The American Journal of Surgical Pathology 26(12): 1597–1604, 2002

Sinonasal Undifferentiated Carcinoma, Nasopharyngeal-Type Undifferentiated Carcinoma, and Keratinizing and Nonkeratinizing Squamous Cell Carcinoma Express Different Cytokeratin Patterns

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Sinonasal undifferentiated carcinoma (SNUC) is a highly aggressive malignant neoplasm that is often difficult to distinguish from other poorly differentiated carcinomas arising in the sinonasal tract. To search for a differential cytokeratin (CK) expression that could be useful for diagnostic purposes, we compared the expression of a large panel of CKs in a series of 6 SNUCs, 10 poorly differentiated squamous cell carcinomas (SCCs), 10 nonkeratinizing squamous cell carcinomas (NKSCCs), and 5 nasopharyngeal-type undifferentiated carcinomas (NPTCs). SCC, NKSCC, and NPTC frequently showed immunoreactivity for CK5/CK6, CK8, CK13, and CK19. In addition, SCC and NKSCC expressed CK14, which was not detected in NPTC, and SCC expressed CK7 (60% of cases) and CK4 (30% of cases), which were absent in NKSCC and NPTC. Three NKSCCs were associated with a Schneiderian papilloma, and the results of the immunostaining were similar in the two components, with the exception of CK4 and CK7, which were expressed by the papilloma and not by the carcinoma. In contrast to other carcinomas, SNUC was characterized by the exclusive expression of CKs of simple epithelia, such as CK8 (100% of cases), CK7 (50% of cases), and CK19 (50% of cases). Thus, there are significant differences in the pattern of CK expression between SNUC, SCC, NKSCC, and NPTC, which could be of diagnostic aid. Moreover, these findings support the hypothesis that SNUC is a separate entity from SCC and NPTC of the sinonasal tract.

Key Words: Nasal cavity—Paranasal sinuses—Undifferentiated carcinoma—Squamous cell carcinoma—Nonkeratinizing squamous cell carcinoma—Nasopharyngeal carcinoma—Immunohistochemistry—Cytokeratins.

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Carcinomas of the nasal cavities and paranasal sinuses represent about 3% of head and neck malignancies.[11] The majority of these carcinomas belong to the group of squamous cell carcinoma (SCC) that comprises two basic histomorphologic subtypes: conventional keratinizing SCC and nonkeratinizing squamous cell carcinoma (NKSCC, cylindrical cell carcinoma or transitional-type carcinoma).[12,16] These tumors present a wide range of differentiation, and although well-differentiated variants are easily recognizable, poorly differentiated lesions may show considerable overlap in their histologic features, making their distinction difficult particularly on small biopsies.

More recently, an undifferentiated variant of sinonasal carcinoma, possibly arising from the Schneiderian epithelium, has been recognized as a separate entity from a group of undifferentiated tumors, which included also anaplastic carcinomas.[5,9] These tumors pursue a highly aggressive behavior and histologically are composed of sheets, nests, or ribbons of small- and medium-sized cells, with frequent necrosis and vascular invasion. Epithelial differentiation is usually rudimentary; therefore, sinonasal undifferentiated carcinoma (SNUC) may be difficult to distinguish from several nonepithelial neoplasms, such as melanoma, lymphoma, rhabdomyosarcoma, and olfactory neuroblastoma. In addition, poorly differentiated carcinomas, including nasopharyngeal-type undifferentiated carcinoma (NPTC), which may occasionally involve or arise in the nasal cavities and paranasal sinuses, may be difficult to distinguish from SNUC on pure morphologic basis.

In this study we examined the keratin expression patterns in a series of poorly differentiated and nonkeratinizing carcinomas of the sinonasal tract, including SCC, NKSCC, NPTC, and SNUC, to determine which keratin profile may be informative for differential diagnostic purposes between these entities.

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MATERIALS AND METHODS

Case Selection

Cases were retrieved from a database containing 160 cases of primary carcinomas of the nasal cavities and paranasal sinuses collected at the Department of Human Pathology and Oncology of the University of Florence Medical School between January 1966 and December 2000. All available hematoxylin and eosin-stained slides were reviewed, and the diagnosis was confirmed by two of the authors (A.F. and M.S.). Cases with paraffin blocks suitable for the immunohistochemical analysis were selected for this study. Through this search, we identified six cases of SNUC, occurring in four men and two women (median age 60 years, range 47–67 years), and five cases of NPTC involving the nasal cavities and paranasal sinuses, occurring in four men and one woman (median age 57 years, range 42–64 years). Ten cases of poorly differentiated SCC and 10 cases of NKSCC were then selected from a group of 96 SCCs arising in the nasal cavities and paranasal sinuses.

