Sinonasal Undifferentiated Carcinoma: A 10-Year Experience

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Purpose: Sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive malignancy of the paranasal sinuses and nasal cavity. Of the few reported series, most indicate a dismal prognosis. In this report, the clinical presentation, histopathologic criteria used for diagnosis, mode of treatment, and outcome are evaluated in seven patients with SNUC.
Materials and Methods: Seven patients with SNUC treated at the University of Cincinnati between 1983 and 1993 were analyzed retrospectively.
Results: Most of the patients presented with extensive local disease, and two patients also had cervical metastases. All except one were treated using a multimodality approach. Four of the seven patients died of disease (DOD), with a mean survival of only 11.5 months following treatment. Inability to eradicate local disease was responsible for treatment failure in all cases. Three patients have achieved short-term control of disease following combined therapy, but one is at high risk for recurrence.
Conclusion: SNUC was associated with an overall poor prognosis in our series despite aggressive treatment. Control of local disease was the central therapeutic consideration. Intensive multimodality therapy is recommended for all patients with SNUC.

Sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive malignancy of the paranasal sinuses and nasal cavity that was recognized only eight years ago as a separate clinicopathological entity.[1] Therefore, it is not surprising that only a small number of patients with SNUC have been described in the medical literature. Most reported series indicate a dismal prognosis despite the use of multimodality therapy.[1-5] In view of the paucity of information regarding this disease, we have reviewed our experience with seven patients with SNUC treated at the University of Cincinnati over a 10-year period. The clinical presentation, extent of disease, histopathological criteria used for diagnosis, mode of treatment, and outcome were evaluated in our series. Overall, we found that SNUC carries a poor prognosis despite multimodality therapy. Control of local disease is the major therapeutic challenge, with local recurrence being the most common reason for treatment failure.

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METHODS AND MATERIALS

The Tumor Registry of the University of Cincinnati Medical Center was reviewed for cases of sinonasal malignancy coded as undifferentiated or anaplastic carcinoma, olfactory (esthesio) neuroblastoma, and malignant lymphoma from 1970 through 1994. Seven cases that fulfilled the established histopathological and immunohistochemical criteria of sinonasal undifferentiated carcinoma[1] were identified. The hospital records of these seven patients were scrutinized for their age, sex, occupational and smoking history, physical and radiographic findings, site and extent of involvement of neoplasm, modes of therapy, and follow-up information.

Clinical Features

The baseline clinical data for the patients reviewed are shown in Table 1. All seven patients were male, and their ages varied from 22 to 83 years, with a mean age of 57.9 years. Only one patient had a history of smoking, and none reported exposure to noxious fumes, nickel, or wood dust

TABLE 1. Patient Profile and Extent of Disease

Patient	Age	Presenting Symptoms	Radiologic Extent of Disease	Regional or Distant Metastases	Pathological Extent of Disease
1	49	epistaxis, facial pain	NC, E, M, S, O	cervical metastases	NC, E, M, S, O
2	75	epistaxis, nasal congestion	NC, E, M, O	none	NC, E, M, O
3	55	occipital headache, nasal congestion	NC, E, O	none	NC, E, O, D
4	76	epistaxis, decreased vision & pain left eye	NC, E, O	none	NC, E, O
5	83	recurrent epistaxis	NC, E*	none	N/A
6	22	N/A	NC, E, M, S, O, SB	cervical metastases	N/A
7	45	anosmia, nasal congestion, decreased vision both eyes	NC, E, M, S, O, B*	none	N/A

*Bilateral disease.
Abbreviations: B, brain; D, dura; E, ethmoid sinus; M, maxillary sinus; N/A, not available; NC, nasal cavity; O, orbit; S, sphenoid sinus; SB, skull base.

particles. The most common presenting symptoms were epistaxis (four patients), nasal congestion (three patients), and vague facial pain (three patients). Two patients complained of decreased visual acuity, one of whom was noted to have bilateral papilledema on ophthalmoscopy. The second patient had normal visual acuity.

