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Sinonasal Undifferentiated Carcinoma

Immunohistochemical Profile and Lack of EBV Association

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The role of Epstein-Barr virus (EBV) in the development of sinonasal undifferentiated carcinoma (SNUC) remains unresolved. Reports of EBV-positivity in SNUC may reflect inclusion of lymphoepithelioma-like carcinomas within this group. In addition, SNUC have been incompletely characterized immunohistochemically, and their undifferentiated appearance often requires such ancillary studies to aid in their distinction from other high-grade neoplasms. To address these two issues, 25 cases of SNUC diagnosed between the years 1983 and 1999 were selected from our files. EBER in situ hybridization (ISH) was performed on the paraffin-embedded tissue by using ^{3}H-labeled EBER-1 RNA probes. Neoplasms with sufficient tissue (22 of 25) were evaluated immunohistochemically for Ki-67, p53, chromogranin, synaptophysin, placental alkaline phosphatase (PLAP), CD99, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), neuron-specific enolase (NSE), and latent membrane protein-1 (LMP-1). The median patient age was 58 years (range, 20–81 years), with a male-to-female ratio of approximately 3:1. The most common tumor location was the nasal cavity (18 cases), followed by the ethmoid and maxillary sinuses. Median survival was 18 months. All 25 tumors were negative for EBER-1 by ISH. Ki-67 was negative in one case, 1+ in nine, 2+ in six, 3+ in five, and 4+ in one. P53 was negative in nine, 1+ in five, 2+ in two, 3+ in none, and 4+ in six. CD99 expression was strongly positive in 3 of 22 (14%) and completely negative in the remainder. Variably intense focal staining for EMA was present in 4 of 22 (18%). NSE faintly stained 4 of 22 (18%). Chromogranin, synaptophysin, PLAP, CEA, and LMP-1 were negative (0 of 22). Our results suggest that EBV does not play a role in the development of SNUC. Strict histologic criteria are necessary to avoid confusion with lymphoepithelioma-like carcinoma or other high-grade malignancies in this region. The finding of occasional CD99-positive cases adds SNUC to the growing list of CD99-positive neoplasms.

Key Words: Epstein-Barr virus—Lymphoepithelioma, undifferentiated carcinoma—Immunohistochemistry—Carcinoembryonic antigen—p53—EBER-1—CD[illegible] Epithelial membrane antigen—Neuron-specific eno[illegible] Chromogranin, synaptophysin—Placental alkaline phospha[illegible] LMP-1.

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Sinonasal neoplasms are a biologically heterogen[illegible] group, which often pose a considerable diagnostic [illegible] lenge. Included in this diverse group of neoplasm[illegible] sinonasal undifferentiated carcinoma (SNUC), a [illegible] formly high-grade tumor of the nose and paranas[illegible] nuses composed of small and medium-sized cells [illegible] quently accompanied by extensive necrosis and vas[illegible] permeation. Although typically composed of some[illegible] larger cells, SNUC may be confused with small [illegible] cell" tumors of the sinonasal region, including [illegible] noma, lymphoma, and olfactory neuroblastoma. [illegible] tumors are currently differentiated from SNUC [illegible] combination of microscopic features (e.g., H[illegible] Wright rosettes, neuropil), clinical features includi[illegible] of origin, and immunophenotype. The close proxi[illegible] the sinonasal region to the nasopharynx raises the [illegible] tional possibility of a destructive undifferentiated [illegible] pharyngeal carcinoma ("lymphoepithelioma") tha[illegible] extended into the paranasal sinuses or nasal cavi[illegible] such cases, distinction from SNUC has traditio[illegible] rested on histologic findings. The universal asso[illegible] of Epstein-Barr virus (EBV) with undifferentiated [illegible] pharyngeal carcinoma suggests that the presence [illegible] tent EBV infection may provide a marker for disti[illegible] ing nasopharyngeal carcinoma from SNUC. Ho[illegible] several publications have raised the possibility of [illegible] positivity in SNUC.[10,11,14,15]

The aim of this study was to examine a series of [illegible] gently defined SNUC for latent EBV infection by [illegible] in situ hybridization and to further characterize these [illegible] and aggressive tumors clinically and immunohistochem[illegible]

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MATERIALS AND METHODS

Tissue Acquisition and Histopathologic Diagnosis

Twenty-eight cases initially diagnosed as SNUC between the years 1983 and 1999 were collected from the general and consultation files (S.E.M.) of the University of Virginia Medical Center (26 cases) and the Mount Sinai Hospital (2 cases). Each tumor was reviewed by two of the authors (L.A.C., S.E.M.). Twenty-five met the morphologic criteria for SNUC as originally defined by Frierson et al.[6] and had additional tissue available for study. Some clinical, light microscopic, and immunohistochemical features of eight cases in this series have been previously reported.[2,6,7]

