, Richardson Laboratory, Kingston, Ontario, Canada.