Extent of Disease

The extent of local disease was assessed in all patients by physical examination, computed tomography (CT) scan, and magnetic resonance imaging (MRI). Most patients had extensive disease on presentation. Five patients were diagnosed with unilateral SNUC, whereas two patients had bilateral sinus or nasal cavity involvement. Four patients showed tumor involvement of the unilateral maxillary sinus, ethmoid sinus, nasal cavity, and orbit. In three of these patients, the sphenoid sinus was additionally involved. Moreover, one of these patients showed extensive skull base erosion on CT scan, whereas another had obvious frontal lobe invasion on MRI (Fig 1). Overall, the sphenoid sinus and the orbit were involved with tumor in three and six patients, respectively. Disease was limited to the nasal cavity and ethmoid sinus in two patients. Both had unilateral tumor in the nasal cavity, ethmoid sinus, and orbit.

In two patients, cervical metastases were detected on physical examination. None of the patients had evidence of distant metastases based on the results of a chest x-ray and liver function tests.

Pathological staging of tumor extent was possible in the four patients who underwent surgical resection (Table 1). In three of the patients, the pathological and radiologic assessment of disease extent was comparable. However, in the remaining patient, surgical exploration suggested and histopathological analysis confirmed focal extension of tumor through the cribriform plate with involvement of a small area of dura, which was not definitively shown on preoperative radiologic imaging studies.

Histopathology

The histopathological appearance of the tumor was similar in each of the seven cases and consisted of medium-sized polygonal cells arranged mainly in nests and sheets (Fig 2). The round to oval-shaped nuclei showed moderate pleomorphism and typically contained a large nucleolus. The cytoplasm was pale and eosinophilic in appearance and small-to-moderate in amount. Mitotic activity in the tumor was brisk. Necrosis of both individual tumor cells and central areas of tumor islands were significant. There was extensive tumor involvement of vascular channels and two cases showed perineural involvement. Immunocytochemical staining for cytokeratin and epithelial membrane antigen was positive in all cases and neuron-

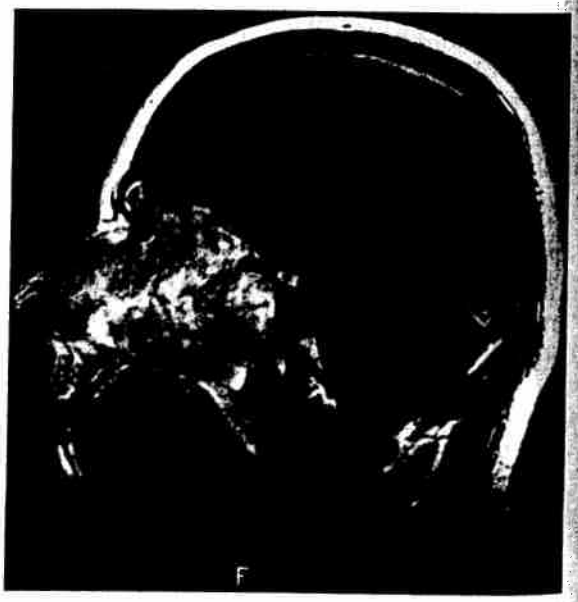

Fig 1. MRI scan showing invasion of the frontal lobe in a patient who displayed remarkably few symptoms.

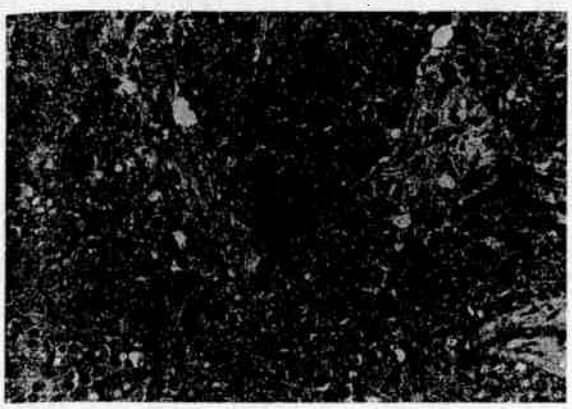

Fig 2. Typical area of sinonasal undifferentiated carcinoma showing nests and sheets of malignant cells with round to oval-shaped vesicular nuclei, prominent nucleoli, and many (black arrows) mitoses (hematoxylin-eosin stain, original magnification ×200).

specific enolase was positive in three. The S-100 protein and leukocyte common antigen were negative in all cases. Tests for desmin and anti–human melanoma antibody-45 (HMB-45) were performed in several cases, and in each instance, the results were negative.

