Columnar Cell Carcinoma of the Thyroid: Report of Three Additional Cases

JORGE A. FERREIRO, MD, IAN D. HAY, MB, PhD, AND RICARDO V. LLOYD, MD

Columnar cell carcinoma is a recently described variant of thyroid carcinoma that has been associated with an aggressive clinical course. The authors describe three new cases of columnar cell carcinoma occurring in two women and one man aged 62, 46, and 46 years, respectively. The tumors ranged in size from 1 to 7.5 cm, and two of the tumors were associated with distant metastases. One patient died of disease 39 months after presentation. Another patient is alive with distant metastases 27 months after diagnosis. One patient appears to be a long-term survivor with no evidence of metastasis after follow-up of 22 years. This patient had a tumor that was small (1 cm) and encapsulated. DNA ploidy analysis in two tumors showed diploid DNA content, and there was no elevated S phase. All tumors were positive for thyroglobulin and negative for calcitonin and carcinoembryonic antigen (CEA). These findings support the original observation that columnar cell variants of papillary thyroid carcinoma are usually aggressive neoplasms. There does not appear to be an increased incidence of DNA aneuploidy in columnar cell carcinomas to account for their more aggressive behavior. These tumors occur over a wide age range, can metastasize widely, and are not usually responsive to radioactive iodine or chemotherapy. Hum Pathol 27:1156–1160. Copyright © 1996 by W.B. Saunders Company

Key words: columnar cell carcinoma, thyroid gland, papillary carcinoma.

Abbreviations: CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; HPF, high power field; H&E, hematoxylin-eosin.

Several variants of papillary carcinoma of the thyroid gland have been described, some of which have been thought to be associated with a worsening prognosis including the tall cell and diffuse sclerosing variants. Columnar cell carcinoma of the thyroid gland was described in 1986 by Evans. He reported two patients with thyroid tumors characterized by columnar epithelium and marked nuclear stratification that were associated with an aggressive clinical course. Since then, five other cases have been well documented in the literature. An additional nine cases have been reported in abstract form. Although most cases of columnar cell carcinomas have had a poor prognosis, some, particularly encapsulated tumors, have had an uneventful course, although the follow-up periods have been short. The authors describe three additional cases of columnar cell carcinoma of the thyroid gland, one of which appears to be a long-term survivor.

MATERIALS AND METHODS

All papillary carcinomas (1,500) in the Mayo Clinic files were examined microscopically to identify histological subtype. Three examples of columnar cell carcinoma were identified (0.2% incidence). For these neoplasms to be classified as a columnar cell carcinoma, more than 50% of the tumor was required to be composed of characteristic columnar cell areas with marked pseudostratification. Tissues were processed in the usual manner with fixation in 10% neutral buffered formalin, dehydration, and paraffin embedding. Sections were cut and stained with hematoxylin-eosin. In addition, immunohistochemistry was performed on paraffin-embedded tissues by a modified avidin-biotin conjugate procedure. All three tumors were examined with anticalcitonin (Dako, Carpinteria, CA 1:20 dilution), antithyroglobulin (Dako, 1:1,000 dilution), anti-S-100 (Hospital for Sick Children, 1:2000 dilution), anti-keratin 34/3E12 (DAKO, 1:20 dilution; polyclonal CEA, DAKO, 1:800 dilution), anticytokeratin (Dakh, 1:1,000 dilution), antibody to epithelial membrane antigen (EMA) (Dako, 1:100 dilution), and antikeratin 34/IE12 (DAKO, 1:10 dilution). Clinical information was obtained by review of the patients' charts.

Flow cytometry was performed on paraffin-embedded tissue in three cases. Analysis of DNA ploidy and percentage S phase (%S) were examined using either a FACS analyzer or FACScan flow cytometer (Becton Dickinson, San Jose, CA) as described by Witzig et al. Tissue preparation included cutting three 50-μm sections from the paraffin blocks and preparing a nuclear suspension via the modified Hedley technique. Nuclei were stained with propidium iodide and sonicated. Channel selection, the use of control material, and rejection of data have been previously described. The DNA histogram was analyzed for DNA ploidy, %S, and %G2M by use of the Modfit Software program (Verity Software Inc., Topsham, ME). A rectangular model of this program was used to determine these percentages. The histogram analysis, the debris subtraction method (single-cut), and the modeling of the cell cycle are detailed by Witzig et al.