Immunohistochemical Analysis

Formalin-fixed, paraffin-embedded tissues were used for immunohistochemical study by the avidin-biotin-peroxidase method with monoclonal antibodies listed in Table 1. Only those cases showing >5% tumor cell positivity were considered positive. Negative controls were obtained by replacing the primary antibody with nonimmune mouse serum.

In Situ Hybridization

The Epstein-Barr virus (EBV) status was examined by in situ hybridization using the INFORM EBER Probe kit following the manufacturer's instruction with the Bench-Mark automated system (Ventana Medical Systems, Tucson, AZ, USA). As a negative control, the EBV probe was replaced by Tris buffer or a sense probe. These procedures consistently resulted in no detection of signals. Tissues of EBV-positive oral hairy leukoplakia were used as positive controls.

RESULTS

Pathologic Findings

Poorly differentiated SCCs consisted of solid masses of pleomorphic polygonal cells with a variable amount of eosinophilic cytoplasm and a large hyperchromatic nucleus, sometimes with prominent nucleoli. Minimal areas of keratinization and rare intercellular bridges were observed in all cases (Fig. 1). Necrosis was a common feature, together with infiltration by inflammatory cells (granulocytes and lymphocytes). In six cases the invasive carcinoma was associated with dysplastic changes of the surface epithelium or with in situ carcinoma.

NKSCCs were characterized by a proliferation of anastomosing ribbons composed of cylindrical cells oriented perpendicular to the surface, with pale eosinophilic cytoplasm and oval nucleus, with one or more nucleoli (Fig. 2). Mitotic activity was usually brisk. Focal areas of keratinization were observed in one lesion. In four instances the lesion was less differentiated and contained larger nests of pleomorphic tumor cells with areas of necrosis. Three NKSCCs developed in association with Schneiderian papilloma (Fig. 3). In two instances the two lesions were synchronous, whereas in one instance an NKSCC developed after four recurrences of the Schneiderian papilloma. In four other examples NKSCC was associated with severe dysplasia/in situ carcinoma of the surface epithelium.

NPTCs consisted of irregular syncytial-like sheets of cells with indistinct margins and oval or round vesicular nuclei with prominent nucleoli, associated with an inflammatory infiltrate composed of lymphocytes and plasma cells (Fig. 4). Mitotic figures were readily identifiable in all cases, although tumor necrosis was never detected. In all cases epithelial tumor cells were positive for EBER, whereas the inflammatory infiltrate was negative.

Histologically, SNUCs had the morphologic features previously defined by Frierson et al.[5] They were composed of nests, sheets, or ribbons of round to oval cells, with large nucleus and a small amount of cytoplasm (Fig. 5). Chromatin was more frequently homogeneous and nucleoli were often prominent. Presence of a high mitotic rate and large areas of necrosis were common features. A

TABLE 1. *Antibodies used in this study*

Antibody	Dilution	Pretreatment	Source
Cytokeratin 4	1:100	10 mM citrate buffer, microwave (35 min)	Novocastra, Newcastle Upon Tyne, UK
Cytokeratin 5/6	1:20	10 mM citrate buffer, microwave (35 min)	Roche, Indianapolis, IN, USA
Cytokeratin 7	1:800	0.5% protease XIV 20°C (15 min)	Bio Genex, San Ramon, CA, USA
Cytokeratin 8	1:4	0.5% protease XIV 20°C (15 min)	Becton Dickinson, San Josè, CA, USA
Cytokeratin 10	1:50	0.5% protease XIV 20°C (15 min)	Novocastra
Cytokeratin 13	1:50	10 mM citrate buffer, microwave (35 min)	Novocastra
Cytokeratin 14	1:40	10 mM citrate buffer, microwave (35 min)	Novocastra
Cytokeratin 19	1:100	0.5% protease XIV 20°C (15 min)	Bio Genex

