Sinonasal undifferentiated carcinoma: A ray of hope

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In 1987, we published a case series of a newly-described, highly malignant neoplasm, termed *sinonasal undifferentiated carcinoma*, in which treatment results were poor. In this updated study, we report the followup for the original three surviving patients and for six additional cases whose tumors were diagnosed between January 1987 and October 1991. These data suggest that the prognosis for patients with localized disease may be better than originally described. (OTOLARYNGOL HEAD NECK SURG 1993;108:697-700.)

In 1987, we described the clinical and pathologic findings of a case series of sinonasal undifferentiated carcinoma (SNUC), an aggressive neoplasm arising in the nasal cavity and paranasal sinuses.[1] Clinically, these tumors are characterized by extensive sinonasal tissue destruction, with frequent involvement of the orbit and anterior cranial fossa. We have been impressed by the paucity of significant symptoms in relation to the extent of disease at the time of diagnosis (Fig. 1). Histologically, SNUC is composed of pleomorphic cells with a high nuclear-cytoplasmic ratio that are arranged in nests, sheets, and trabeculae (Fig. 2). As mentioned in the original study, the differential diagnosis for neoplasms composed of small or medium-sized cells in the sinonasal region includes esthesioneuroblastoma,[2] lymphoma,[3] rhabdomyosarcoma, melanoma, and lymphoepithelioma. SNUC usually can be distinguished from these neoplasms on the basis of light microscopy, but occasionally immunohistochemistry or, less often, electron microscopy is required. Distinguishing SNUC fronm olfactory (esthesio)neuroblastoma is sometimes difficult.[4] SNUC has a greater number of mitotic figures, more nuclear pleomorphism, extensive necrosis, and vascular invasion. Esthesioneuroblastoma typically consists of small

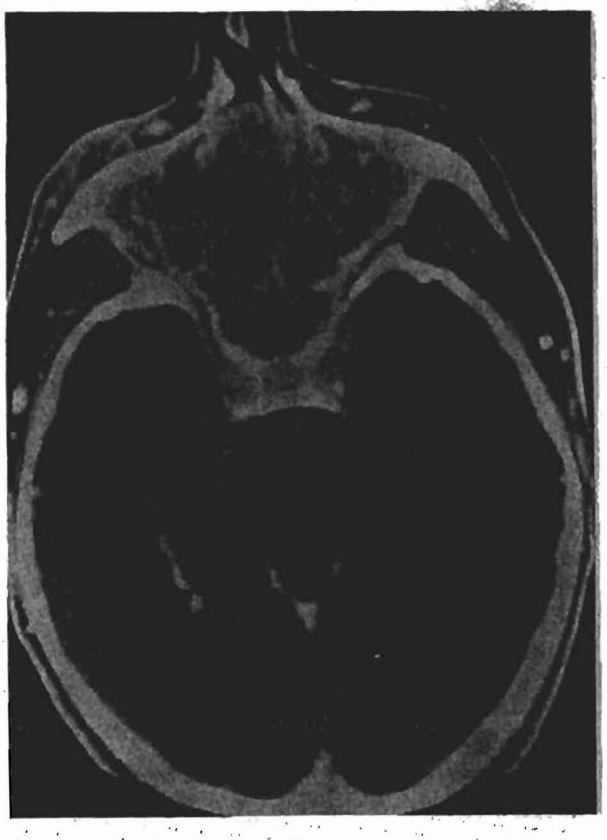

Fig. 1, A and B. Axial computerized tomographs reveal massive extent of disease in a patient reporting only nasal discharge and loss of smell.

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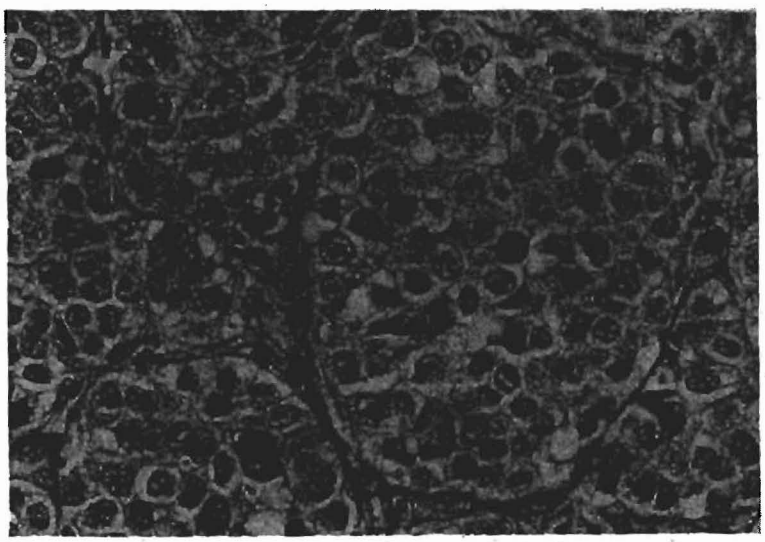

Fig. 2. The cells of SNUC show pleomorphic nuclei with prominent nucleoli. Numerous mitotic figures are present *(arrow)*.

uniform cells with neurofibrillary processes and, sometimes, Homer Wright rosettes.