Primary Treatment

The therapeutic regimen for each patient was determined by the extent of the disease, the era in which the patient was seen, the physician's philosophy, and the patient's wishes (Table 2). Four patients were treated with radical surgery followed by radiation therapy. The postoperative radiation dose ranged from 59.4 Gy to 64.8 Gy in 1.8 Gy fractions delivered to the affected region using a three-field technique. Although the two cases with clinically evident nodal metastases also received bilateral neck irradiation, only one of these was treated with neck dissection. One patient treated with surgery and postoperative radiotherapy also received two cycles of cisplatinum concurrent with the radiation.

Two patients received primary radiation therapy and chemotherapy. One patient had cervical metastases, and the other patient showed extensive intracranial extension of tumor on MRI scan. In the latter case, the patient (No. 7) received multi-agent chemotherapy comprised of cisplatin (25 mg/kg/m^2 × 3 days), etoposide (100 mg/kg/m^2 × 3 days), and fluorouracil (750 mg/kg/m^2 × 4 days) over four monthly cycles with the first two cycles being given during radiotherapy. In addition, one patient (No. 5) refused surgery and chemotherapy and was treated with radiation therapy only.

RESULTS

At the time of this report, four of the seven patients with SNUC have died of their disease (DOD), whereas three have no evidence of disease (NED) either clinically or radiographically (Table 2). The mean survival for the overall group was 12.3 months from the time of initial treatment, with a range of 6 to 19 months. The mean survival following therapy for DOD patients was 11.5 months. Failure to eradicate local disease was responsible for death in all four cases. Two of the DOD patients received combined radical surgery and postoperative radiotherapy, and one of these patients also received chemotherapy. The remaining two DOD patients received combined radiation and chemotherapy, and

TABLE 2. Initial Treatment and Outcome

	Initial Treatment				Follow-up	
Patient	Surgery	Radiation Therapy	Chemotherapy	Disease Status	Survival (months)	Treatment Failures
1	CFR, O, ND	61.4 Gy postoperative	2 cycles cisplatinum concurrent with radiation	DOD	8	local recurrence, distant metastases (skin, liver)
2	CFR, O	64.8 Gy postoperative		DOD	6	local recurrence, intracranial extension
3	CFR, O	59.4 Gy postoperative		NED	11	none
4	CFR, O	59.4 Gy postoperative		NED	15	none
5	None	60.0 Gy		DOD	19	local recurrence
6	None	70.0 Gy to primary and necks	multiple drug regimen used after radiation	DOD	13	residual local disease
7	None	54.0 Gy to primary	3 cycles of 5-FU, cisplatinum, and VP-16 concurrent with radiation	NED	14	none

Abbreviations: CFR, craniofacial resection; DOD, died of disease; 5-FU, fluorouracil; ND, neck dissection; NED, no evidence of disease; O, orbital exenteration; VP-16, etoposide.

radiation therapy alone, respectively. In addition, one patient developed distant metastases. Three DOD patients had extensive local disease at presentation, whereas one (No. 5) had focal disease, which represented a recurrence.

Regarding the three NED patients, the follow-up interval is 11, 14, and 15 months, respectively. Progress is monitored by regular clinical examinations and periodic MRI scans. Two of these patients had locally confined disease at the time of diagnosis, whereas the other patient had extensive disease involving the anterior cranial fossa, which responded dramatically to combined radiation therapy and chemotherapy.

