Primary intracranial esthesioneuroblastoma (olfactory neuroblastoma)

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A case of esthesioneuroblastoma (olfactory neuroblastoma) is reported. Its onset was that of an intracranial tumor, and it subsequently recurred four times. At autopsy, 4 years and 8 months after the onset of symptoms, metastases were found in the cerebrospinal pathways and visceral organs. The literature on this relatively rare neoplasm is reviewed with special reference to the unusual clinical presentation and biological behavior of the tumor.

Key Words - esthesioneuroblastoma - olfactory neuroblastoma - intracranial tumor - visceral metastases - cerebrospinal metastases

The esthesioneuroblastoma, or olfactory neuroblastoma, is an uncommon but well-known clinicopathological entity which generally makes itself known as a nasal tumor with nasal obstruction or epistaxis. In most cases, it arises superiorly and laterally in the nasal cavity near the ethmoid sinus, but other primary sites have also been reported, such as the nasopharynx and the maxillary sinus.

The tumor is usually slow-growing and considered in most instances to be markedly radiosensitive, although liable to local recurrence. Secondary spread into the cranial cavity following destruction of the cribriform and orbital plates has been known to occur in several instances. Only rarely has the onset been characterized by symptoms of an intracranial tumor. We are reporting in detail the clinical course and pathological findings of such a case.

Case Report

Clinical History. An 18-year-old man entered another hospital with a 6 months' history of headache, diplopia, nausea, and vomiting. A carotid angiogram showed the presence of a large right frontal mass (Fig. 1), and a lateral facial laminogram through the level of the right anterior clinoid process revealed destruction of the medial portion of the right orbital roof. At craniotomy, a massive tumor was found in the right anterior and middle fossae, surrounding the right optic nerve and extending into the right side of the sphenoidal sinus and through the cribriform plate into the right frontal sinus. A subtotal resection was carried out. A postoperative sinus x-ray series confirmed the presence of right frontal sinus involvement by tumor. The patient then received radiation therapy (3600 R in 33 days with a 280 kV orthovoltage machine) to the right frontal region and to the sella turcica.
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Fig. 1. Anteroposterior view of left carotid arteriogram, showing massive displacement of the anterior cerebral arteries and marked stretching of the right frontopolar arteries by a large right anterior fossa mass.

One year later he was admitted to the Palo Alto Veterans' Administration Hospital with a painless lump over the right eye. The right disc was atrophied; the left was pale but not atrophied. There was a right-sided ptosis, and the right eye did not elevate as well as the left. The visual fields were reduced to vision in the right lower temporal and left nasal quadrants. The cerebrospinal fluid (CSF) contained 320 white blood cells (217 neutrophils and 93 lymphocytes) per ml, 130 mg% of protein and 49 mg% of sugar. An electroencephalogram showed sharp and slow waves over the right frontal area. Skull films still showed an intracranial mass in the right anterior fossa, roof of the right orbit, and cribriform plate, with extension into the right frontal and maxillary sinuses. At operation, tumor was again found to fill the entire right anterior fossa and part of the right middle fossa. It seemed to be encapsulated on the cerebral side and could be bluntly dissected from the brain. Because it also involved the orbital and cribriform plates it had to be sectioned to remove it from the surface of the bone. Radiation therapy (6100 R in 73 days on a 4.8 MeV linear accelerator) was given postoperatively.

Except for a wound infection, the patient was relatively well for the next 20 months. He was then readmitted with tenderness in the middle of the forehead. This seemed to be due both to tumor recurrence and to the development of an incisional abscess. Carotid angiograms revealed recurrent extra-axial tumor filling the right anterior fossa. Tumor vascularity within the right orbit was noted (Fig. 2). Selective right external carotid arteriography showed extensive tumor vascularity in the right side of the face and supra-orbital regions, and in the right maxillary sinus (Fig. 3). At operation, the growth was found to involve the right orbit and the paranasal, frontal, and ethmoid sinuses; it had also infiltrated the dura. Exenteration of the frontal sinuses was carried out.

