p27^{kip1} Expression Distinguishes Papillary Hyperplasia in Graves' Disease from Papillary Thyroid Carcinoma

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In most cases, the histopathologic and cytologic distinction between Graves' disease and papillary thyroid carcinoma is relatively easy, but on occasion Graves' disease may simulate a thyroid papillary carcinoma. For example, papillary fronds with fibrovascular cores may be present in both Graves' disease and papillary carcinoma. p27^{kip1} (p27) is a cyclin-dependent kinase inhibitory protein that has been shown to be an independent prognostic factor in a variety of human tumors. Our previous studies of p27 expression in hyperplastic and neoplastic endocrine lesions showed that the level of p27 was quite different in these two conditions. To determine if this distinction could also be made between Graves' disease and papillary carcinoma, we analyzed expression of p27 and other cell cycle proteins in a series of cases of Graves' disease with papillary hyperplasia and a series of papillary thyroid carcinomas. Formalin-fixed paraffin-embedded tissues from 61 randomly selected patients with thyroid disease, including 29 cases of Graves' disease with papillary architectural features and 32 cases of papillary carcinoma, were analyzed for expression of p27, Ki-67, and DNA topoisomerase II α (topo II α) by immunostaining. The distribution of immunoreactivity was analyzed by quantifying the percentage of positive nuclei that was expressed as the labeling index (LI) plus or minus the standard error of the mean. The papillary hyperplasia of Graves' disease had a p27 LI of 68.2 ± 3.1 (range, 24 to 88), whereas papillary carcinomas had a LI of 25.6 ± 2.5 (range, 12 to 70) ($P < .0001$). No significant differences in Ki-67 or topo II α expression were identified between papillary hyperplasia in Graves' disease and papillary carcinoma. These results indicate that p27 protein expression is significantly higher in papil-

lary hyperplasia of Graves' disease compared to papillary carcinoma, which may be diagnostically useful in difficult cases.

KEY WORDS: Graves' disease, Ki-67, p27, Papillary carcinoma, Topoisomerase II α .

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Although most cases of papillary hyperplasia of Graves' disease can be differentiated from papillary carcinoma based on histologic and cytologic features, some cases of Graves' disease may simulate papillary carcinoma, especially in small biopsy specimens. Histologic features simulating malignancy include well-developed papillary fronds with fibrovascular cores, large vesicular nuclei, and extension outside the thyroid gland (1). Other histologic features, such as nuclear cytology, lack of stromal desmoplasia, and psammoma bodies, may help to differentiate papillary hyperplasia of Graves' from papillary carcinoma (1); however, the distinction between these entities may still, on occasion, be difficult. Thus, additional diagnostic tools that may assist in this distinction would be clinically useful.

Recent studies have shown that p27^{kip1} (p27) expression has diagnostic and prognostic significance in a variety of human cancers, including endocrine tumors (2-6). p27 is a cyclin-dependent kinase inhibitor protein that helps to regulate the transition from the G1 to the S phase of the cell cycle (7, 8). In endocrine tissues, p27 protein immunoreactivity is usually higher in hyperplastic endocrine lesions compared to endocrine neoplasms, especially in the parathyroid (9). In the thyroid, p27 expression has been shown to distinguish some benign from malignant thyroid neoplasms (2-4). Analysis of p27 expression has shown a higher percentage of cells immunostaining for p27 in normal thyroid compared to thyroid neoplasms (2). p27 may also have some prognostic significance in thyroid malignancies (10).

Ki-67 antigen is a marker of proliferation that is expressed in all phases of the cell cycle except G0 (11). Topoisomerase II α (topo II α) is also a proliferation marker (12–14) and functions to prevent nondisjunction and chromosome breakage in mitosis (15, 16). Topo II α has been used recently to assess proliferative activity in neoplasms (12–14). Proliferative activity has shown some utility in separating some benign from malignant thyroid neoplasms, but overlap in proliferative indices between these entities exists (3, 17, 18). Thus, a combination of analyses for inhibitors of cell cycle proliferation such as p27 and proliferation markers such as Ki-67 and topo II α may provide more insight into the behavior of tumors than the use of single markers.

The goals of this study are to evaluate the expression of p27, Ki-67, and topo II α in papillary hyperplasia of Graves' disease and papillary carcinoma of the thyroid and the usefulness of these immunohistochemical markers in distinguishing between these diseases in unusual cases.

