Temporal Bone and Sinonasal Inverted Papilloma

The Same Pathological Entity?

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**Background:** Inverted papilloma involving the temporal bone is an extremely rare occurrence. Reports in the literature suggest a higher recurrence rate and association with squamous cell carcinoma in Schneiderian-type papillomas of the middle ear than in sinonasal Schneiderian-type papillomas.

**Objectives:** To investigate the expression of apoptosis-related proteins, markers of cell proliferation activity, and sex hormone receptors in temporal bone inverted papillomas and to compare this entity with sinonasal papillomas.

**Design and Subjects:** We investigated 2 rare cases of inverted papilloma of the temporal bone and a control group of 6 cases of sinonasal inverted papilloma. The expression of p53, Mib-1, p27, and progesterone and estrogen receptors was determined.

**Results:** In the 2 cases of temporal bone inverted papilloma, p53 expression was 43.75% and 4.92%; p27 expression was higher in temporal bone inverted papilloma (82.45% and 70.53%) than in the sinonasal inverted papilloma group. One of our 2 cases of temporal bone Schneiderian-type papilloma was positive for progesterone receptor.

**Conclusions:** The expression of progesterone receptor in 1 of our 2 cases and in the only other case reported in the literature may imply some degree of hormonal dependence of temporal bone inverted papilloma. Our analysis of the expression of apoptosis-related proteins, markers of cell proliferation activity, and sex hormone receptors does not allow us to demonstrate that temporal bone and sinonasal inverted papilloma are different pathological entities.

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INVERTED PAPILLOMA (Schneiderian-type papilloma) is a relatively rare benign epithelial neoplasm with a tendency toward local aggressiveness and multicentricity. These lesions most commonly originate from the mucosa of the lateral nasal wall and can involve the paranasal sinuses, orbits, and anterior skull base. Sinonasal inverted papilloma more commonly occurs in men than in women. Inverted papilloma occurring in the pharynx, nasopharynx, lacrimal sac, and temporal bone have been described. Inverted papilloma involving the temporal bone is an extremely rare occurrence. To our knowledge, only 15 cases have been reported. Inverted papilloma of the temporal bone occurred with a female-male ratio of 2:1.

A review of the literature reveals higher recurrence rates and an association with squamous cell carcinoma in Schneiderian-type papillomas of the middle ear compared with inverted papillomas of the nose and paranasal sinuses. The expression and interaction of apoptosis-related proteins and markers of cell-proliferation activity in Schneiderian-type papilloma of the temporal bone have not been considered. We simultaneously examined the expression of p53, Mib-1, and p27 in 2 cases of inverted papilloma of the middle ear and mastoid and compared the results with a control group of sinonasal inverted papilloma cases.

The hypothesis of a different sex steroid hormone influence in sinonasal and temporal bone inverted papilloma has been considered. Progesterone receptor (Prg-r) and estrogen receptor expression were determined in the 2 groups.

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**METHODS**

**CASES**

A total of 8 cases of (2 of the temporal bone and 6 sinonasal) Schneiderian-type papillomas were evaluated (Table). In case 1, a 54-
scores between temporal bone and sinonasal inverted papillomas (control group), with 20 minutes in a citrate buffer (10mM, pH 6.0).

The sections were pretreated in a microwave oven (750 W) for immunohistologic examination. For each sample, p53, Mib-1, squamous cell carcinoma association. All tissue samples were fixed in 10% formalin and embedded in paraffin wax.

**IMMUNOHISTOCHEMISTRY**

From each of the 8 tissue blocks, 5-μm sections were cut for immunohistologic examination. For each sample, p53, Mib-1, p27, and progestrone and estrogen reactivity were evaluated. The sections were pretreated in a microwave oven (750 W) for 20 minutes in a citrate buffer (10mM, pH 6.0).

The antibodies used were p53 (clone DO-1, prediluted mouse antibody; Immunotech, Marseilles, France), Ki-67 (clone MIB-1, mouse antibody diluted 1:100; DAKO Corp, Glostrup, Denmark), p27 protein (clone 1B4 mouse antibody diluted 1:20; Novocastra, Newcastle, England), Pgr− (clone PR88 mouse antibody diluted 1:50; Biogenex, San Ramon, Calif), and estrogen receptor (clone ER D3 mouse antibody diluted 1:50; Biogenex).