The patient re-entered the hospital 4 months later with painless swelling of the right eyelid and with increased nasal discharge. The swelling seemed to be due partly to infection and partly to tumor

Fig. 2. Right lateral common carotid arteriogram showing stretching of the distal right ophthalmic arterial branches (arrows), with prominent tumor vascularity in right orbit (arrowheads).
FIG. 3. Right lateral selective external carotid arteriogram showing widespread tumor blushes over the right side of the face (arrow), supraorbital region (arrowhead) and maxillary sinus (double thin arrows).

regrowth. Because of this he was treated with antibiotics and a course of Vincristine followed by Cytoxan. This resulted in a modest reduction in the size of the tumor. Because of rapid regrowth, a radical resection consisting of partial removal of the maxilla and complete exenteration of the right orbit was carried out. Exploration of the sphenoid sinus and left orbit revealed no tumor. A pedicle skin graft covered the defect over the right side of the face. The postoperative course was marred by wound infections, which were finally cleared with drainage and antibiotics. The patient remained well for a month after the infection cleared. He then developed epistaxis, and tumor was found in both nostrils. This mass rapidly grew under the skin graft, and he died 1 month later, 4 yrs 8 mos after the onset of symptoms.

Postmortem Examination. Intracranially, both anterior fossae (the left more than the right) were filled with a pink, mainly extracerebral tumor measuring 7 x 5.5 cm. The tumor had excavated the main portion of the orbital gyri of both frontal lobes (Fig. 4), extended superiorly to invade and partly replace both frontal poles, especially on the left, and spread in continuity along the dura of the falx to which it was firmly attached. Anteriorly and medially it had destroyed the gyri recti and extended up to the septum pellucidum. Separate discrete masses of firm subdural growth, 2.5 x 2 cm, were found on either side of the falx (Fig. 4).

Intracranial tumor was continuous with growth that replaced the sphenoid, ethmoid and frontal sinuses, the cribiform plate, and the right orbit. The mass extended under the skin flap over the right side of the face and raised it so as to form a 500 cc protuberance where the right orbit and accessory sinuses had been present. Both nostrils and the nasal septum were involved. The intranasal portion of the tumor was fungating and had grown to within 1 cm of the external nares.

Small irregular tumor nodules lined the ventricular ependyma of the frontal horns of both lateral ventricles (Fig. 4). Multiple small metastatic deposits, measuring less than 0.5 cm in diameter, were noted in the subarachnoid space over the convexity of the frontal lobes, the inferior surfaces of the

FIG. 4. Coronal section of postmortem specimen showing massive tumor excavating the medial orbital portions of frontal lobes. A discrete subdural metastasis compresses the cortex on the medial side of the left superior frontal gyrus. Confluent nodules of ventricular growth line the frontal horns.
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cerebellar hemispheres, and in the cerebello-medullary angles. One nodule, 1 cm in diameter, was found to occupy the lingula of the cerebellum; another, somewhat smaller, was noted in the midportion of the vermis; and a third in the left flocculus. Two larger nodules, measuring up to 1.5 cm in diameter, were present in the basal leptomeninges, excavating the basis pontis. Twelve tiny subpleural deposits, ranging from 0.1 to 0.5 cm in diameter, were found bilaterally in the lungs, six beneath the capsule of the liver, and several in the vertebral bone marrow, especially in the lower thoracic and lumbar areas. The remainder of the visceral organs, including the adrenals, sympathetic chains, and retroperitoneal space, were free of tumor.

**Histological Findings.** The microscopic structure of the tumor at autopsy was essentially similar to that of the original surgical biopsy and its subsequent three recurrences. The cells were arranged in dense sheets and convoluted cords, with conspicuous palisading around blood vessels in some fields (Fig. 5). In other areas, the cells appeared as loose or denser clusters, with an abundant network of reticulin fibers both around and among single cells and separating small tumor cell aggregates (Fig. 6). Under high power, the tumor cells were mostly carrot- or spindle-shaped, with a poorly defined cytoplasm and small irregular oval or round nuclei with a generally dense chromatin network. Occasionally, paler nuclei were found, which were finely stippled; nucleoli were also seen. A striking feature, noted at the time of the first and third recurrences and in the autopsy specimen but not in the original surgical biopsy, was a pattern of neuroblastic (Homer Wright) rosettes, in which the tumor cells were arranged around a pale delicate eosinophilic fibrillary matrix (Fig. 7).

Mitoses were frequent. The phosphotungstic acid hematoxylin (PTAH) stain failed to demonstrate neuroglial fibers, although these were well seen in the adjacent invaded cerebral parenchyma. A Bielschowsky silver impregnation for axons on frozen tissue performed on the material from the first recurrence disclosed strongly argyrophilic cell processes originating from the tumor cells, which often had a tapering shape (Fig. 8).