In Situ Hybridization Studies

The EBV RNA in situ hybridization studies were performed by using an antisense RNA probe to a portion of the EBER-1 RNA as previously described,[8,22] a region of the EBV genome known to be actively transcribed in latently infected cells. In vitro transcription to generate ^{3}H-labeled riboprobes was performed as previously described. Four-micron–thick sections were cut from paraffin blocks of zinc–formalin-fixed tissues and mounted on 3-aminopropyltriethoxysilane–coated slides. Sections were deparaffinized, dehydrated, predigested with proteinase K, and then hybridized overnight at a concentration of 0.2 μg/mL/Kb complexity of probe. An antisense actin probe also was applied to parallel sections of each case to control for RNA preservation. After stringent washing, detection via autoradiography with a light hematoxylin and eosin counterstain was performed. In each run, known EBV-positive and EBV-negative tissues were included as positive and negative controls. The in situ hybridization results were evaluated by using dark-field microscopy for grain distribution with bright field optics to confirm morphology.

Immunohistochemical Studies

Using the avidin-biotin immunoperoxidase technique described elsewhere,[17] 4-μm sections of each neoplasm were evaluated for Ki-67 (1:50, Immunotech, Miami, FL, USA), p53 (1:100, BioGenex, San Ramon, CA, USA), chromogranin (1:200, BioGenex), synaptophysin (1:10, Dako, Santa Barbara, CA, USA), placental alkaline phosphatase (PLAP) (1:200, BioGenex), CD99 (1:50, BioGenex), carcinoembryonic antigen (CEA) (1:100, BioGenex), epithelial membrane antigen (EMA, 1:800, Dako), neuron-specific enolase (NSE) (1:400, BioGenex), and latent membrane protein-1 (LMP-1) (1:50, Dako).[20] The primary antibody was omitted for the negative control. Sections from appropriate tissues containing the desired antigens served as positive controls. Antigenic reactions were semiquantitatively scored on the basis of percentage positive cells, as follows: 0% = 0, 1%–25% = 1+, 26%–50% = 2+, 51%–75% = 3+, and 76%–100% = 4+.

RESULTS

Clinical Features

The clinical data are summarized in Table 1. The median patient age was 58 years (range, 20–81 years), with a male-to-female ratio of approximately 3:1. The most common tumor location was the nasal cavity (18 cases), with five of the tumors extending into the ethmoid sinus and one involving the maxillary sinus. Five cases appeared clinically to have arisen in the maxillary sinus. Orbital destruction was found at the time of initial diagnosis in two cases. One tumor exclusively occupied the ethmoid sinus. Despite large, often destructive tumors, most patients presented with either isolated diplopia or minor complaints of sinus congestion. Work histories were available for 12 patients. Employment was diverse and, with the exception of one individual employed in the chrome plating industry and described in our initial study,[6] no obvious employment-related exposures could be identified. Seven of the 12 patients with available histories were known smokers (58%).

No standardized treatment approach has been developed for SNUC. Patients invariably received radiation therapy, to both their tumors and lymph node drainage areas, either as the major modality or in association with surgery. Many received extensive surgical resections, including craniofacial resections in an attempt to completely remove local disease. Lymph node dissections were performed occasionally, primarily in patients with clinically obvious metastases. Variable chemotherapeutic regimens were performed, including treatment of two patients with high-dose chemotherapy and autologous bone marrow transplant.

Follow-up information was available for 16 cases. Local recurrence was found in 9 (56%), and 12 (75%) developed metastatic disease, which in most cases was extensive. Eight patients (50%) had confirmed cervical node involvement, and in one patient, cervical adenopathy was the presenting symptom. Two patients received high-dose chemotherapy and bone marrow transplants and had extended survival, but both eventually died of recurrent disease 9 years after the initial diagnosis. A total of 13 patients died as a result of disease (81%), with a median survival of 18 months. Follow-up durations for the remaining three patients were 7 months, 9 months, and 10 years; the first two of these patients were undergoing treatment for local recurrences at the time of this report. The last is the only long-term disease-free survivor.