The sections were preincubated with super block (Ultra-Tek HRP, ScyTek Laboratories Inc, Logan, Utah) for 10 minutes to block nonspecific background staining and then incubated for 45 minutes at room temperature. The second layer was incubated in biotinylated prediluted antibody (Ultra-Tek HRP Anti Polyvalent) for 10 minutes. Finally, the sections were incubated with streptavidin peroxidase complex (Ultra-Tek HRP) for 10 minutes. Between incubations the sections were washed in phosphate-buffered solution (pH 7.00) for 3 minutes. The color was developed using 3,3′-diaminobenzidine (DAKO Corp) for 4 minutes. Sections were counterstained with Mayer hematoxylin.

**IMAGE ANALYSIS DETERMINATIONS**

The expression of p53, Mib-1, p27, Prg-r and estrogen receptor proteins was evaluated by the “Cires” workstation image analysis system (Zeiss, Jena, Germany), consisting of a conventional light microscope (Axioskope model; Zeiss) connected to a 3-CCD color video camera (KY-F55BE; JVC, Yokohama, Japan). The images were captured by a frame grabber (Kontron, Eching, Germany) and then analyzed. The frame grabber and the image analysis program, operating online with the camera, were hosted in a personal computer. During all measurement sessions, illumination was kept constant at a fixed value and the stray light effect reduced by Koehler’s illumination setting.

In each case, 20 randomized, nonoverlapping frames were evaluated at ×20 magnification, counting a total minimum of 600 cells and expressing the result as the percentage of positively labeled cells out of the total. Percentages over 5% of specifically nuclear-stained cells were considered positive. The degree of Prg-r-positive immunostaining of the nuclei was evaluated as labeling index (LI), indicating the percentage of nuclear area labeled by the antibody and expressed as a mean percentage of the nuclear-positive result; the results were also converted into a qualitative scale ranging from 0 to 3 and corresponding to LI intervals (score 0: LI<1%; score 1: 1%≤LI<10%; score 2: 10%≤LI<20%; score 3: LI≥20%).

**STATISTICAL ANALYSIS**

Statistical analysis was performed with SAS statistical software 6.12 release (SAS Institute Inc, Cary, NC). The χ² tests were used to compare variables between groups. We considered a P value less than .05 to be significant.

**RESULTS**

Overexpression of p53 was identified in 1 of the 2 cases of Schneiderian-type papilloma of the temporal bone and in 4 (67%) of the 6 control group cases. The expression of p53 in the 2 cases of temporal bone inverted papilloma was 43.75% and 4.92%. In the control group, the only case of association between inverted papilloma and squamous cell carcinoma (case 3) presented p53 expression of 73.58%. Mean expression of p53 in the control group without considering case 3 was 4.83%. Expression of p53 was limited at basal and parabasal layers in all the evaluated cases. In case 3 (inverted papilloma with squamous cell carcinoma), relatively diffuse p53 immunopositivity was observed in squamous cell carcinoma.
Mib-1 immunopositive cells were restricted to the basal epithelial cell layers. The expression of Mib-1 in the 2 cases of temporal bone inverted papilloma was 1.90% and 12.54%. Strongest Mib-1 positivity in control group was described in case 3 (inverted papilloma with squamous cell carcinoma) and in case 8.

In all considered cases of temporal bone and sinonasal Schneiderian-type papillomas, p27 immunoreactivity was identified throughout the epithelium other than the basal cells. The strongest positivity (82.45% and 70.53%) was determined in temporal bone inverted papilloma; the weakest, in the case of sinonasal inverted papilloma associated with squamous cell carcinoma (43.42%).

Expression of Prg-r was determined in 1 case of temporal bone inverted papilloma (case 1 [man]), with a labeling index score of 2, and in 2 cases of sinonasal inverted papilloma (case 3 [man] and case 5 [woman]), with labeling index scores of 2 and 3, respectively. All evaluated cases proved negative for estrogen receptor. The results of the immunohistochemical reactions carried out and statistical analysis are reported in the Table.

**COMMENT**

Schneiderian-type papillomas are benign epithelial tumors with a significant tendency to recur after surgery and to be associated with malignancy. Inverted papilloma constitutes between 0.5% and 4% of all nasal tumors. Inverted papilloma involving the temporal bone as a primary lesion or as an extension of a sinonasal papilloma is an extremely rare occurrence: to our knowledge, there have been only 15 reported cases in the literature.1-3,6-13

Recurrence rates for sinonasal Schneiderian-type papilloma have been reported to be 67% with limited surgery and 10% to 13% with an aggressive surgical approach.14-16 Despite the scarcity of cases, the recurrence rate seems to be higher in temporal bone inverted papilloma. Recurrence has been described in all cases treated by a limited approach with myringotomy and excision of the lesion or simple excision of the lesion. Nevertheless, recurrences have also been reported in 7 (54%) of the 13 cases undergoing more aggressive surgery ( tympanomastoidectomy, mastoidectomy, or subtotal temporal bone resection).