CASE REPORTS

Case 1

A 62-year-old woman developed paraplegia resulting from a mass in the 10th thoracic region of the spinal cord. A decompression laminectomy was performed, and the pathology report was "papillary carcinoma, origin uncertain." Subsequently, a mass was noted in the right lobe of the thyroid. At surgery, a large, hard mass was noted that appeared to extend grossly beyond the confines of the thyroid. A total thyroidectomy was performed, but no lymph node dissection was done because no enlarged lymph nodes were present. The patient received radioactive iodine. Two years later, the
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Patient developed local recurrence of her tumor in the neck and later developed numerous lung metastases. She died of metastatic disease 39 months after initial diagnosis. No autopsy was performed. A 6 × 4.5 × 3 cm tumor was present in the right thyroid and showed extensive extrathyroidal invasion. The tumor was composed of papillary structures and glands lined by cells that showed marked pseudostratification (Fig 1). The nuclei were round to oval, with some clearing and nuclear grooving. Cytoplasmic invaginations were not identified. The cytoplasm was sparse and clear to amphophilic. The mitotic rate was 1 to 2 mitoses per 10 high power fields (HPFs). No psammoma bodies were seen. The vertebral body metastasis showed a similar histological appearance.

Case 2
A 46-year-old man had a firm nodule detected in the right thyroid gland during routine physical examination. A fine-needle aspiration of this mass was reported as "neoplastic cells, uncertain type." At time of surgery, the right lobe of the thyroid gland was replaced by a nodular, firm, locally invasive carcinoma. A near-total thyroidectomy and lymph node dissection was performed. Thirteen of 15 lymph nodes were involved by metastatic carcinoma. Postoperatively, the patient has developed pulmonary, hilar lymph node, bone, and subcutaneous/dermal metastases that have been treated with radioactive iodine. He is alive 27 months after diagnosis. The right thyroid gland was replaced by a firm, gray mass, 7.5 × 4.5 × 3 cm. Extrathyroidal extension was present. The tumor was composed predominantly of columnar cell carcinoma with both papillary structures and follicles. In addition, some areas of follicular variant of papillary carcinoma were present adjacent to columnar cell carcinoma (Fig 2). In addition, a rare psammoma body was present in areas of columnar cell carcinoma (Fig 2, inset). The mitotic rate was 2 mitoses per 10 HPFs. Although the nuclei of the columnar cell carcinoma areas were oval with minimal grooving, nuclear clearing, and rare cytoplasmic invaginations into the nucleus were interspersed.

Case 3
A 46-year-old woman was found to have a nodule in the right lobe of the thyroid on routine clinical examination. At the time of surgery, a discrete nodule was noted in the right lobe, and a near-total thyroidectomy was performed. Because no lymphadenopathy was noted, a neck dissection was not performed. The patient was not administered radioactive iodine. She has had follow-up of 22 years, with no evidence of recurrence or metastasis. A 1-cm-diameter, well-circumscribed mass was present in the right thyroid. The histological appearance was similar to case no. 1 (Fig 3). The nuclei showed some degree of grooving but no prominent clearing. The mitotic rate was low (0 to 1 per 10 HPFs). Colloid in the center of the glands was largely absent. No psammoma bodies were observed.

