CDX2 Expression in Some Variants of Papillary Thyroid Carcinoma

To the Editor

The publication of the article of Enriquez et al1 coincided with the final steps of our study on the expression of CDX2 in normal and neoplastic follicular-derived cells of the human thyroid gland. Enriquez et al1 evaluated CDX2 expression in 11 cases of columnar cell variant (CCV) of papillary thyroid carcinoma (PTC) and in thyroid tissue microarrays (TMAs) composed of normal tissue, 38 cases of benign lesions (Hashimoto disease, Graves disease, lymphocytic thyroiditis, multinodular goiter, and papillary hyperplasia), and 33 samples of neoplastic conditions (8 follicular carcinomas, 9 conventional PTC, 2 tall cell variants of PTC, 2 poorly differentiated carcinomas, 6 anaplastic carcinomas, 4 medullary carcinomas, 4 Hürthle cell adenomas, and 2 follicular adenomas). Enriquez et al1 identified CDX2 expression in 6 (55%) of the 11 cases of CCV of PTC, but not in any other benign or malignant thyroid lesions. They only found focal or diffuse CDX2 immunoreactivity in tumors with pure columnar cell morphologic features (6/9 cases) but not in 2 cases with only focal columnar cell/mixed features. They concluded that CDX2 is selectively expressed in CCV of PTC and can be used to distinguish it from other variants of PTC with overlapping morphologic features.

We used a TMA composed of 10% formalin-fixed, paraffin-embedded thyroid tissue samples: 50 follicular adenomas, 75 PTCs (35 classic subtype, 27 follicular variant, 4 solid variant, 2 tall cell variant, 2 diffuse sclerosing variant, 4 cribriform morular variant [CMV; 2 sporadic and 2 associated with familial adenomatous polyposis]), 48 follicular carcinomas (34 minimally invasive, 14 widely invasive), 15 normal thyroid tissue. The TMA was built using a tissue arrayer device (Beecher Instruments, Sun Prairie, WI), including duplicate 1.6-mm cores of each type of tissue per case. All 216 samples and additional controls were collected from files of the Pathology Department of Clinical University Hospital of Santiago de Compostela, Spain. Clinical data were collected from the pathology reports and clinical files. The local ethics and scientific committees approved this study. H&E slides were simultaneously reviewed by 2 pathologists (J.C.-T. and L.A.-L.) and the tumors classified using the World Health Organization criteria2 with the Turin proposal for poorly differentiated carcinomas3; cases with doubtful PTC features were excluded. The immunohistochemical study was performed on 4-μm-thick paraffin sections of the TMA blocks using a peroxidase-conjugated dextran-labeled polymer (EnVision FLEX, Dako, Glostrup, Denmark) to avoid misinterpreting endogenous biotin or biotin-like activity in cell cytoplasm or in nuclei as positive staining, with an automated link platform (Autostainer Link 48, Dako). The primary antibodies were used as follows: CDX2 (clone DAK-CDX2, ready-to-use, 30 minutes, high pH, Dako), thyroid transcription factor-1 (TTF-1) (clone 8G7G3/1, ready-to-use, 30 minutes, low pH, Dako), thyroglobulin (polyclonal, ready-to-use, 20 minutes, low pH, Dako), and calcitonin (polyclonal, ready-to-use, 20 minutes, high pH, Dako). In the interpretation of positive immunoreactivity against anti-CDX2, only unequivocal nuclear staining was considered positive.