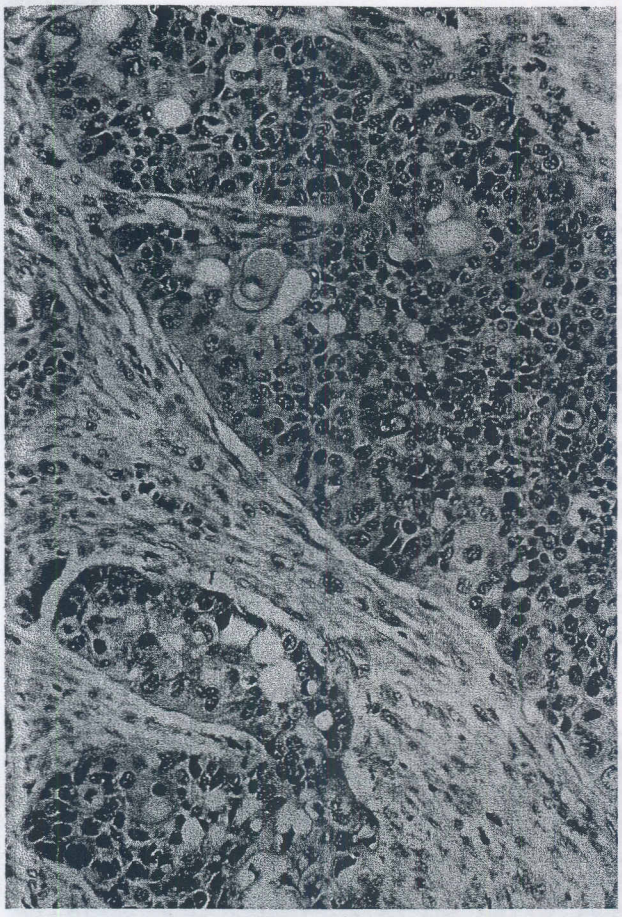

FIG. 1. Poorly differentiated squamous cell carcinoma of the nasal cavity. There is focal keratinization in the larger tumor nest.

small number of inflammatory cells in association with areas of necrosis were documented in two cases. The surface epithelium was present in three samples and showed features of mild dysplasia in one. In no case there was EBER expression by neoplastic epithelial cells.

Immunohistochemistry

The results of the immunohistochemical studies are summarized in Table 2. With the exception of cytokeratin 10 (CK10), which was always absent in our series of carcinomas, all CKs tested were expressed at various extent and in variable combinations in SCC, NKSCC, NPTC, and SNUC.

Nine of 10 (90%) SCCs showed uniformly intense cytoplasmic staining for CK5/CK6 (Fig. 6A), CK8 (Fig. 6B), CK13 (Fig. 6C), and CK19. CK14 expression was detected in eight cases (80%). The immunostaining was diffuse and intense in four carcinomas (Fig. 6D), whereas in the remaining four reactivity was limited to several scattered isolated cells or small groups of cells in the center of neoplastic islands. Uniformly diffuse staining for CK7 was detected in six carcinomas (60%), whereas CK4 immunoreactivity involved several isolated foci of neoplastic cells in three cases (30%).

Of the NKSCCs, 9 of 10 (90%) expressed CK5/CK6 (Fig. 6E), CK8 (Fig. 6F), and CK19 with diffuse distribution of the immunostaining. CK13 and CK14 were present in eight carcinomas (80%), predominantly with diffuse staining of the malignant cells (five cases) (Fig. 6G, H), or with positivity limited to small groups of malignant cells (three cases). In the three cases of NKSCC associated with Schneiderian papilloma, the epithelium of the papilloma showed strong diffuse immunoreactivity for CK5/6, CK14, and CK19, whereas CK4 (Fig. 7A), CK7 (Fig. 8A), CK8, and CK13 showed predominantly immunostaining of the suprabasal layers; the invasive carcinoma component was positive for CK5/CK6, CK8, CK13, CK14, and CK19, with CK4 and CK7 being positive in a few scattered cells (<5% of tumor cells) or completely absent (Figs. 7B and 8B). To confirm these findings, we stained 10 additional cases of