TABLE 1. *Clinical features of 25 patients with sinonasal undifferentiated carcinoma*

Case	Age	Sex	Initial sites of involvement	Recurrence	Metastases	Outcome
1	61	M	L nasal cavity, R ethmoid sinus	Yes	Liver Cervical nodes	DOD at [illegible]
2	58	M	L ethmoid sinus	Yes	Widely disseminated	DOD at [illegible]
3	31	M	R nasal cavity, R ethmoid Intracranial extension	No	R cervical nodes	DOD at [illegible]
4	81	M	R maxillary sinus	No	Widely disseminated	DOD at [illegible]
5	67	M	L neck	No	Widely disseminated	DOD at [illegible]
6	39	F	Nasal cavity, maxillary sinus, orbit	Yes	Widely disseminated (bone marrow, multiple vertebrae, ribs, cervical nodes)	DOD at [illegible]
7	57	M	Nasal cavity	At 5 yrs	Cervical nodes	DOD at [illegible]
8	70	M	Nasal cavity	At 3 yrs	No	DOD at [illegible]
9	35	M	Nasal cavity	No	Bone marrow	DOD at [illegible]
10	67	M	L nasal cavity	No	L cervical nodes	NED at [illegible]
11	20	F	Nasal cavity, R maxillary sinus	At 11 mos	Bone marrow R cervical nodes	DOD at [illegible]
12	48	F	Nasal cavity	At 8 yrs	No	DOD at [illegible]
13	59	M	Nasal cavity, orbit, ethmoid, maxillary sinus Intracranial extension	No	Cervical nodes	DOD at [illegible]
14	71	F	R maxilla, R ethmoid	At 3 yrs	R cervical nodes	DOD at [illegible]
15	53	F	Nasal cavity	N/A	N/A	N/A
16	77	M	Nasal cavity	N/A	N/A	DOD
17	41	F	Left maxillary sinus	N/A	N/A	N/A
18	31	M	Left nasal cavity	N/A	N/A	N/A
19	61	M	Orbit/maxillary sinus	N/A	N/A	N/A
20	66	M	R nasal cavity	N/A	N/A	N/A
21	69	M	R nasal cavity	N/A	N/A	NED at [illegible]
22	40	M	R nasal cavity	N/A	N/A	N/A
23	60	M	Nasal cavity, ethmoid sinus	N/A	N/A	N/A
24	25	M	Maxilla	No	No	NED at [illegible]
25	45	M	Nasal cavity	Yes	No	AWD at [illegible]

* Bone marrow transplant recipients.
DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease; N/A, information not available.

Light Microscopic Observations

Sinonasal undifferentiated carcinoma were composed of small to medium-sized cells with large, ovoid nuclei, generally high nuclear-to-cytoplasmic ratios, and correspondingly small amounts of eosinophilic cytoplasm (Table 2). In thin sections, distinct cell borders could be appreciated. Most SNUC showed extensive coagulative necrosis, often with areas of central "comedonecrosis" in larger cell nests (Fig. 1). Nuclear chromatin was usually homogeneous and coarse, although a minority of cases manifested more vesicular chromatin reminiscent of lymphoepithelioma. Although a few SNUC lacked conspicuous nucleoli, a single prominent nucleolus was typically present. In spite of the overall "high-grade" appearance of the tumors, nuclei were typically rather uniform

TABLE 2. *Discriminating histologic features of sinonasal undifferentiated carcinoma (SNUC) versus lymphoepithelioma (LE)*

	SNUC	LE
Location	Sinonasal tract	Nasopharynx
Architecture	Festoons, nests, often with a delicate fibrous background	Single cells or syncytial aggregates
Cellular features	Distinct cellular borders	Indistinct cellular borders
Chromatin pattern	Homogeneous, frequently coarse	Vesicular
Nucleoli	Prominent, single	Not prominent, often inapparent
Mitotic rate	Brisk, many apoptotic cells	Variable
Necrosis	Usually present and extensive, often geographic pattern	Infrequent
Vascular permeation	Common	Not common
Brisk lymphoplasmacytic inflammation	Not a feature	Always present

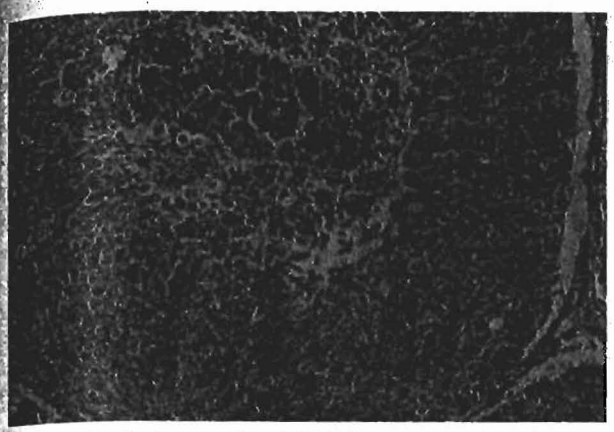

FIG. 1. Typical example of SNUC showing a large tumor nest demarcated by a thin band of stroma. The malignant cells rim the periphery of the nest before undergoing necrosis in a "comedo" pattern.