The main clinical data of patients and the immunostaining results are listed in Table 1. All cases were negative for calcitonin, and all samples, except for the undifferentiated carcinomas, were positive for TTF-1 and Image 1E and Image 1F. Thyroglobulin expression was noted in all adenomas, well-differentiated carcinomas (excluding the 4 cases of CMV of PTC), and poorly differentiated carcinomas, but no reactivity was found in undifferentiated carcinomas. Interestingly, strong and diffuse nuclear CDX2 was only detected in all tumor cells of 1 case of classic PTC Image 1A and Image 1B and in the morular foci of the 4 cases of CMV of PTC Image 1C and Image 1D. All H&E slides from the only CDX2-positive classic PTC were re-revised, but columnar cell features were not found, and CDX2 positivity was confirmed in additional paraffin blocks of this case. This PTC occurred in a 40-year-old woman (T2N0M0) treated...
The apparently incongruent CDX2 expression in some PTCs fits very well with the intestinal-like (“noncommitted differentiation”) phenotype that our group proposed for PTCs many years ago. Along with the papillary (“villous”) architecture, mucin production, high-molecular-weight keratin expression, and infiltrative growth pattern with lymph node metastasis, CDX2 expression additionally supports our hypothesis of an intestinal line of differentiation for PTCs in contrast to an endocrine-like line for follicular carcinomas and a neuroendocrine-like line for medullary carcinomas.

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José Cameselle-Teijeiro, MD, PhD
Lara Alberte-Lista, MD
Diego Peteiro-González, MD
Ihab Abdulkader-Nallib, MD, PhD
Rosa Reyes-Santías, MD, PhD
Department of Pathology
Clinical University Hospital
Health Research Institute of Santiago de Compostela (IDIS)
University of Santiago de Compostela
Santiago de Compostela, Spain

Paula Soares, PhD
Manuel Sobrinho-Simões, MD, PhD
Pathology Department
Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP)
Hospital de São João
Porto, Portugal

Table 1
CDX2, TTF-1, Thyroglobulin, and Calcitonin Expression in Normal and Neoplastic Follicular Cells of the Thyroid

<table>
<thead>
<tr>
<th>Type of Sample</th>
<th>No.</th>
<th>Mean (Range) Age, y</th>
<th>Female Sex, No. (%)</th>
<th>CDX2</th>
<th>TTF-1</th>
<th>TG</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal thyroid</td>
<td>15</td>
<td>59.4 (25-81)</td>
<td>6 (40)</td>
<td>0</td>
<td>15</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>50</td>
<td>46.02 (14-82)</td>
<td>42 (84)</td>
<td>0</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>75</td>
<td>47.64 (11-83)</td>
<td>56 (74.6)</td>
<td>5</td>
<td>75</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>48</td>
<td>50.4 (21-78)</td>
<td>34 (70.8)</td>
<td>0</td>
<td>48</td>
<td>48</td>
<td>0</td>
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<tr>
<td>Poorly differentiated carcinoma</td>
<td>15</td>
<td>65.7 (37-83)</td>
<td>11 (73.3)</td>
<td>0</td>
<td>15</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>13</td>
<td>66.2 (41-82)</td>
<td>8 (61.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TTF-1, thyroid transcription factor-1; TG, thyroglobulin; CT, calcitonin.


References

with total thyroidectomy, radioactive iodine (100 mCi), and thyroid-stimulating hormone suppression, and the patient is well with no evidence of disease 111 months after surgery.

We agree with Enriquez et al that CDX2 expression is detected in some PTCs; however, because we found strong CDX2 expression in 1 case of classic PTC, we cannot confirm that CDX2 is exclusively expressed in the CCV of PTC. The diagnosis of CCV of PTC should be made on the basis of morphologic features. Because CDX2 expression is limited to the morular foci in the CMV of PTC and because CCV of PTC shows significant morphologic overlap with the CMV of PTC (pseudostratified columnar cells, coexistence of solid areas, and elongated empty follicles resembling tubular glands), we believe that CDX2 may play a role in cell differentiation in these 2 types of PTC. Our results show, on the other hand, that CDX2 expression has limited usefulness as a marker for distinguishing CCV of PTC from other PTC variants.

