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ESTHESIONEUROBLASTOMA

A report of seven cases

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The biologic behavior of esthesioneuroblastoma in seven patients, treated from 1978 to 1989, is reviewed. The patients were initially treated with surgical resection (2 cases), radiation alone (1 case) or a combination of radiation and surgery (4 cases). The radiation dose ranged from 30 to 62 Gy. Operations were performed via a transmaxillary approach (2 cases), lateral rhinotomy approach (3 cases) and craniofacial approach (1 case). Four of the seven patients experienced local recurrence, occurring after disease-free intervals as long as 6 years. The other three patients died of distant metastasis within one year after initial treatment. The effectiveness of radiation therapy varied, and in some patients a dose of 60 Gy was not enough to control microscopic disease. One patient developed bone marrow metastases which was fatal due to the ensuing pancytopenia. One patient developed a brain metastasis. Hyams' histopathologic staging of the tumor appeared to be related to prognosis.

Berger (1) first described 'L'esthesioneuroepitheliome olfactif' in 1924. To date, barely 200 cases have been recorded in the world literature. Esthesioneuroblastoma is a rare nasal neoplasm, arising from neuroepithelial elements in the olfactory membrane in the superior portion of the nasal cavity. It occurs in all ages, with a range of 3 to 79 years of age. The incidence shows a bimodal distribution with peaks in the second and sixth decades of life (3). The distribution between the sexes is roughly equal. As in all intranasal tumors, the symptoms are non-specific and include epistaxis, anosmia, and nasal obstruction. Due to this lack of symptoms, most patients are diagnosed late in the course of the disease. Esthesioneuroblastoma usually appears as a red or fleshy mass in the nasal vault. Symptoms of local invasion, such as proptosis or headache, are usually evident at diagnosis.

Light microscopic study reveals features similar to classical childhood neuroblastoma. In an upper nasal neoplasm, the presence of a fibrillary intercellular background in conjunction with Homer-Wright pseudorosettes is considered to be diagnostic of olfactory neuroblastoma. However, these hallmarks are not always evident, and confusion with other primary tumors of the nasal cavity and paranasal sinuses, such as lymphoma, undifferentiated carcinoma, and extramedullary plasmacytoma is possible. Therefore, immunohistochemistry and electron microscopy are necessary for the histologic diagnosis.

Although slowly growing, esthesioneuroblastomas are locally invasive and can metastasize to regional lymph nodes, lung, or bone. No treatment combination had been convincingly successful (2–4). However, the reports give limited information due to small numbers of cases, lack of long-term follow-up, and varied treatment methods. No single report contains information necessary to devise an optimal treatment for this rare tumor. Nor are randomized

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treatment trials practical for such tumors. Therefore, the accumulated experiences of various institutions may be useful for choice of treatment.

The present paper reviews the results of our treatment in 7 cases of esthesioneuroblastoma.

Material and Methods

Between 1978 and 1989, seven patients (2 females, 5 males; age 17–73 years) with esthesioneuroblastoma were treated at the Tokyo University Hospital. Staging was based on clinical presentation, physical findings, and roentgenographic findings as proposed by Kadish et al. (2). In this system stage A means disease confined to the nasal cavity, stage B disease confined to the naval cavity and paranasal sinuses, and stage C local or distant spread beyond these structures. Computed tomography (CT) was used to determine the tumor extent. One patient had stage A, 4 had stage B; and 2 stage C disease. Histologic specimens were reviwed by one of the authors (NM) and classified according to Hyams' histological staging system (5, 6) (Table).

Initial treatment was surgical resection (cases 1 and 2), radiation therapy (case 5) or a combination of irradiation and surgery (cases 3, 4, 6, and 7). The operations were performed via transmaxillary approach (cases 1 and 2), lateral rhinotomy approach (cases 3, 4, and 7), or craniofacial approach (case 6).

All radiotherapy was given with megavoltage (^{60}C or, more commonly, 10 MV photons). Irradiation alone was employed for case 5, while cases 3, 6, and 7 received postoperative irradiation and case 4 both pre- and postoperative irradiation. An anterior fixed field was used in cases 1 and 3. Anterior and lateral fields were used in cases 2 and 5. A complex, individualized treatment technique (for example, one anterior and two opposed lateral fields) was employed in cases 4, 6, and 7 after CT definitions of the tumor volume.