within a given example (Fig. 2). Malignant cells were arranged in sheets, nests, wide trabeculae, or ribbons, and many showed a vaguely organoid growth pattern. Mitotic activity was invariably brisk, often with many more than 10 mitotic figures per 10 high-power fields. Vascular invasion was usually extensive, with tumor cells completely filling and distending vascular lumina. Severe dysplasia or carcinoma in situ was documented in the overlying mucosa in two cases. Scattered acute and chronic inflammatory cells were present in the stroma, often in areas of necrosis, but a dense lymphoid or lymphoplasmacytic infiltrate was invariably absent. By definition, tumors with glandular or squamous differentiation, syncytial growth with numerous interspersed lymphocytes, intercellular fibrils, or Homer Wright rosettes were excluded. Flexner-Wintersteiner rosettes were not seen in any cases.

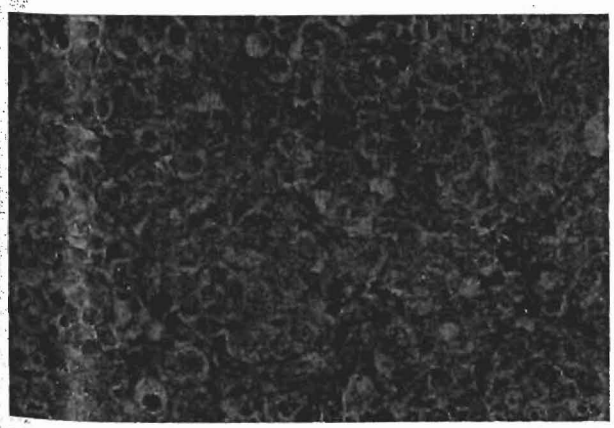

FIG. 2. Another example of SNUC, showing the relative uniformity of high-grade nuclei. This feature is distinct from that of nasopharyngeal carcinoma, which shows more intratumoral nuclear variability.

FIG. 3. Strong CD99 immunostaining of SNUC. This pattern differs from that of Ewing's sarcoma and primitive neuroectodermal tumor, which shows a distinct membranous accentuation. Unlike this example, most examples of SNUC were completely negative for CD99.

In Situ Hybridization and Immunohistochemistry

Twenty-five SNUC were studied for the presence of EBV, and 22 cases had sufficient material for additional immunohistochemical stains. All cases were suitable for EBER-1 interpretation by in situ hybridization as demonstrated by some preservation of actin mRNA signal. There was no demonstrable EBER-1 expression over background levels in any case. All tumors studied were completely negative for LMP-1 (0 of 22). All tumors also were immunophenotypically negative for chromogranin, synaptophysin, CEA, and PLAP. Cases 2, 4, and 6 (3 of 22, 14%) strongly expressed CD99 (MIC-2) (Fig. 3), although they lacked the characteristic membranous pattern seen in Ewing's sarcoma and peripheral primitive neuroectodermal tumors. The remaining examples of SNUC were completely negative for CD99. Four tumors showed weak staining for NSE (16%). Immunostaining for Ki-67 was negative in one case, 1+ in nine, 2+ in six, 3+ in five, and 4+ in one. Intensity of Ki-67 staining varied among the nuclei in a given tumor but was diffuse throughout the tumor within a given case (Fig. 4). P53 was negative in nine, 1+ in five, 2+ in two, 3+ in none, and 4+ in six (Fig. 5). The level of p53 protein in nonneoplastic cells was not detectable. Variably intense focal staining for EMA was present in 4 of 22 (18%).

DISCUSSION

Epidemiologic and molecular data support a causative role for EBV in the development of undifferentiated nasopharyngeal carcinoma ("lymphoepithelioma"), endemic Burkitt's lymphoma, infectious mononucleosis, posttransplantation lymphoproliferative disorder, sinonasal T-cell lymphoma, and Hodgkin's lymphoma.[9] Given