In the material from the autopsy speci-
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FIG. 7. Photomicrographs showing tumor cells arranged in neuroblastic (Homer Wright) rosettes. 
Left: H & E, X 120. Right: H & E, X 400.

Men, tumor had invaded the dura, leptomeninges, and cerebral parenchyma; the transition in the latter case was often abrupt. Tumor in the cribriform plate was histologically identical with the intracranial mass; it filled the marrow spaces and eroded the bone. Tumor found in the paranasal sinuses, nose, and right side of the face, as well as the metastases in the lingula of the cerebellum, the lungs, liver (Fig. 9), vertebral marrow and, microscopically, in the pontine and medullary subarachnoid spaces and in the fourth ventricle, all showed the same histological features as the primary neoplasm. Sections from the spinal cord and its roots were free of tumor.

Discussion

Esthesioneuroblastomas are generally thought to be derived from the neurosensory receptor cells of the olfactory mucosa. Several other sites have also been suggested as an origin. These include the olfactory placode, which is the primordium of the olfactory organ that ultimately contributes to the neuroepithelial elements of the olfactory mucosa; the
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Fig. 9. Photomicrograph of metastatic tumor in the liver. H & E, X 160.

ganglion of Loci, a collection of autonomic nerve cells and fibers which is situated at the anterior end of the olfactory placode, the sphenopalatine ganglion, which is located outside the nasal cavity; and the vomeronasal organ of Jacobson, a vestigial organ in the anteroinferior portion of the nasal septum. These alternative theories have on the whole been met with skepticism. In favor of an origin from adult cells of the olfactory mucosa is the fact that identical tumors have been produced experimentally in animals with nitrosoamine, nitrosopiperazine, and nitrosopiperidine compounds.

From the histological point of view, the features demonstrated in our present case fulfill the diagnostic criteria established for this neoplasm by previously published reports. Noteworthy in this regard were the striking arrangements in sheets, cords (Fig. 5), and neuroblastic rosettes (Fig. 7). The demonstration of an abundant stroma of reticulin fibers surrounding nests of tumor cells was also characteristic of neuroblastomas both of the central and the peripheral nervous system, as was the failure to demonstrate neuroglial fibers in the tumor with PTAH stain. Finally, the positive argyrophilia of the cell processes with Bielschowsky's silver impregnation in the second surgical biopsy specimen (Fig. 8) were also characteristic.

The unusual clinical presentation of this neuroblastic neoplasm necessitates a brief mention of two other alternatives, namely, a metastasis from a primary visceral neuroblastoma, or a primary intracerebral neuroblastoma with extracranial extension. The likelihood of metastasis from a primary sympathicoblastoma originating in the adrenergic or in the sympathetic chain was ruled out in this case by a detailed autopsy. As to a primary intracerebral neuroblastoma, a rare and somewhat controversial neoplasm, the histological features are certainly consistent with this possibility, but virtually all tumors of this derivation have been reported in patients under 10 years old. As far as we are aware, neither direct extension to extracranial structures nor the development of visceral metastases from such a neoplasm have been reported, although neither of these theoretical complications can be ruled out.

By contrast, the esthesioneuroblastoma is a tumor which is known to be found predominantly in adolescents and young adults, and the occurrence of metastases in distant sites is well documented. Moreover, retrospective examination of the original skull x-rays in our patient confirms that the tumor was unquestionably present in the frontal sinus from the early stages of the clinical history, even though it did not present with the symptoms of a nasal or paranasal sinus neoplasm. A review of the literature discloses five other instances of patients with olfactory neuroblastoma in whom the first symptoms were those of an intracranial tumor. The chief features of these cases are tabulated in Table 1. While this clinical presentation must therefore be regarded as exceptional, subsequent spread to the intracranial cavity in patients who originally showed signs of either a nasal or paranasal sinus lesion has been documented in at least 16 instances. Thus, the clinical history, radiological findings, and histological appearances of the present case are, taken collectively, entirely consistent with the known chief features that have been reported in olfactory neuroblastoma.
The neurosurgical implications of the intracranial extension of this tumor have been fully discussed by Robinson and Solitare. A radiological feature of interest in our case was the extreme tumor vascularity demonstrated by angiography (Figs. 2 and 3). This unusual finding was previously recorded by David, et al., who noted premature arteriovenous filling and a delayed venous phase, mimicking a cirsoid aneurysm; and by Jakumeit, who observed pathological vascularization and early venous filling in the orbit and maxillary sinus in his first case.