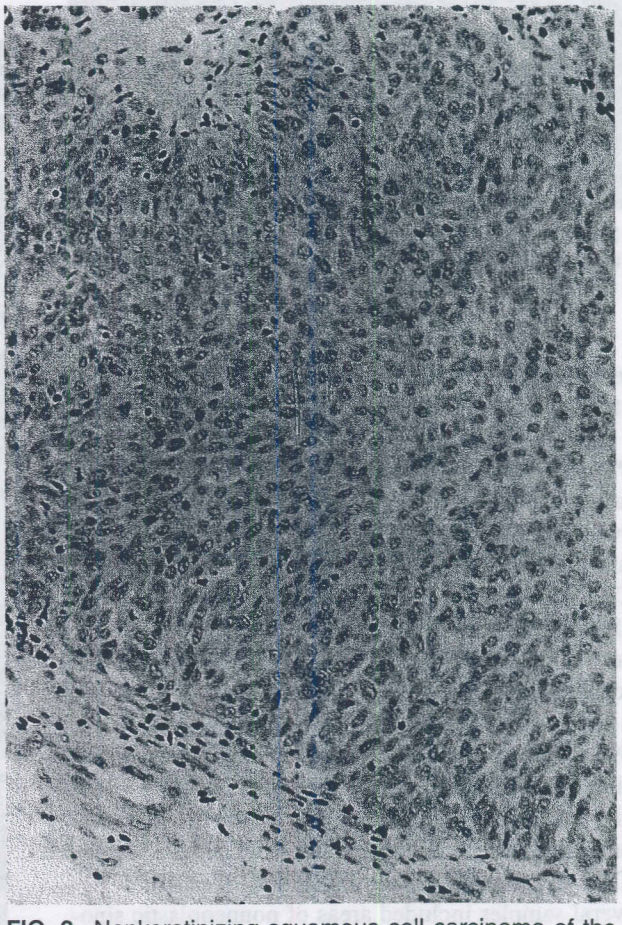

FIG. 2. Nonkeratinizing squamous cell carcinoma of the nasal cavity. Tumor cells show pale eosinophilic cytoplasm and oval nucleus, with one or more nucleoli. At the periphery of this area, tumor cells have a cylindrical shape.

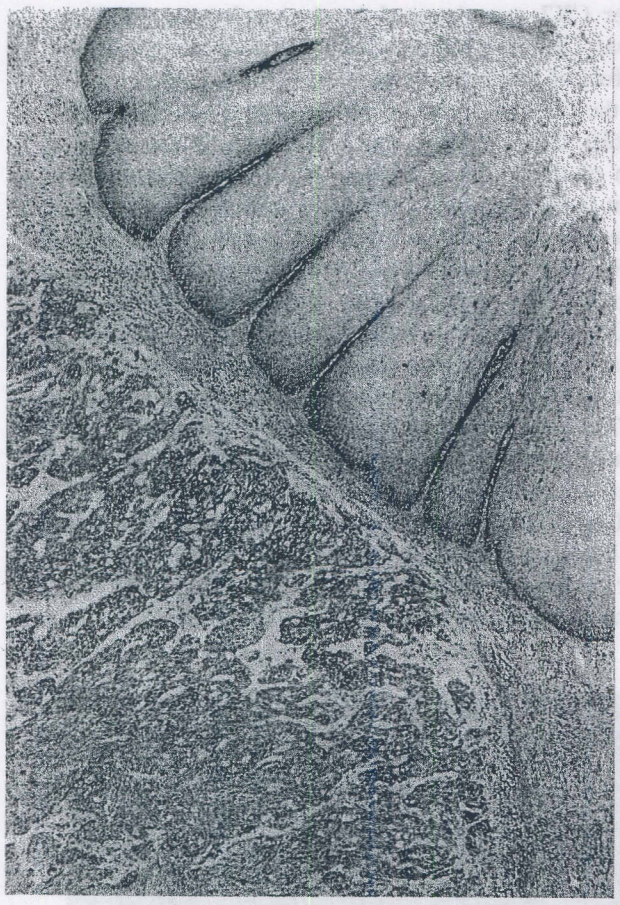

FIG. 3. Nonkeratinizing squamous cell carcinoma (bottom) in the subepithelial stroma of a Schneiderian papilloma (top).

Schneiderian papilloma (both exophytic and inverted) with the same panel of cytokeratins, and similar results were obtained (data not shown).

NPTC showed a pattern of cytokeratin expression similar to that of SCC and NKSCC. Neoplastic epithelial cells were positive for CK5/CK6 (Fig. 6I), for CK8 (Fig. 6J), and for CK13 (Fig. 6K) in 4 of 5 cases (80%), and for CK19 in all cases. No expression of CK4, CK7, CK10, and CK14 (Fig. 6L) was detected.

The CK repertoire of SNUC was more restricted and included the diffuse expression of CK8 in 100% of the cases (Fig. 6N), whereas CK7 and CK19 were detected in 50% of the cases, with two carcinomas showing expression of both CK7 and CK19 and remaining cases showing expression of either CK7 or CK19. Immunostaining with antibodies against CK4, CK5/CK6, CK13, and CK14 gave negative results (Fig. 6M, O, P).

Several samples included areas of nonneoplastic sinonasal mucosa in the preparations. The surface columnar epithelium as well as mucosal glands were strongly immunopositive for CK7 and CK19. CK8 expression was detected predominantly in the superficial layers of the surface epithelium, whereas the basal layers showed immunoreactivity for CK14. The glandular epithelium expressed both CK8 and CK14.

DISCUSSION

CKs are a large family of polypeptides of the cytoskeleton, which are classified and numbered based on the isoelectric point and molecular weight.[13] Two main subfamilies of CKs have been recognized: the acidic type A (class I, CK9–CK20) and the neutral-basic type B (class II, CK1–CK8). Filaments are formed by heterodimers of a particular type A CK joined to a particular type B CK. Expression patterns of CKs have been correlated with different pathways of epithelial differentiation, allowing the distinction of several epithelial cell subtypes. In recent years several studies have underscored the usefulness of CK polypeptides as diagnostic tumor markers, and CK typing proved to be useful in cases in which accurate diagnosis may be difficult on pure histologic basis.