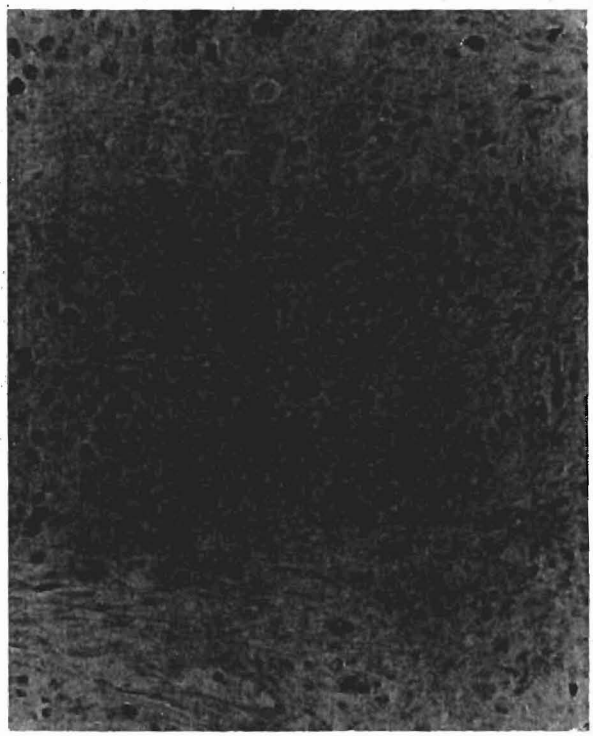

FIG. 4. Ki-67 immunohistochemistry of sinonasal undifferentiated carcinoma showing expression in the majority of malignant cells, but with heterogeneous intensity.

the variety of tumors in the sinonasal and nasopharyngeal region associated with EBV infection, we questioned whether SNUC also might be related to EBV. The ability to detect and localize EBV in tissue sections by in situ hybridization and more recently by immunohistochemistry[21] has been extremely useful in addressing questions concerning a potential link between EBV and malignancy.

Hwang and Tsai[11] studied nasopharyngeal and sinonasal tumors for EBV RNA by in situ hybridization. Their study did not support a role for EBV in the development of sinonasal tumors, but, unlike the current series, they examined a variety of tumor types arising in the sinonasal region. Because the three remaining studies evaluating the association of EBV with carcinomas of the sinonasal region have shown controversial results, we collected the largest series of SNUC to clarify this issue. The previously largest study[15] evaluated 22 SNUC and subdivided the tumors into 11 "Western" and 11 "Asian" cases. A significant subset of Asian SNUC (7 of 11) was associated with EBV, whereas all Western cases were negative for EBV. Importantly, the Asian SNUC that showed EBV positivity were limited to those showing features similar to anaplastic large cell lymphoma, or mimicking undifferentiated nasopharyngeal carcinoma. The latter were designated as SNUC with lymphoepithelioma-like features. Sinonasal undifferentiated carcinoma of "Western" subtype showed typical morphology and were negative for EBV. Leung [illegible] studied a variety of carcinomas arising in the sinonasal region that included one "undifferentiated" carcinoma showing EBER-1 positivity. This case involved the nasal cavity, orbit, and nasopharynx with cervical nodal metastases, and appeared histologically similar to cases interpreted as SNUC with lymphoepithelioma-like features in the study of Lopategui et al.[15] In a study by [illegible] et al.,[10] 13 cases of SNUC were evaluated, and EBV was found in five examples. However, illustrations of the SNUC were not available, and it was not possible to correlate the positive cases with their histologic features.

The previous finding of EBV limited to those cases of so-called SNUC with unconventional morphology raises the strong possibility that this morphologic subset is distinct from true SNUC. In particular, cases designated in prior studies as "SNUC with lymphoepithelioma-like features" may, in fact, be "lymphoepithelioma-like carcinomas" arising in or secondarily involving the sinonasal region. "Lymphoepithelioma-like" carcinomas that are histologically identical to so-called nasopharyngeal lymphoepithelioma may occur in a wide variety of organs. Epstein-Barr virus has been documented in LEC arising in the stomach, salivary gland, lung, and thymus.

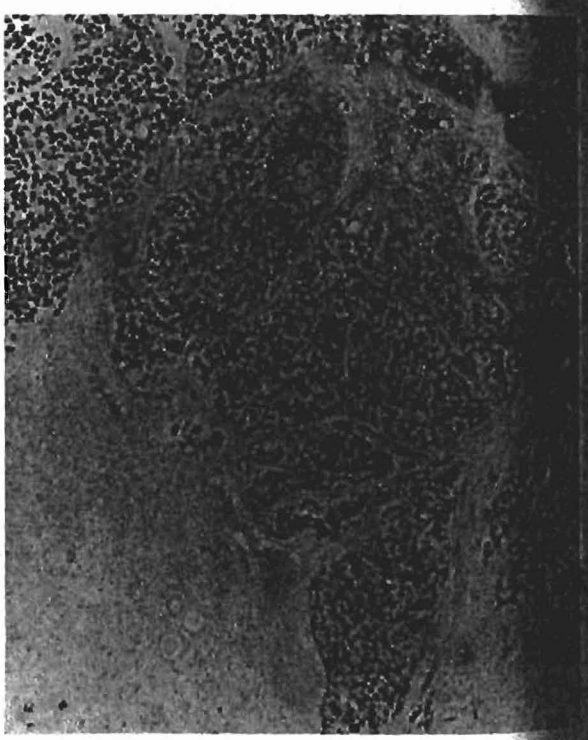

FIG. 5. p53 immunohistochemistry of sinonasal undifferentiated carcinoma illustrates strong overexpression in virtually all of the malignant cells. This patient survived 2 years after resection and bone marrow transplantation. Two other patients with strong p53 staining showed long survival. Most other tumors showed lack of p53 staining or limited staining in a few cells.