The distinction between SNUC and esthesioneuroblastoma is clinically important, because the behavior and prognosis differ. Whereas esthesioneuroblastoma is slow-growing and has a relatively favorable prognosis, SNUC is a more rapidly progressing neoplasm associated with extremely poor survival rates. Eight of the eleven previously reported patients with SNUC died, with an average survival of only 12.4 months. To provide additional clinical and therapeutic information, we report the followup on the three surviving patients and six patients more recently diagnosed. In addition, we describe a more aggressive treatment protocol that has resulted in an improved prognosis for patients with limited disease.

METHODS AND MATERIAL

The records from the Departments of Otolaryngology–Head and Neck Surgery and Pathology, as well as those from the McIntire Tumor Registry at the University of Virginia, were reviewed for the period January 1987 through October 1991. Histologic slides of SNUC were identified. Further clinical data were obtained from hospital records and patient interviews.

RESULTS

Six patients with SNUC were treated between January 1987 and October 1991. There were four men and two women, with a mean age of 51.8 years (median age, 61 years). The presenting signs and symptoms for this group were similar to those of the original group, the most common being nasal congestion (6 patients), rhinorrhea (2 patients), and epistaxis (2 patients).

The location of the primary tumor, local extent, regional, and distant metastases at the time of diagnosis are shown in Table 1. The tumors involved the nasal cavity in all six patients, the maxillary sinus in five, the ethmoids and sphenoid in four, and the frontal sinus in one patient. Three of the six patients in this group (50%) had orbital involvement on initial evaluation, similar to the six of eleven (55%) in the orginal study. Only two of six patients (33%) had intracranial involvement at presentation, whereas seven of eleven (66%) had it in the original study. Two of six patients (33%) manifested distant metastases (bone, liver), compared to three of eleven (27%—two bone, one liver) in the original study.

The therapy used to treat our more recent group of patients has been standardized to include cyclophosphamide (Cytoxan, Bristol-Myers, Princeton, N.J.), doxorubicin (Adriamycin, Adria Laboratories, Columbus, Ohio), and vincristine chemotherapy (CAV); radiation therapy; and, in appropriate cases, surgical resection (Table 2).

A comparison of the initial with the present data regarding treatment and patient outcome reveals several interesting findings. In the original study there were three patients with no intracranial involvement or distant metastasis. These patients died

Table 1. Tumor extent at time of diagnosis

Patient no.	Nasal cavity	Maxil.	Ethmoid	Frontal	Sphen.	Local extension	Regional metastasis	Distant metastasis
1	Left	+	+	–	+	Medial orbit	–	–
2	Left	+	–	–	+	Through cribriform abutting dura of anterior cranial fossa	–	–
3	Right	–	+	–	+	Medial orbit	Right cervical node	Bone
3	Bilateral	+	+	–	–	Right medial orbit, anterior cranial fossa	–	–
5	Right	+	–	–	–	Infratemporal fossa, pterygoid region	–	Liver
6	Right	+	+	+	+	–	–	–

Table 2. Initial therapy and patient status

Patient no.	Initial therapy	Status
1	CAV Craniofacial resection 55 Gy postoperative radiation	Alive, NED at 52 months
2	CV 50 Gy preoperative radiation Craniofacial resection	Alive, NED at 43 months
3	CAV	DOD at 8 months
4	CAV V-P 16 65 Gy radiation	Alive with local disease at 33 months
5	CAV 50 Gy radiation	DOD at 7 months
6	CAV 50 Gy preoperative radiation Medial maxillectomy Total ethmoidectomy Sphenoidectomy	Alive, NED at 18 months

C, Cyclophosphamide (Cytoxan); *A*, doxorubicin (Adriamycin); *V*, vincristine; *NED*, no evidence of disease; *DOD*, dead of disease; *V-P 16*, etoposide.

however, have extensive local tumors (with involvement of the skull base or infratemporal fossa), not amenable to surgical resection. They were treated with radiation therapy alone or in combination with chemotherapy. In the more recent group, there were three patients without intracranial or distant disease. Each was treated with adjuvant radiation therapy, chemotherapy, and surgical resection. All three in the original study died of disease an average of 36 months after diagnosis, whereas the three in the current study have no evidence of disease an average of 53.6 months after diagnosis. Patients with intracranial spread or distant metastasis or both had poor outcomes in both studies.

Of the three survivors from the original study, two have subsequently died of local disease, 13 and 61 months after diagnosis. Only one patient is alive without disease 79 months after diagnosis (9% survival). Of the six more recent cases, four (67%) are alive, having survived an average of 40.5 months after diagnosis. Three of these four patients had no intracranial disease or distant spread, and are alive without evidence of disease an average of 53.6 months after diagnosis. The fourth survivor had intracranial involvement at diagnosis, and is currently alive with disease at 33 months. The two nonsurvivors died within 8 months of diagnosis, each having had distant metastases at the time of initial examination.

DISCUSSION

Because of the improvement in survival in our more recent patients, we have now adopted a standard regimen of preoperative cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine, and radiation therapy (50 Gy) before definitive surgical resection in those patients without distant metastasis and without extensive intracranial in-

volvement. Although the numbers are small, the data suggest that patients without intracranial or metastatic disease may have improved survival with this multimodal approach. A larger number of patients and long follow-up intervals are necessary to prove that these SNUC patients have an improved outcome using this therapeutic regimen.

CONCLUSION

In our original report, patients with SNUC had a grave outcome. With this additional information, it appears that patients without extensive brain involvement or distant metastasis at initial presentation have a better treatment outcome. We believe this is evidence supporting an aggressive therapeutic approach for patients with more localized disease.

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