The association of sinonasal Schneiderian-type papilloma and squamous cell carcinoma varies from 1% to 13%.15 The incidence of malignancy associated with temporal bone inverted papilloma has been reported in the literature in 6 (40%) of 15 cases.

The importance of the p53 tumor suppressor gene in head and neck cancerogenesis processes has been demonstrated. The aim of recent studies has been to investigate the expression of p53 in sinonasal papillomas. Saegusa et al,17 Franzmann et al,18 and Mirza et al19 reported p53 expression in 0% (0 of 28), 0% (0 of 12), and 8% (2 of 25), respectively, of the considered cases of sinonasal inverted papilloma without associated carcinoma. Caruana et al13 and Mirza et al19 found p53 expression in 2 of 8 and in 1 of 2, respectively, cases of sinonasal inverted papilloma exhibiting evidence of dysplasia. Overexpression of p53 was demonstrated in 75% (3 of 4) and 81% (21 of 26) of the cases of sinonasal Schneiderian-type inverted papilloma with associated carcinoma reported by Caruana et al13 and Buckwald et al,20 respectively. To our knowledge, we present the first attempt to determine p53 expression in temporal bone inverted papilloma samples. Our case 1 specimen (middle ear Schneiderian-type papilloma) presented 43.75% positive nuclei.

p27 Is known to regulate the progression from G1- to S-phase–mediating cell cycle arrest. Loss of p27 expression has been correlated with increase of cell proliferation in cell tumors.17 In the present article, the weakest p27 immunopositivity was determined in the case of sinonasal inverted papilloma associated with squamous cell carcinoma. In both cases of temporal bone Schneiderian-type papilloma, p27 was highly expressed. The limited number of cases did not allow us to demonstrate an inverse correlation between p27 and Mib-1 expression for temporal bone and sinonasal inverted papillomas considered.

Sinonasal inverted papilloma more commonly occurs in men than in women, with an overall predominance ranging from 2.6:1 to 6:1.20 Reports in the literature on inverted papilloma of the temporal bone indicate a female-male ratio of 2:1. The hypothesis that the influence of sex steroid hormone receptors differs in sinonasal and temporal bone inverted papilloma should be considered.

There is a dearth of studies regarding sex hormone receptor expression in sinonasal inverted papilloma. Sivonen21 studied 14 cases of sinonasal inverted papilloma by dextran-coated charcoal assay for sex steroid hormone receptors, for which all the considered cases were negative. Lapco and Barnes,22 using an avidin-biotin-peroxidase staining technique, found no expression of estrogen receptor and Prg-r in the 17 analyzed samples, except for 1 case that presented weak positivity for Prg-r. Positive staining for Prg-r was described in 2 of the 6 control group cases of sinonasal inverted papillomas. The highest percentage of positive Prg-r staining was described in the case of sinonasal inverted papilloma with associated squamous cell carcinoma (Figure 1). None...
of our cases of sinonasal Schneiderian-type papilloma was positive for estrogen receptor.

To our knowledge, Seshul et al10 have reported the only case of temporal bone inverted papilloma that attempts to determine the expression of sex steroid hormone receptors. The specimen proved to be Prg-r positive and estrogen receptor negative. One of the 2 cases of temporal bone Schneiderian-type papilloma reported by us presented positivity for Prg-r (Figure 2). Two of 3 cases of inverted papilloma of temporal bone evaluated for the presence of Prg-r (1 in the present article and 1 by Seshul et al10) proved to be positive. Despite the scarcity of cases, the influence of Prg-r on temporal bone inverted papilloma growth should be considered. Hormonal receptors in other type of tumors have been successfully recognized as targets for hormonal therapy.

Although review of the pertinent literature seems to indicate that inverted papillomas of the temporal bone differ epidemiologically and pathologically from sinonasal inverted papillomas, our analysis of the expression of apoptosis-related proteins, markers of cell proliferation activity, and sex hormone receptors fails to demonstrate that they are different pathological entities.

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REFERENCES