Epstein-Barr virus positivity in sinonasal tumors with lymphoepithelioma-like features among Asian patients ("Asian" SNUC) suggests an ethnic proclivity to develop tumors with this morphologic pattern. The association between EBV and LEC in the salivary gland and lung also appears particularly strong in Asians, whereas the association of EBV with gastric and thymic LEC appears independent of racial background.[11]

We believe that there has been confusion in the literature regarding the definition of true SNUC, and inclusion of some LEC within this group, particularly in Asian patients, accounts for purported EBV-positive "SNUC." Unlike SNUC, LEC is composed of cells with markedly vesicular nuclei, inconspicuous or absent nucleoli, indistinct cell borders creating a cytoplasmic "syncytium," and a prominent lymphoplasmacytic infiltrate (Fig. 6, Table 2). The often prominent necrosis of SNUC, including comedo-like necrosis, and prominent vascular invasion, are not typical features of LEC.[6] When one excludes cases with features of LEC, the previous data do not support a relationship of SNUC and EBV. This is confirmed by our own series of 25 rigorously defined SNUC, all of which were negative for EBV EBER-1 RNA.

It is well recognized that a variety of phenotypic cell types may be present within a given tumor. Included within the category of SNUC are cases with typical morphology that show neuron-specific enolase (NSE) positivity. This immunophenotypic expression raises the possibility that these tumors represent so-called "large cell neuroendocrine carcinoma." It also could be argued that the trabecula (Fig. 7) and organoid growth patterns seen in some SNUC are light microscopic evidence in support of neuroendocrine differentiation. However, our experience with far more common large cell carcinomas of the lung has indicated that these features are at best weak indicators of neuroendocrine differentiation at the immunohistochemical level and are often overtly misleading. Furthermore, they are absent from many SNUC.

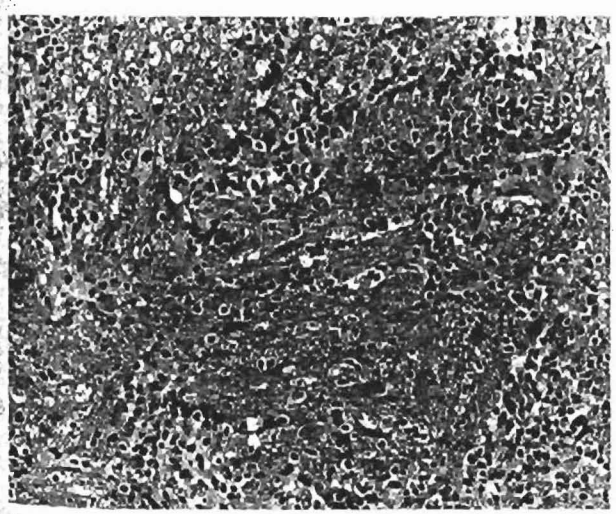

FIG. 6. Typical nasopharyngeal carcinoma with a syncytial growth pattern without distinct nests, and numerous intimately associated lymphocytes. The nuclei are more variable within a given tumor than the nuclei in SNUC.

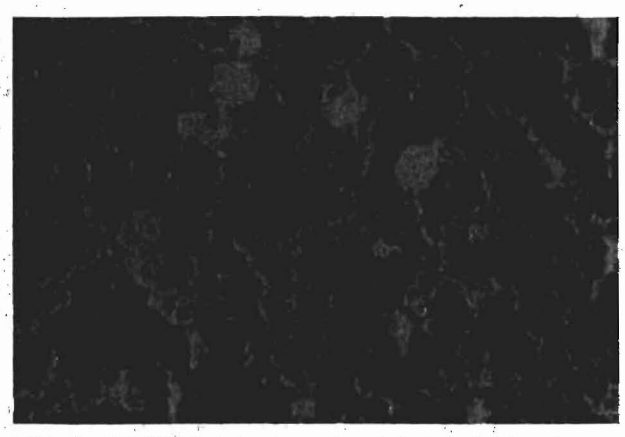

FIG. 7. SNUC showing prominent festooning and powdery cytoplasm. Neuron-specific enolase was weakly positive, although chromogranin and synaptophysin were completely negative.