MATERIALS AND METHODS

Cases and Tissues

Formalin-fixed paraffin-embedded tissues from 61 randomly selected patients who underwent thy-

roid surgery at the Mayo Clinic, Rochester, Minnesota between 1987 and 1995 were used. These included 29 cases of Graves' disease with papillary architectural features and 32 cases of papillary carcinoma. Hematoxylin- and eosin-stained sections were reviewed independently by three of the authors (LAE, OMY, RVL) for verification of diagnoses (Fig. 1). Clinical history and follow-up information were obtained by chart review.

Immunohistochemical Analysis

Formalin-fixed, paraffin-embedded tissue sections were cut at 5 μ m and treated with 0.1 mol/L citrate, pH 6.0, in an 800-W microwave oven for 15 min for antigen retrieval before immunostaining. The sections were then incubated with the primary antibodies overnight at room temperature. Antibodies to anti-p27 (Transduction Laboratory, Lexington, KY) were used at a 1:1000 dilution. Immunostaining was done with the elite avidin-biotin-peroxidase kit (Vector Laboratories, Burlingame, CA), according to the manufacturer's specifications. Slides were counterstained with hematoxylin for 1 second. All cases were also immunostained for Ki-67 with antibody MIB-1 (AMAC, Westbrooke, ME) at a 1:50 dilution and for DNA topoisomerase II

FIGURE 1. Histologic examples of thyroid tissues analyzed and expression of p27. A, Graves' disease with papillary formations. B, papillary carcinoma showing prominent papillae. C, papillary structures in Graves' disease with many nuclei staining strongly for p27 and a LI of 84%. D, papillary carcinoma with a few nuclei staining for p27 and a LI of 21%.

α with an anti-topo II α antibody (DAKO, Carpinteria, CA) at a 1:200 dilution. Tonsil tissues were used as positive controls for p27, Ki-67, and topo II α . Normal mouse serum was substituted for the primary antibodies as a negative control.

Quantitative and Statistical Analysis

The distribution of immunoreactivity was analyzed by quantifying the percentage of positive nuclei in each case without knowledge of the diagnosis or outcome. Only areas with papillary features were analyzed in the Graves' disease cases. The percentages of cells expressing p27, Ki-67, and topo II α were determined by counting 1000 cells per slide with the aid of an ocular 10 $\times$ 10-mm grid (LJ). p27 immunoreactive cells were randomly counted over a minimum of 20 high-power fields. Ki-67 positive cells and topo II α positive cells were counted in areas of highest density staining over a minimum of 10 high-power fields, because of the low percentage of cells staining positive for Ki-67 and topo II α in the benign tissues. The percentage of immunoreactive cells in each case was expressed as the labeling index (LI). When 10% of the cases were blindly recounted for p27, Ki-67, and topo II α , the labeling indices did not vary more than 10% from the original count. p27, Ki-67, and topo II α labeling indices were expressed as the mean plus or minus the standard error of the mean. Comparisons between papillary hyperplasias of Graves' disease and papillary thyroid carcinomas were made using χ^2 tests and Wilcoxon Rank Sum tests.

RESULTS

The clinical features for both groups of patients are summarized in Table 1. Patients with Graves' disease were significantly younger than those with papillary carcinoma, which probably reflects the use of surgical treatment rather than radiotherapy in younger patients with Graves' disease. None of the patients with Graves' disease developed metastatic disease or died of disease, whereas 17 of the 32 patients with papillary carcinoma had metastases in neck lymph nodes, and two died of disease.

The histologic features of the lesions are illustrated in Figure 1. Cases of papillary hyperplasia in Graves' disease showed well-developed papillary structures, some of which contained fibrovascular cores. Occasional large vesicular nuclei were iden-

tified, and some cases showed extension into skeletal muscle. Papillary carcinomas were of the usual type, showing prominent papillae with fibrovascular cores and characteristic cytologic features.

Immunohistochemical staining revealed nuclear localization of p27, Ki-67, and topo II α in both nonneoplastic and neoplastic thyroid tissues (Fig. 1). Analysis of p27 expression showed a higher percentage of cells in papillary hyperplasia of Graves' disease immunostaining for p27 compared to cases of papillary carcinoma (Table 2). The papillary hyperplasia of Graves' disease had a p27 LI of 68.2 ± 3.1 (range, 24 to 88), while papillary carcinomas had a LI of 25.6 ± 2.5 (range, 12 to 70) ($P < .0001$) (Fig. 2). Thirty of 32 (94%) papillary carcinomas had a p27 labeling index less than 47, whereas 26 of 29 (90%) of cases of papillary hyperplasia of Graves' disease had a p27 LI greater than 47. Among the papillary carcinomas, p27 did not discriminate between those with metastases from those without metastases or among patients who died of disease, although this may be related to low sample numbers in these groups.