DISCUSSION

SNUC is a distinctly uncommon aggressive malignancy that commonly produces few symptoms despite extensive disease (Table 1). Most patients with SNUC present with tumor involving multiple sinuses and the nasal cavity. In addition, invasion of the orbit or cranial vault is a frequent occurrence. Most reported series include few survivors despite aggressive treatment.[1-5]

Undifferentiated neoplasms composed of small- to medium-sized cells should be considered in the differential diagnosis of SNUC. Although a detailed histopathological differential diagnosis is beyond the scope of this paper, the quite distinctive microscopic features of SNUC usually serve to distinguish it from rhabdomyosarcoma, lymphoma, melanoma, lymphoepithelioma, small cell undifferentiated carcinoma, and olfactory neuroblastoma. If the histopathological findings are consistent with a diagnosis of rhabdomyosarcoma, lymphoma or melanoma, immunohistochemical staining with myogenous markers (desmin and muscle-specific actin), leukocyte common antigen, and melanoma markers (S-100 protein and HMB-45) will aid in differentiating these lesions. It is essential, however, not to confuse olfactory neuroblastoma with SNUC because the former has a much better prognosis. Olfactory neuroblastoma, unlike SNUC, is typically composed of small cells with sparse cytoplasm and a small round nucleus without a large nucleolus. Intercellular fibrillary material is present in the majority of cases of olfactory neuroblastoma, whereas rosettes are present less commonly. In addition, use of immunohistochemical markers facilitates the differentiation between these two lesions. Tests for S-100 protein will have positive results in scattered Schwann cells in tumor nests of olfactory neuroblastoma but negative results in SNUC. However, tests for epithelial membrane antigen will have positive results in most cases of SNUC but negative results in olfactory neuroblastoma.

Overall survival with SNUC is extremely poor in nearly all previously reported series regardless of the treatment regimen used.[1-5] Of the 11 patients with SNUC described by Levine et al[3] in their original report in 1987, long-term control of the disease has been achieved in only 9%. Recently, Deutsch et al[6] noted improved survival in three patients with locally advanced SNUC treated with chemotherapy (cyclophosphamide, doxorubicin, and vincristine) followed by radiation and then radical surgery. Involvement of multiple sinuses, extension into the orbit, and cribiform plate invasion (dura not involved) was considered locally confined disease. Of the remaining three patients in their series with more extensive disease, two have DOD (distant metastases) and one is alive with local disease despite multimodality therapy. As a result of their experience, the authors recommend initial chemotherapy and radiation for *all* patients with SNUC, regardless of disease extent. Surgical resection is then undertaken if the patient is without intracranial involvement of tumor or metastatic disease. In a similar mode, neoadjuvant chemotherapy followed by radiation, then surgery, has recently been reported to improve survival in stage III and IV squamous cell carcinoma of the paranasal sinuses.[7]

The results in our seven patients, admittedly treated with a variety of therapeutic regimens, unfortunately mirrored the earlier reports on SNUC in terms of the overall poor prognosis. However, three patients in our study clinically show NED with a mean follow-up interval of 13.3 months. Two of these patients had isolated local disease and received radical surgery and postoperative radiation. Short-term control of their disease has been achieved. The remaining NED patient had extensive intracranial involvement initially and is at high risk for recurrence.

The treatment philosophy at our institution for SNUC reflects the highly aggressive behavior of this malignancy, and therefore we believe that multimodality therapy is recommended for all patients with SNUC. Specifically, radical surgery (craniofacial resection, orbital exenteration) and postoperative radiation therapy are used in cases of isolated, locally advanced disease. Distant metastases, extensive skull base erosion, invasion through the dura, or patient refusal contraindicate radical surgery. Chemotherapy plus radiation therapy are preferable in these circumstances. In our series, the number of patients and length of follow-up do not permit us to draw any conclusions regarding the overall efficacy of our treatment approach in patients with SNUC. However, we concur with previous reports that this is a highly lethal malignancy requiring multimodality therapy, and we emphasize that control of local disease is the central issue. In our view, the role of neoadjuvant chemotherapy in patients with locally confined sinonasal malignancies is unclear at the present time. Further investigation is clearly warranted based on encouraging results in a small number of patients reported from other centers.[6-7] Ideally, a randomized prospective trial comparing chemotherapy, radiation, and surgery versus surgery and postoperative radiation should be conducted in patients with locally confined SNUC. Because of the small numbers encountered, this could best be achieved by a multi-institutional study over a number of years.

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