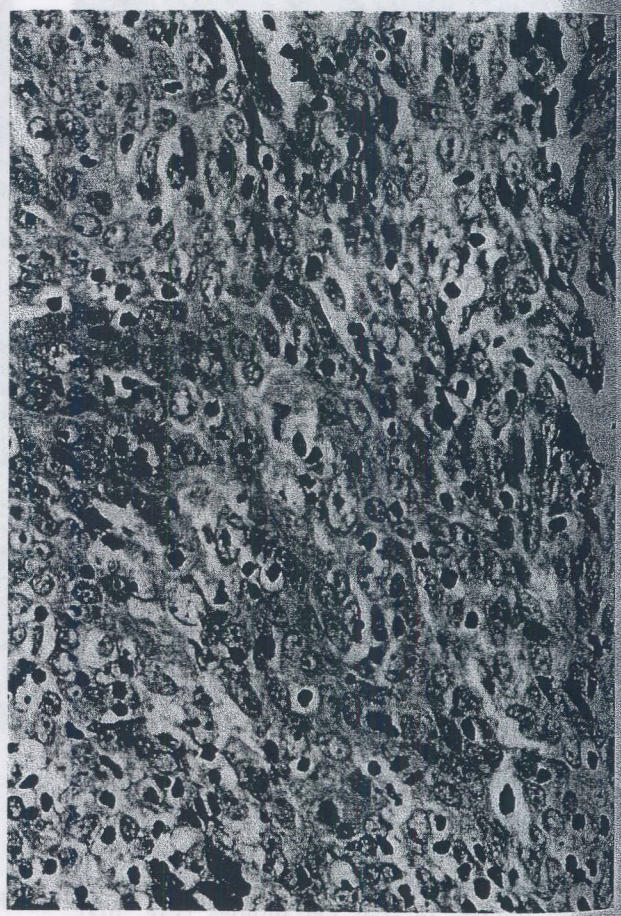

FIG. 4. Nasopharyngeal-type undifferentiated carcinoma. The tumor cells show indistinct margins and oval or round vesicular nuclei with prominent nucleoli. Numerous lymphocytes are associated with the neoplastic proliferation.

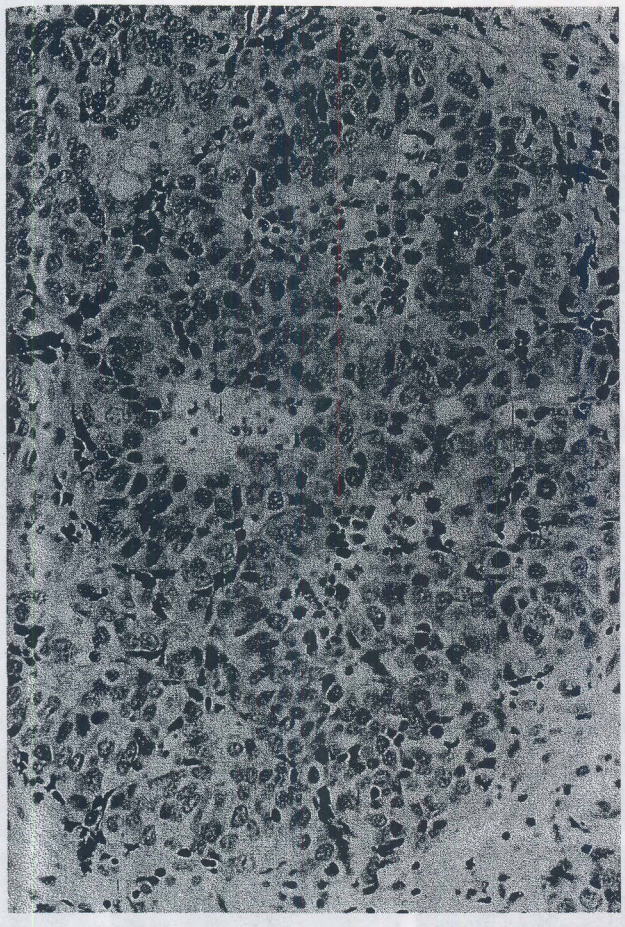

FIG. 5. Sinonasal undifferentiated carcinoma. Tumor cells are arranged in nests, with central areas of necrosis. Nuclei are relatively uniform and often contain a prominent nucleolus.