A somewhat more convincing argument can be raised that SNUC with NSE positivity are large cell carcinomas with occult neuroendocrine differentiation, indicating that special techniques are required to detect neuroendocrine features. Such tumors have not been defined as an entity in the ENT system, but in the lungs they have been noted to have large nucleoli, a common feature of SNUC and a finding not attributed to tumors classically described as "neuroendocrine."[23] In the current study, we identified four SNUC with focal weak NSE reactivity that were completely negative for synaptophysin and chromogranin. Focal weak NSE positivity in the absence of other neuroendocrine antibody reactivity may possibly be attributed to the known antibody cross-specificity of NSE.[1] However, such cross-reactivity has been largely or completely eliminated with the use of monoclonal antibody preparations as those used in the current study. One previous report of SNUC and EBV with occasional NSE-positive cases did not examine other neuroendocrine markers.[10] In this study, identifying 5 of 13 SNUC positive for EBV, three SNUC were also NSE positive, but whether the NSE-positive cases were among the EBV-positive cases cannot be ascertained.[10] SNUC may show abortive neuroendocrine differentiation. In addition to occasional cases showing weak NSE staining, we documented rare neurosecretory-type granules in our original study of SNUC.[6] No evidence exists that such cases have a distinct biologic behavior. Their response to chemotherapy, in comparison with NSE-negative case, requires additional study.

Although SNUC usually consists of medium-sized cells, it may occasionally manifest as a "small blue cell

tumor." We therefore were interested in the utility of CD99 for discriminating SNUC from Ewing's sarcoma/peripheral neuroectodermal tumor (PNET) and other CD99-positive small cell lesions, including lymphoblastic lymphoma and rhabdomyosarcoma. In addition to these small cell neoplasms, a growing number of morphologically diverse proliferations has recently been identified with CD99 positivity, including myxoid solitary fibrous tumor,[18] myxoid synovial sarcoma,[13] sclerosing perineuroma,[4] leukemia cutis,[3] and calcifying aponeurotic fibroma.[5] CD99 also reacts with various normal cells such as normal granulosa and Sertoli cells.[20] The finding of occasional SNUC with strong CD99 immunostaining (Fig. 3) indicates that this marker is not useful for discriminating SNUC from the family of CD99-positive small blue cell tumors and adds SNUC to the growing list of CD99-positive neoplasms.

Sinonasal undifferentiated carcinoma were highly variable in expression of p53 and the proliferation marker Ki-67. The number of cases studied precluded statistical significance in correlating p53 and proliferation indices with biologic parameters. However, of the cases with available follow-up, the range of p53 or Ki-67 staining was highly variable among SNUC with widely different lengths of survival (no statistically significant correlation). In fact, two SNUC with survival of 9 and 10 years showed diffuse, strong p53 positivity (one example, case 5). Although accumulation of p53 protein is usually interpreted as a surrogate marker for a mutation in the gene, elevated levels of wild-type p53 have been reported to result in a positive immunohistochemical reaction.[19] Studies at the molecular level will be necessary to further evaluate the relationship of p53 and SNUC.

Overall, cases showing strong p53 expression showed concomitant strong Ki-67, although a few cases fell outside this general observation. One case with a high level of p53 expression also showed frequent Ki-67 expression. One could hypothesize that the high proliferative index makes this particular tumor more chemoresponsive, but given the overall poor prognosis of SNUC, we do not espouse this view. We cannot fully explain the finding of some cases showing a low level of expression of Ki-67 in such a mitotically active tumor. Scrutiny of these cases indicated that these were represented by small biopsy material in which there was significant necrosis, or limited to intravascular tumor only.

The initial reports of SNUC regarded it as a malignancy with a dismal prognosis.[7] This factor, coupled with the rarity of SNUC, has resulted in few cases with long-term follow-up study. Follow-up data for the original series of cases suggested that the prognosis for patients with localized disease might be better than initially thought.[2] The current study documents three cases with extended survival (cases 7, 10, and 2). Two of these patients (cases 7 and 12) received autologous bone marrow transplantation, and one of the transplant re- subsequently underwent a second radical proce- remove recurrent disease. Both of these patients s- 9 years after diagnosis but ultimately died of emphasizing that 5-year disease-free survivals ca- equated with cure for SNUC. One patient (case mains free of disease 10 years after tumor resecti- median survival of patients in our study was months. This natural history is similar to the resu- earlier study that examined survival among patie- SNUC, with four of seven patients dead of disea- ing survived a mean of 11.5 months after therap- though disseminated metastases were common, fa- eradicate local disease with extension into the adjacent tissues (e.g., brain, orbit) was the cause o- in most patients.

In summary, our findings indicate that if stringe- tologic criteria are applied to the diagnosis of S- then the tumor is not associated with EBV. Tumo- the appearance of a lymphoepithelioma-like carc- should be excluded from the category of SNUC nasal undifferentiated carcinoma may occasionally strong CD99 positivity, and tumors show highly va- reactivity for p53 and Ki-67. Sinonasal undifferen- carcinoma also may show abortive neuroendocrin- ferentiation at the immunohistochemical and ultras- tural level. This is of unknown significance. Alt- most patients die of disease within months, in ra- stances, patients may survive for many years.