Papillary carcinomas had a higher Ki-67 LI (4.8 ± 0.7 ; range, 1.4 to 22) than papillary hyperplasia of Graves' disease (3.7 ± 0.4 ; range, 0.9 to 9.4), although the difference was not statistically significant. There was no difference in the topo II α LI in papillary carcinomas (4.7 ± 0.6 ; range, 1 to 16) compared to Graves' disease (4.2 ± 0.3 ; range, 1.1 to 8.6).

DISCUSSION

In the present study, p27 expression showed striking differences between papillary hyperplasia of Graves' disease and papillary carcinomas. As a group, the cases of papillary hyperplasia of Graves' disease had a greater than twofold higher p27 LI than the papillary carcinomas, although some overlap occurred between the two groups. The biologic significance of reduced p27 expression in carcinomas compared to hyperplasia is uncertain. Since hyperplastic tissues show increased proliferative activities (but usually have fewer genetic alterations than true neoplasms), the development of genomic instability with neoplasms is probably associated with decreased p27 expression (19). The practical implications of this study is that p27 immunostaining may be a useful adjunct in distinguishing un-

TABLE 1. Clinical and Pathologic Features of Cases of Graves' Disease and Papillary Carcinoma

Diagnosis	N	Mean Age (years)	Female/Male	Follow-up (years)	Metastases	Died of Disease
Graves' disease	29	24.3	25/4	4.8	0	0
Papillary carcinoma	32	53.2	24/8	7.5	17	2

TABLE 2. Distribution of p27, Ki-67 and Topoisomerase II α in Graves' Disease and Papillary Carcinoma

	N	Labeling Index		
		p27	Ki-67	Topo II α
Graves' disease	29	68.2 $\pm$ 3.1 (range, 24 to 88)	3.7 $\pm$ 0.4 (range, 0.9 to 9.4)	4.2 $\pm$ 0.3 (range, 1.1 to 8.6)
Papillary carcinoma	32	25.6 $\pm$ 2.5 ^a (range, 12 to 70)	4.8 $\pm$ 0.7 (range, 1.4 to 22)	4.7 $\pm$ 0.6 (range, 1 to 16)

^a $P < .0001$.

FIGURE 2. The distribution of p27 LIs and the mean LI for both the cases of Graves' disease and the cases of papillary carcinoma. Papillary hyperplasia in Graves' disease had more than twofold higher mean p27 LI than papillary carcinomas.

usual cases showing papillary hyperplasia in Graves' disease from papillary carcinomas.

Recent studies have shown that p27 expression has diagnostic utility in a variety of endocrine tumors. In the pituitary, p27 expression is different between normal and neoplastic pituitary (20), and between functioning from nonfunctioning pituitary tumors (21). Analysis of p27 expression in parathyroid tissues showed significant differences between normal parathyroid glands, hyperplasia, adenomas, and carcinomas (9). Normal parathyroid glands had the highest levels of p27 expression, followed by hyperplasia, adenomas, and carcinomas (9). p27 has been shown to differentiate benign from malignant adrenal medullary and adrenal cortical tissues (2, 22).

In the thyroid gland, normal thyroid tissues and multinodular goiters have shown higher p27 labeling indices than thyroid neoplasms (2, 3). Among thyroid neoplasms, follicular adenomas have demonstrated higher p27 labeling indices than follicular carcinomas (2–4). Analysis of p27 expression in follicular adenomas and cases of follicular variant of papillary carcinoma has shown significantly more nuclei staining for p27 in the follicular adenoma group than in the follicular variant of papillary carcinoma group (23). Thus, the results of our study showing the higher p27 labeling index in the cases of papillary hyperplasia of Graves' disease compared to papillary carcinoma are consistent with

previous reports demonstrating increased p27 expression in benign compared to malignant thyroid tissues.

A recent study reported that thyroid malignancies expressing p27 show an uncommon cytoplasmic localization of p27 protein in association with cyclin D3 expression and high Cdk2 activity, as compared to the nuclear localization of p27 in benign thyroid tissues (24). Cyclin D3 appeared to induce the formation of p27/cyclinD3/Cdk complexes in the cytoplasm, thus decreasing the amount of p27 available to interact with and thereby inhibit Cdk2 in the nucleus (24). No significant differences were identified in the immunostaining pattern of localization of p27 between the papillary carcinomas and the papillary hyperplasia of Graves' disease in our study, but more investigation is needed into this putative novel mechanism of overcoming the inhibition of p27 in thyroid cells.