Our analysis of a series of carcinomas of the sinonasal tract using a large panel of monoclonal antibodies against CKs has shown that relevant differences do exist between SCC, NKSCC, NPTC, and SNUC.

We observed a substantial overlap in the CK pattern of NKSCC and SCC, even if only poorly differentiated examples of SCC were included in our analysis. Both tumor types expressed CKs of stratified squamous epithelia, such as CK5/CK6, CK13, and CK14, which are commonly found in SCCs of different origin, including those arising in the head and neck area.[4,8,21,22] In addition, the CK expression profile of NPTC was similar to that of SCC and NKSCC, with the exception of CK14, which was absent in all the samples of NPTC tested. CK4 was found only in individual cells in a few cases of SCC and NKSCC of the sinonasal tract. Similarly, low levels of this CK have been detected in SCCs of the tongue, esophagus, and larynx.[21,22] Finally, CK10, which is considered a marker for keratinization,[18] was never detected in our series of carcinomas, possibly because we selected only carcinomas with no or little evidence of keratinization. Alternatively, this may indicate differential expression of CK10 by SCC of different origin.

From the simple keratins, CK8 and CK19 were equally expressed by SCC, NKSCC, and NPTC, whereas CK7 was found only in SCC. These simple keratins are present in the majority of SCCs derived from nonkeratinizing epithelia or from columnar epithelia, and they are usually absent in SCCs arising directly from keratinizing squamous epithelia.[19,22] CK7 and CK19 positivity has been documented with variable frequency in SCCs arising in the head and neck area, including the sinonasal tract.[1,3,8,14,22–24] The expression of simple epithelia keratins in SCCs arising from pseudostratified columnar epithelium of the respiratory tract is a well-known phenomenon, which has been explained assuming that these tumors arise from a columnar cell that retains the expression of its simple keratin pattern.[19]

The distinction between NKSCC and SCC of the sinonasal tract may be difficult on occasion, especially when areas of squamous metaplasia are present in an NKSCC. Although the differences in the CK pattern between these two subtypes are limited, according to our analysis the presence of CK4 and CK7 supports the diagnosis of SCC.

It is well known that modification of the CK pattern may occur during malignant transformation.[24] Our analysis included NKSCCs associated with concomitant or previous Schneiderian papilloma, in which the invasive malignant component of the lesion was characterized by loss of CK4 and CK7 expression in comparison with the epithelium of the papilloma. Although the number of such cases was small, we suggest that immunostaining for CK4 and CK7 could be potentially useful to confirm the presence of malignant transformation in Schneiderian papilloma.

SNUC is a highly aggressive tumor, usually presenting with an advanced clinical stage and with short survival periods.[5,6,9,15] It is regarded as an undifferentiated carcinoma of putative Schneiderian origin, based on the rudimentary epithelial differentiation observed at the ultrastructural level, where small desmosomes but no tonofilaments have been identified, and on the immunohis-

TABLE 2. *Cytokeratin (CK) immunoreactivity in sinonasal poorly differentiated squamous cell carcinoma (SCC), non-keratinizing squamous cell carcinoma (NKSCC), nasopharyngeal-type undifferentiated carcinoma (NPTC), and sinonasal undifferentiated carcinoma (SNUC)*

	CK 4	CK 5/6	CK 7	CK 8	CK 10	CK 13	CK 14	CK 19
SCC	3/10	9/10	6/10	9/10	—	9/10	8/10	9/10
NKSCC	—	9/10	—	9/10	—	8/10	8/10	9/10
NPTC	—	4/5	—	4/5	—	4/5	—	5/5
SNUC	—	—	3/6	6/6	—	—	—	3/6