No patient was lost to follow-up, nor did any patient die during the follow-up period of a cause other than the tumor.

Case reports

Case 1. A 37-year-old woman had noted progressive right nasal obstruction and epistaxis for 6 months. She underwent transmaxillary resection of her tumor at another hospital in July 1976. The tumor involved the right nasal cavity and right maxillary sinus (stage B). Histopathology gave the erroneous diagnosis benign lymphocytic infiltration. Nineteen months later, recurrent tumor was found in both nasal cavities and the right maxillary sinus and a second transmaxillary partial resection of the tumor was performed. The histopathologic diagnosis was now reported as 'capillary hemangioma'. Postoperative irradiation was started through an anterior portal. However, irradiation was stopped at 25 Gy, when the residual tumor had disappeared. Twenty-two months later, recurrent tumor was noted in the ethmoid sinuses with intracranial invasion. A craniotomy was performed and the intracranial tumor was resected. The histopathologic diagnosis esthesioneuroblastoma was now finally established. The tumor was graded as Hyams' grade III. The patient then received 63 Gy to her ethmoid sinuses and intracranial tumor bed through an anterior portal. Eight months later, recurrent tumor was found again in the ethmoid sinuses with intracranial invasion. A third transmaxillary operation was performed to remove tumor from the ethmoid sinuses. After this operation, the patient underwent craniotomy and resection of the intracranial tumor. Now, the tumor was histopathologically evaluated as Hyams' grade IV. Bilateral nodal metastases developed in the neck 12 months later, and recurrent tumor was noted in the nasal cavity 36 months later. The patient refused further treatment and died almost 4.5 years after the last operation.

Case 2. A 50-year-old man had noted nasal obstruction and epistaxis. A nasal tumor resected via the transmaxillary approach at another hospital in March 1979 was found to be an esthesioneuroblastoma. The tumor involved the left nasal cavity, left maxillary sinus and left ethmoid sinuses (stage B). Forty months later, recurrent tumor was discovered in the left nasal cavity. The tumor was histopathologically graded as Hyams' grade II. The patient received 60 Gy to his left nose and maxillary sinus through anterior and left lateral portals. The nasal lesion resolved. Two years later, he developed recurrent tumor in the left nasal cavity.

Table

Hyams' histopathologic grading system

	Grade I	Grade II	Grade III	Grade IV
Cytoarchitecture	Lobular	Lobular	±Lobular	±Lobular
Mitotic rate	0	Low	Moderate	High
Nuclear pleomorphism	None	Slight	Moderate	Marked
Fibrillary matrix	Prominent	Present	Slight	None
Rosettes	±Pseudorosettes	±Pseudorosettes	True rosettes	None
Necrosis	None	None	Mild	Extensive

'±' means that this feature may be seen, but not necessarily seen. In the present series the presence of rosettes was disregarded for the grading.

The tumor was histopathologically designed as Hyams' grade II. A second transmaxillary resection of the recurrent tumor was performed. Six years after the second operation recurrent tumor was found in the left nasal cavity and ethmoid sinuses. This time, the tumor was histologically graded as Hyams III. Craniofacial resection was then performed. Five months later, nodal metastases developed in the left neck and radical neck dissection was performed. Again, the tumor was graded as Hyams III. The patient has then been free of disease for 1 year.

Case 3. A 52-year-old man had noted progressive nasal obstruction over a 10-year period. A lateral rhinotomy was performed in September 1980 and the tumor was found to involve the frontal sinus with intracranial invasion (stage C). It was histologically graded as Hyams II. Postoperative irradiation was delivered to the frontal sinus, nasal cavities and left maxillary sinus through an anterior portal. However, the radiation therapy was stopped at 36 Gy, when the tumor in the nasal cavity and maxillary sinus had disappeared. The patient then underwent craniotomy and resection for the intracranial tumor. This patient has remained free of disease for 10 years.