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REFERENCES

1. Chejfec G, Faulkner S, Grimius L, et al. Synaptophysin marker for pancreatic neuroendocrine tumors. *Am J Surg* 1987;11:241–7.
2. Deutsch BD, Levine PA, Stewart FM, et al. Sinonasal undi- tiated carcinoma: a ray of hope. *Otolaryngol Head Neck* 1993;108:697–700.
3. Dorfman DM, Kraus M, Perez-Atayde AR, et al. CD99 (MIC-2) immunoreactivity in the diagnosis of leukemia cuti- *Pathol* 1997;10:283–8.
4. Fetsch JF, Miettinen M. Sclerosing perineuroma: a clinico- logic study of 19 cases of a distinctive soft tissue lesion predilection for the fingers and palms of young adults. *Am Pathol* 1997;21:1433–42.
5. Fetsch JF, Miettinen M. Calcifying aponeurotic fibroma: copathologic study of 22 cases arising in uncommon sites *Pathol* 1998;29:1504–10.
6. Frierson HF, Mills SE, Fechner RE, et al. Sinonasal undi- ated carcinoma: an aggressive neoplasm derived from Schn- rian epithelium and distinct from olfactory neuroblastoma *Surg Pathol* 1986;10:771–9.

7. Frierson HF, Stewart FM, Mills SE, et al. Sinonasal undifferentiated carcinoma: a distinctive and highly aggressive neoplasm. *Laryngoscope* 1987;97:905–8.
8. Gaffey MJ, Frierson HF, Weiss LM, et al. Human papillomavirus and Epstein-Barr virus in sinonasal Schneiderian papillomas. *Am J Clin Pathol* 1996;106:475–82.
9. Gaffey MJ, Weiss LM. Association of Epstein-Barr virus with human neoplasia. *Pathol Annual* 1992;27:55–74.
10. Gallo O, Simonetta D, Graziani P, et al. Detection of Ebstein-Barr virus genome in sinonasal undifferentiated carcinoma by use of in situ hybridizatoin. *Otolaryngol Head Neck Surg* 1995;112:659–64.
11. Hwang TZ, Tsai ST. EBER in situ hybridization differentiates carcinoma originating from the sinonasal region and the nasopharynx. *Anticancer Res* 1998;18:4581–4.
12. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinoma. *Am J Clin Pathol* 1995;103: 308–15.
13. Krane JF, Bertoni F, Fletcher CDM. Myxoid synovial sarcoma: an underappreciated morphologic subset. *Mod Pathol* 1999;12: 456–62.
14. Leung SY, Yuen ST, Chung LP, et al. Epstein Barr Virus is present in a wide histologic spectrum of sinonasal carcinoma. *Am J Surg Pathol* 1995;19:994–1001.
15. Lopategui JR, Gaffey MJ, Frierson HF, et al. Detection of Epstein-Barr viral RNA in sinonasal undifferentiated carcinoma from Western and Asian patients. *Am J Surg Pathol* 1994;18:391–8.
16. Righi PD, Francis F, Aron BS, et al. Sinonasal undifferentiated carcinoma: a 10 year experience. *Am J Otolaryngol* 1996:17;167–71.
17. Sheibani K, Tubbs RR. Enzyme immunohistochemistry: technical aspects. *Semin Diagn Pathol* 1984;1:235–50.
18. Somerhausen NSA, Rubin BR, Fletcher CDM. Myxoid solitary fibrous tumor: a study of seven cases with emphasis on differential diagnosis. *Mod Pathol* 1999:12:463–71.
19. Soong R, Robbins PD, Dix BR, et al. Concordance between p53 protein overexpression and gene mutation in a large series of common human malignancies. *Hum Pathol* 1996;27:1050–5.
20. Stevenson AJ, Chatten J, Bertoni F, et al. CD99 (p30/32MIC-2) neuroectodermal/Ewing's sarcoma antigen as an immunohistochemical marker. *Appl Immunohistochem* 1994;2:231–40.
21. Stewart JP, Arrand JR. Expression of the Epstein-Barr virus latent membrane protein in nasopharyngeal carcinoma biopsy specimens. *Hum Pathol* 1993;24:239–42.
22. Stoler MH, Nichols GE, Symbula M, et al. Lymphocyte predominance Hodgkin's disease: evidence for a K light chain restricted monotypic B-cell neoplasm. *Am J Pathol* 1995;146:812–8.
23. Wick MR, Berg LC, Hertz MI. Large cell carcinoma of the lung with neuroendocrine differentiation. *Am J Clin Pathol* 1992;97: 796–805.