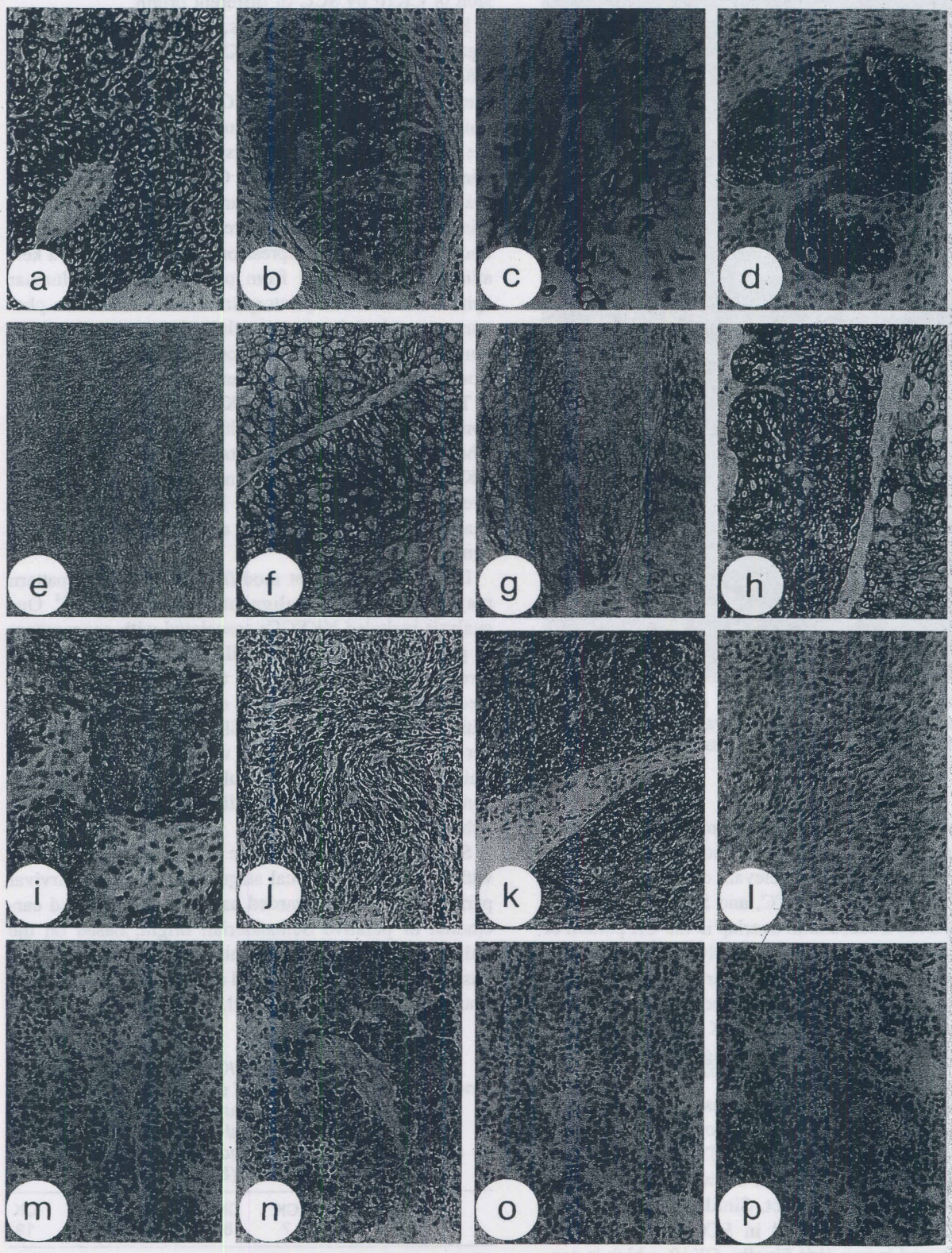

FIG. 6. Comparison of the immunohistochemical cytokeratin staining patterns of poorly differentiated SCC (first row), NKSCC (second row), NPTC (third row), and SNUC (fourth row). Results from the immunostainings for CK5/CK6 (first column), CK8 (second column), CK13 (third column), and CK14 (fourth column) are reported.

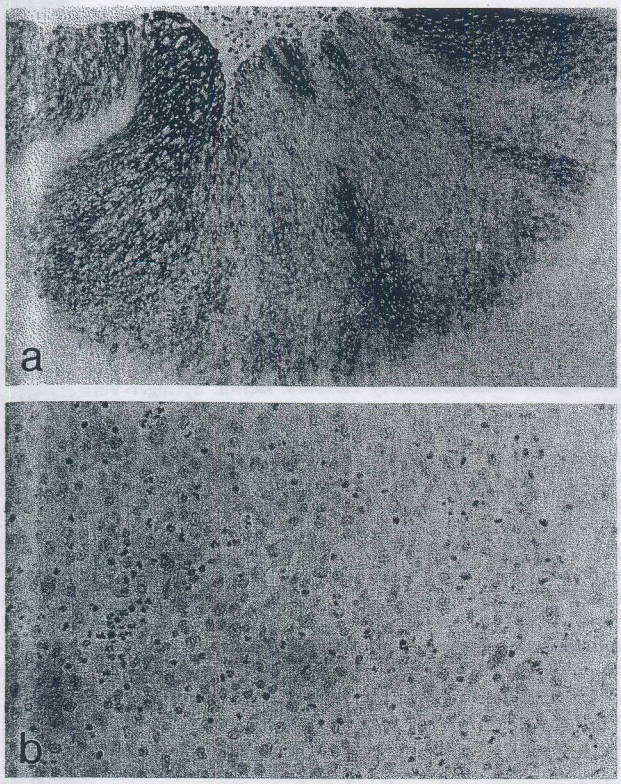

FIG. 7. Nonkeratinizing squamous cell carcinoma arising in association with Schneiderian papilloma. CK4 is expressed by the papilloma **(A)** but not by the invasive carcinoma **(B)**.