Case 4. A 35-year-old man had noted progressive nasal obstruction and epistaxis for several months. CT showed right-sided nasal tumor with invasion of the right ethmoid and maxillary sinuses and opacification of the right frontal sinus (stage B). Biopsy of the nasal tumor was performed in December 1989 and gave the erroneous histopathologic diagnosis undifferentiated carcinoma. Intraarterial infusion of 3 000 mg of 5-FU and 100 mg of cisplatinum via a superficial temporal artery and 26 Gy of preoperative irradiation through anterior and right lateral portals were given. After completion of radiotherapy, a lateral rhinotomy was done to remove residual tumor. The histopathologic diagnosis was now changed into esthesioneuroblastoma of Hyams' grade II. Neuron-specific-enolase (NSE) was positive. The patient was given 36 Gy of postoperative irradiation. Twelve months later, recurrent tumor was noted in the right nasal cavity and the right orbit. The tumor was now graded as Hyams III. The patient received 130 mg cisplatinum, 50 mg pirarubicin and 20 mg pepleomycin and 80 Gy of radiotherapy was now given and the lesions disappeared macroscopically. However, one month later, his right eye vision had deteriorated and CT revealed intracranial tumor. Craniofacial resection was tried but the tumor had invaded the carvernous sinus, optic nerve and internal carotid artery and could not be removed. The tumor was histopathologically graded as Hyams IV. Further 31 Gy of postoperative radiotherapy and chemotherapy were given but the patient died 5 months after the last surgery.

Case 5. A 17-year-old woman had experienced epistaxis for several months. Biopsy of a right-sided nasal mass in March 1983 disclosed esthesioneuroblastoma. CT showed a tumor on the right nasal cavity with invasion of the right ethmoid and maxillary sinuses and opacification of the right sphenoid sinus (stage B). The tumor was graded as Hyams III. The patient received 30 Gy to her nose and right maxillary sinus through anterior and right lateral portals. Surgery was planned to be performed 1 or 2 months after completion of the irradiation. However, one month after radiotherapy, she developed bilateral neck node metastases. Irradiation of the neck through lateral opposed fields was started. During this treatment the patient noted back pain and was found to have increased level of serum lactate dehydrogenase (LDH). Radiography revealed a compression fracture of T8. Bone marrow aspiration showed diffuse tumor cell infiltration (82% tumor cells). After two cycles of chemotherapy with cisplatinum and doxorubicin, the tumor cells in the marrow decreased to 3.4%. However, the patient refused a third course of chemotherapy and died of pneumonia after 2 months.

Case 6. A 39-year-old man had experienced epistaxis during several months. Biopsy from the right nasal cavity in September 1987 disclosed esthesioneuroblastoma. Craniofacial resection was performed. The tumor involved right nasal cavity, ethmoid sinuses, right periorbita and cribriform plate (stage C). It was graded as Hyams III. The patient then received 50 Gy of postoperative radiation to the cribriform region and nasal sinuses. Three months later, the patient developed a metastasis in the frontal lobe near the sagittal sinus, without evidence of local recurrence. The intracranial tumor was subtotally resected and now graded as Hyams III. Postoperative irradiation with 50 Gy was given. However, another brain metastasis was found within the radiation field. The patient died of persistent brain tumor although he received 26 Gy of additional irradiation.

Case 7. A 73-year-old man presented with nasal obstruction. Biopsy of the left nasal cavity in June 1989 disclosed esthesioneuroblastoma. At lateral rhinotomy the tumor was found to invade the left nasal cavity, left maxillary sinus, and periorbita of the left orbit (stage C). The tumor was graded as Hyams IV. The involved areas were excised. The patient received 60 Gy of postoperative irradiation to the ethmoid sinuses and nasal cavities. At the end of radiation therapy, the patient complained of lumbago. Bone scan revealed multiple bone metastases. Three months later, he developed a lymph node metastasis in the neck and subsequently died of pneumonia.