The aberrant nuclear CDX2 expression in morular structures was previously reported in different organs. CDX2, an intestine-specific homeobox gene transcription factor, is not only expressed in normal intestinal mucosa but also in colonic adenocarcinoma and nongastrointestinal tumors. Morular structures sharing a selective expression of CDX2 and CD10 have a very low proliferative index and characterize the so-called “family tumors containing morules with cells displaying biotin-rich optically clear nuclei,” but the biological meaning of these morphologic structures remains unknown.

The apparently incongruent CDX2 expression in some PTCs fits very well with the intestinal-like (“noncommitted differentiation”) phenotype that our group proposed for PTCs many years ago. Along with the papillary (“villous”) architecture, mucin production, high-molecular-weight keratin expression, and infiltrative growth pattern with lymph node metastasis, CDX2 expression additionally supports our hypothesis of an intestinal line of differentiation for PTCs in contrast to an endocrine-like line for follicular carcinomas and a neuroendocrine-like line for medullary carcinomas.
Classic papillary thyroid carcinoma (A) showing diffuse nuclear expression of CDX2 (C) and thyroid transcription factor-1 (E). Cribriform morular variant of papillary thyroid carcinoma (B) showing nuclear expression of CDX2 in morular foci (D) and diffuse nuclear positivity for thyroid transcription factor-1 (F) (A-F, ×400).
Correspondence

The Authors’ Reply

We thank Dr Cameselle-Teijeiro and colleagues for their interest in our article on CDX2 expression in the columnar cell variant (CCV) of papillary thyroid carcinoma (PTC). We are happy to know that they share an interest in CDX2 expression in thyroid cancer and read their finding of CDX2 expression in a few classic PTCs with great interest.

To date we have seen CDX2 expression only in tumors with CCV histology, but similar to their findings, we have also observed CDX2 expression in tumors with cribriform morular variant (CMV) histology (unpublished data). Similar to the experience of Dr Cameselle-Teijeiro et al, we have also observed that the cytology of CCV and CMV is similar to that seen in colonic adenomas; this makes the CDX2 expression even more interesting. However, we have not observed other gastrointestinal immunophenotypes, most notably cytokeratin 20 expression, in any thyroid tumors with CDX2 expression.

We applaud the effort by Cameselle-Teijeiro et al to evaluate CDX2 in a larger series of PTCs; it enhances our understanding of CDX2 expression in thyroid carcinoma of noncolumnar morphology. Their finding of 1 (1.4%) of 71 PTCs (excluding the 4 CMV) does not statistically contraindicate findings of our prior study, which found no CDX2 expression in 11 PTCs. Rather, it confirms our prior finding that CDX2 is not normally expressed in thyroid cancers of noncolumnar type. It would be interesting to know whether the whole section of the CDX2-positive classic PTC has been evaluated to assume the finding of “strong and diffuse (all tumor cells)” CDX2 reactivity in this case, as shown on the thyroid tissue microarray sample.

In principle, all histologic diagnosis should be made based on morphologic evaluation rather than immunohistochemical staining only. We agree that criteria to differentiate CCV from classic PTC are purely based on morphologic features rather than immunohistochemical findings. Even in our prior study, some of the CCVs were CDX2 negative but were still classified as CCV. The same principle should apply to a morphologic classic PTC with CDX2 reactivity. However, the strikingly overwhelming difference in CDX2 expression between CCV (at least 55%) and classic PTCs (0%-1.4%) does indicate to pathologists that CDX2 has a useful ancillary role when columnar morphology is questionable. We believe the more important intent of our study is to report the high incidence of CDX2 expression in CCV thyroid cancer and caution pathologists that CDX2-positive tumor without papillary or follicular features could be a thyroid primary, and that a CDX2-positive tumor with columnar morphology in the thyroid does not always have a gastrointestinal primary origin.

Mirian Enriquez, MD
Zubair Baloch, MD, PhD
Kathleen Montone, MD
Paul Zhang, MD
Virginia A. LiVolsi, MD
University of Pennsylvania Medical Center
Philadelphia, PA

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