tochemical identification of CKs and epithelial membrane antigen.[2,5,10] Although it may present abortive neuroendocrine differentiation, with occasional positivity for neuron-specific enolase and rare neurosecretory-type granules at the ultrastructural level,[5] SNUC should be kept separate from neuroendocrine carcinoma of the sinonasal region,[17,20] which is characterized by the expression of other neuroendocrine markers, such as chromogranin and synaptophysin.

Although SNUC is in most cases easily separated from SCC because it does not have evidence of keratinization, poorly differentiated variants of SCC with little or no keratinization may be entered in the differential diagnosis, especially if only small biopsy material is available for diagnosis. Similarly, poorly differentiated variants of NKSCC, characterized by anastomosing ribbons and festoons of anaplastic cells, often accompanied by comedonecrosis,[25] may be difficult to differentiate from SNUC. However, the main differential diagnosis of SNUC is NPTC, either primarily arising in the sinonasal tract or extending in the nasal cavities and paranasal sinuses from the nasopharynx. The most useful histopathologic criteria to discriminate between SNUC and NPTC are the absence of necrosis, the markedly vesicular nuclei with prominent nucleoli, the syncytial growth pattern, and the presence of spindle tumor cells in NPTC.[7] Another relevant difference between these tumors is the presence of EBV in NPTC, whereas, according to two recent reports,[2,7] SNUC lacks association with EBV.

The results of the current study, which is the first detailed analysis of the pattern of CK expression in these neoplasms, indicate that SNUC is characterized by the exclusive expression of simple epithelia-type CKs, with constant presence of CK8, and variable expression of CK7 and CK19. Conversely, CKs expressed by stratified epithelia, such as CK5/CK6, CK13, and CK14 are notably always absent. Thus, negative immunostaining for CK5/CK6 and CK13 in a poorly differentiated carcinoma of the sinonasal tract supports the diagnosis of SNUC and rules out the diagnosis of SCC, NKSCC, and NPTC.

In summary, we found relevant differences in the expression pattern of CKs in SCC, NKSCCC, NPTC, and SNUC. SCC, NKSCC, and NPTC showed immunoreactivity for both stratified and simple epithelia keratins, whereas SNUC was characterized by the expression of simple epithelia keratins only. Our results add to the already established morphologic differences between these entities; further, they support the hypothesis that SNUC is a separate entity from SCC, NKSCC, and NPTC, and not a nonkeratinizing poorly differentiated

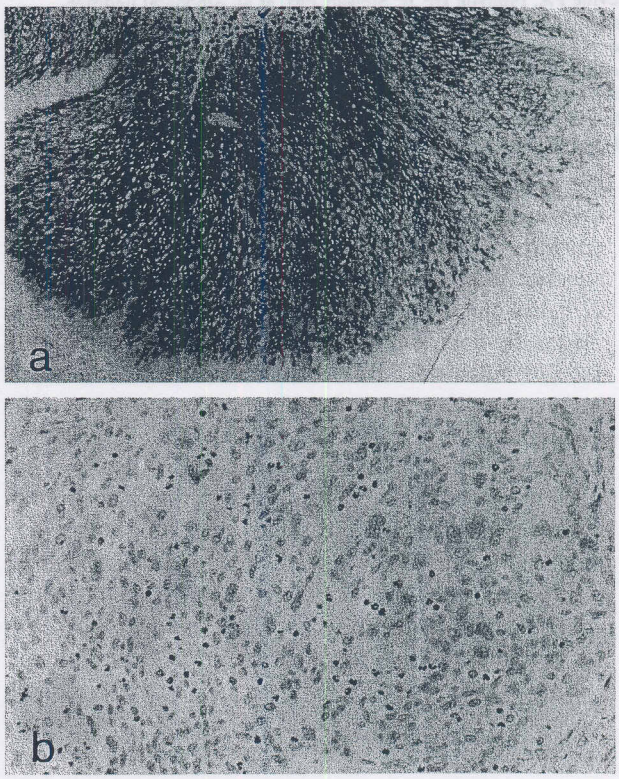

FIG. 8. CK7 expression in a Schneiderian papilloma **(A)**. This CK is absent in the associated invasive carcinoma **(B)**.

variant of SCC. Use of anti-CK5/CK6, -CK13, and -CK14 antibodies provides another means of distinguishing between these tumors. □

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