Discussion

In our experience, local disease was poorly controlled and four of our seven patients got local recurrence. The other three patients died of distant metastases within one year of the initial treatment and might also have had local relapse if they had survived long enough. Our experience indicates that surgery via extra-cranial approach often did not remove all tumor tissue. Surgical treatment via extracranial approach has also been reported to result in a high rate of recurrence (7, 8). Extracranial approach cannot resect tumor en bloc with adequate margins. Biller et al. advocated craniofacial resection without irradiation even for patients with Kadish's stage A and B disease. They achieved local control in four of five patients followed for more than 6 years (9).

En bloc tumor resection may also be necessary for salvage therapy. In our series extracranial tumor resection such as transmaxillary resection or craniotomy for excision of the brain tumor were usually performed as salvage therapy. However, these approaches failed to control recurrent tumors. In all our patients with recurrent disease the tumor invaded the base of the skull and in three of them also the brain (cases 1, 3, and 4). This is consistent with the experience of other authors (10). To treat such tumors, we believe that en bloc craniofacial resection is necessary.

Radiation therapy was used as a primary therapy (case 5), as part of combined therapy (cases 3, 4, 6, and 7) or as salvage therapy (cases 1, 2, 4, 5, and 6). In one case only (case 3) was local control of recurrent disease achieved. Irradiation failed to control microscopic disease, even at a dose of 60 Gy (cases 1, 4). This contradicts the reports of several other authors (11, 12). The discrepancy may be due

to the relatively short follow-up period in other studies. Local recurrence or metastases may occur many years after the primary treatment (8). We thus observed recurrence after disease-free periods as long as 6 years, and metastases in cervical nodes occurred at 6 and 12 years after initial or salvage treatment. Long-term follow-up is thus essential for proper assessment of the results of radiation therapy. Tumors which recurred after radiation therapy seem to be rather radioresistant (cases 1, 4, and 6) and could not be controlled by re-irradiation. On the other hand, the primary response of esthesioneuroblastoma to irradiation is often good, with rapid tumor shrinkage. However, the responsiveness to radiation is neither predictable, nor synonymous with radiocurability. Irradiation may be used preoperatively to facilitate tumor resection and postoperatively in cases with incomplete tumor excision.

One of our patients (case 4) had bone marrow metastases. In the literature, this has been reported in two patients only (13). One of those was a 78-year-old woman who also had metastases in spleen, lung, liver, and adrenals. The other one was a 5-year-old girl who also had metastasis in the spinal cord. These cases demonstrate that esthesioneuroblastoma may behave like neuroblastoma and metastasize to the bone marrow.

In case 6, metastatic disease was found in the frontal lobe, near the saggital sinus, without evidence of local recurrence after craniofacial resection followed by radiation therapy. Extracranial metastases are common in esthesioneuroblastoma and the preferred sites include cervical lymph nodes, lung, abdominal viscera, long bones, and pelvis (10). Several cases with intracranial spread of the tumor have been reported, but a direct growth in continuity with the paranasal tumor has as a rule been evident (14). Only one other report has been published describing a metastasis in the right frontal and parietal cortex without evidence of local recurrence 5 years after the initial treatment (15).

Three histologic variants of esthesioneuroblastoma have been described, i.e., neuroepithelioma with true rosettes, neuroblastoma with pseudorosettes and neurocytoma with neither true rosettes nor pseudorosettes. However, these histologic subtypes do not correlate with the biologic course of the tumor, according to previously published reports (16). Rosettes were seen only in case 6 of the present series. Therefore, we classified our cases according to a variant of the Hyams' histopathologic staging system (Table). In the original Hyams' system, 'no formation of rosettes' indicates grade IV. However, when the other parameters indicated grade II or III, we ignored the parameter 'no formation of rosettes'. We found that the histopathologic grade advanced with each recurrence in cases 1, 2, and 4. This phenomenon is also known to occur in glioma of the brain (17). All three patients who had grade IV disease died (cases 1, 4, and 7). Two of three patients who had grade III disease died (cases 5 and 6). The only patient (case 3) who experienced neither recurrences nor metastases for over 10 years had grade II disease. The initial histopathologic grade in patients who had distant metastases (cases 5, 6, and 7) was III or IV. These observations suggest that the histopathologic grading can have a prognostic value. More aggressive treatment, such as intensive chemotherapy, may be useful for patients with grade III or IV disease.

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