Distant metastasis to extracranial organs is a relatively uncommon occurrence. Of the 128 reasonably well-documented examples from the English, French, and German literature on esthesioneuroblastomas that were accessible to us for review, 23 were recorded as having behaved in this manner. In most instances, metastases were found in the cervical lymph nodes, followed, in order, by the lungs, the bones, and, in rarer examples, the face, the mediastinum, the liver, the abdominal lymph nodes, the spleen, the ovary, and the adrenals. The pattern of distribution of metastases in cases that subsequently spread to the intracranial cavity was essentially similar, except for one example in which extensive dissemination took place along the cerebrospinal pathways, as described in our case. In these two instances, therefore, the pattern of metastatic spread from the intracranial neoplasm presumably resulted from invasion of the leptomeningeal spaces or from breaching of the ventricular ependymal lining (Fig. 4), and followed the well-known mode of cerebrospinal dissemination within the central nervous system.

TABLE 1

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Presenting Symptoms</th>
<th>Age, Sex</th>
<th>Metastases</th>
<th>Duration from Onset of Symptoms</th>
<th>Alive (L) or Dead (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>David, et al., 1960, and Aubry, et al. (Case 1) 1963</td>
<td>headache, diplopia</td>
<td>36 M</td>
<td>cervical</td>
<td>7 mos</td>
<td>L, recurrence</td>
</tr>
<tr>
<td>Gerard-Marchant (Case 3) 1965</td>
<td>vomiting, meningism, bilateral Babinski</td>
<td>10 F</td>
<td>0</td>
<td>14 mos</td>
<td>D (no autopsy)</td>
</tr>
<tr>
<td>Gerard-Marchant (Case 5) 1965</td>
<td>headache, anosmia, vomiting</td>
<td>49 F</td>
<td>0</td>
<td>8 mos</td>
<td>D (autopsy; intracranial extracerebral tumor)</td>
</tr>
<tr>
<td>Dastur and Lalitha 1969</td>
<td>?</td>
<td>32 M</td>
<td>0</td>
<td>12 mos</td>
<td>L, recurrence</td>
</tr>
<tr>
<td>Jakumeit (Case 2) 1971</td>
<td>personality change, decreased libido and potency, headache, nausea</td>
<td>49 M</td>
<td>0</td>
<td>4 yrs</td>
<td>L, recurrence</td>
</tr>
<tr>
<td>Hamilton, et al. 1973</td>
<td>diplopia, vomiting, headache</td>
<td>18 M</td>
<td>frontal &amp; basal meninges, vermis, lateral &amp; 4th ventricles, lungs, liver, bone marrow</td>
<td>4 yrs</td>
<td>D (autopsy)</td>
</tr>
</tbody>
</table>

The prognosis of olfactory neuroblastomas is considerably more favorable than for neuroblastomas originating from the adrenal medulla or the sympathetic nervous system. Large series indicate that in uncomplicated cases 50% of patients with this tumor have a greater than 5-year survival after the initial diagnosis. Several patients are
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known to be alive and well after more than 20 years. From published reports it is clear that long survival may be obtained even in the presence of repeated local recurrence and of distant metastasis, as both, like the primary neoplasm, are quite susceptible to radiotherapy. The most hazardous, and often fatal complications are, as demonstrated in our case, the supervision of intracranial extension through destruction of the cribriform and orbital plates and, secondly, the development of distant metastases. In the series we reviewed the first of these complications occurred in 12.5% of instances, and the second in 18%. In several of the reported cases in which the tumor ultimately spread to the intracranial cavity, it is not clear at what stage in the course of the disease neurological symptoms first made their appearance, but it seems that in most instances this tended to occur at a relatively late phase of the illness, often terminally. However, some survived for periods ranging from 2 to 6 years after the onset of neurological symptoms.

The series, tabulated in Table 1, of patients with esthesioneuroblastomas who originally presented as harboring an intracranial tumor is obviously too small to provide further information on life expectancy after the onset of neurological symptoms. Also, the periods of follow-up on cases reported by others were usually too short to have any significant prognostic value. Our case, like one other, suggests that even when the neoplasm initially presents itself as an intracranial space-occupying lesion the duration of survival from the time of the first symptoms may be a relatively long one, amounting in this instance to 4 years and 8 months. The clinical history, on the other hand, leaves little doubt as to the relentless progressive character of this malignant neoplasm.

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References


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