Recent studies have suggested that the proliferative activity may have some utility in separating some benign from malignant thyroid neoplasms (3, 17, 18). Higher rates of proliferation, as measured by the MIB-1 antibody to Ki-67, have been reported in some malignant thyroid tumors as compared to their benign counterparts (3). In our study, papillary carcinomas tended to have a higher Ki-67 LI than papillary hyperplasia of Graves' disease, although the results did not reach statistical significance.

Topo II α is associated with cell proliferation (12–14) and functions in mitoses to prevent non-disjunction and chromosome breakage (15, 16). Recent studies have indicated that topo II α may have diagnostic or prognostic significance in a variety of tumors including gliomas (25), salivary gland adenoid cystic carcinomas (26), esophageal squamous cell carcinomas (27), gastric and colonic carcinomas (28), adrenal carcinomas (29), and thyroid carcinomas (30). Among thyroid neoplasms, topo II α is more frequently expressed in tumors with more aggressive clinical behavior such as anaplastic carcinomas, tall cell variant of papillary carcinomas, follicular and Hurthle cell carcinomas, and medullary carcinomas (30). The papillary carcinomas in the present study were of the usual type, and they did not show significantly higher levels of topo II α

expression than papillary hyperplasia of Graves' disease.

A relationship has been suggested between Graves' disease and papillary carcinoma of the thyroid (31, 32). Approximately 4% of patients with papillary carcinoma have Graves' disease (1), whereas the incidence of Graves' disease in the general population is approximately 2.7% in women and is approximately only one tenth as frequent in men (33). Additionally, patients with Graves' disease have reportedly had more aggressive thyroid carcinomas than euthyroid patients have had (34). The association of Graves' disease with thyroid carcinoma has raised the suggestion that thyroid-stimulating antibodies causing hyperplasia in Graves' disease may have a role in thyroid tumorigenesis (35). Hyperplastic tissues usually have increased proliferation compared to normal tissues. Interestingly, the cases of Graves' disease in our study had proliferative rates similar to those of the papillary carcinomas. What appeared to separate the two groups was not proliferative activity, but inhibition of proliferative activity by the growth inhibitor p27. The papillary carcinomas expressed less of the cell cycle inhibitor protein p27 than the hyperplastic tissues. One may speculate that although hyperplastic tissues may show increased proliferative rates, it is perhaps the genetic alterations that are probably associated with decreased p27 expression that lead to neoplasia.

In summary, analysis of the cell cycle protein p27 in cases of papillary hyperplasia of Graves' disease and papillary carcinomas demonstrated that p27 expression was significantly higher in Graves' disease within areas of papillary hyperplasia. These results indicate that p27 may be useful in distinguishing between benign and malignant papillary proliferations in the thyroid gland.

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Book Review

Wilkins BS, Wright DH: *Illustrated Pathology of the Spleen*, 181 pp, Cambridge, Cambridge University Press, 2000 (\$100.00).

For a hundred dollars, you could take a short course on the pathology of the spleen and get CME credits, or, for the same amount of money, you could purchase this book, read it in the same time as allotted for the short course, and keep it on your shelf forever. Being a bibliophile and an inveterate adherent of Churchill's dictum (I love to learn but I hate to be taught!), I would always choose the latter, but then, of course, *de gustibus non est disputandum*.

This nice book is an excellent introductory text and is ideally suited for residents learning the basics of splenic pathology. Simultaneously, it could serve in lieu of a refresher course for more seasoned pathologists. It begins with a review of normal anatomy and histology, and then covers all the main topics. I would dare to say

that 95% of all lesions that a moderately busy surgical pathologist will ever encounter in his or her lifetime are covered. I was glad to see that in England, like in our Department, most splenectomies are preceded by traumatic injury. Lymphomas, hematologic diseases affecting the spleen, and other causes of splenomegaly are well covered and illustrated with color photographs. Most figures are very good, except for a few gross specimens photographed on a dark background, which unfortunately are not of best quality. The text is succinct. The final chapter dealing with the key points of differential diagnosis will be useful for both novices and more experienced pathologists. The references are reasonably up-to-date and well chosen.

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