Immunohistochemistry showed strong positive staining with antithyroglobulin in case nos. 2 and 3, and weak positive staining in case no. 1. One case stains positive with antikeratin 34βE12, and one stained focally positive with anti-S-100.
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### TABLE 1. Columnar Cell Carcinoma of the Thyroid Gland: Clinico-pathologic Features of 10 Reported Cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author/Reference No.</th>
<th>Age (yr)/Sex</th>
<th>Size (cm)</th>
<th>Extra-thyroidal Extension</th>
<th>Encapsulated</th>
<th>Lymph Node Metastases</th>
<th>Distant Metastases</th>
<th>Surgical</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Current case</td>
<td>62/F</td>
<td>6 × 4.5 × 3</td>
<td>Y</td>
<td>N</td>
<td>Not done</td>
<td>None</td>
<td>Total thyroidectomy</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>Current case</td>
<td>46/M</td>
<td>7.5 × 4.5 × 3</td>
<td>Y</td>
<td>N</td>
<td>Positive</td>
<td>None</td>
<td>Near total thyroidectomy and neck dissection</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>Current case</td>
<td>46/F</td>
<td>1.0</td>
<td>N</td>
<td>Y</td>
<td>Not done</td>
<td>None</td>
<td>Near total thyroidectomy</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>Evans</td>
<td>34/M</td>
<td>6 × 4 × 4</td>
<td>Y</td>
<td>N</td>
<td>Positive</td>
<td>Chest wall, vertebrae</td>
<td>Lobectomy and isthmectomy</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>Evans</td>
<td>47/M</td>
<td>10 × 6 × 2</td>
<td>Y</td>
<td>N</td>
<td>Negative</td>
<td>Mediastinum, lung, adrenal</td>
<td>Subtotal thyroidectomy and neck dissection</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>Hui et al</td>
<td>21/F</td>
<td>1.5</td>
<td>N</td>
<td>Y</td>
<td>None</td>
<td>None</td>
<td>Total thyroidectomy</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>Sobrinho-Simoes et al</td>
<td>60/M</td>
<td>8 × 5 × 9.5</td>
<td>Y</td>
<td>N</td>
<td>None</td>
<td>Supraclavicular region, brain, lung, soft tissues</td>
<td>Hemithyroidectomy and neck dissection</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>Mizukami et al</td>
<td>63/F</td>
<td>7 × 5 × 3</td>
<td>Y</td>
<td>N</td>
<td>Positive</td>
<td>Lung</td>
<td>Total thyroidectomy plus radical neck dissection</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>Berends and Mouthaan</td>
<td>46/M</td>
<td>10 × 5.5 × 4</td>
<td>Y</td>
<td>N</td>
<td>Positive</td>
<td>Lung</td>
<td>Total thyroidectomy plus lymph node removal</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>10</td>
<td>Gaertner et al</td>
<td>29/F</td>
<td>2.0 and 4.0</td>
<td>Y</td>
<td>N</td>
<td>Positive</td>
<td>Lung, vertebra, mediastinum</td>
<td>Total thyroidectomy plus bilateral neck dissection</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Abbreviations: Y, yes; N, no; RAI, radioactive iodine; RT, radiation therapy; Chemo, chemotherapy; DOD, dead of disease; AND, alive, no disease; AWD, alive, with disease.

Other stains (calcitonin, epithelial membrane antigen, and monoclonal and polyclonal CEA) were negative.

Two neoplasms (case nos. 2 and 3) showed diploid DNA content, and the S-phase and G2M fractions were not elevated. In one of the columnar cell carcinomas (case no. 1), an interpretable DNA histogram could not be obtained.

### DISCUSSION

Columnar cell carcinoma is an important variant of thyroid carcinoma to recognize because of its more aggressive clinical course and possible confusion with metastatic carcinoma. A total of 10 cases of columnar cell carcinoma have been well documented in the literature including the cases reported herein (Table 1). The more aggressive clinical course of columnar cell carcinoma appears to be well documented because 7 of 8 patients with follow-up longer than 1 year have died of their disease. The one long term survivor had a tumor that was small (1 cm) and encapsulated. One other case of columnar cell carcinoma that was small (1.5 cm) and encapsulated has been reported (case 6; Table 1), but no significant follow-up was available for that patient. Of the 9 cases reported in abstract form, 8 were encapsulated or showed only limited invasion. Most of these patients are alive at last follow-up. Small, encapsulated tumors with the histology of columnar cell carcinoma may not necessarily behave in an aggressive fashion.

A variety of prognostic variables is important in determining patient outcome in papillary carcinoma including age, size, distant metastasis, and extrathyroidal extension. Prognostic scoring systems and risk-group classifications have recently been developed that are useful in predicting clinical outcomes in differentiated thyroid carcinoma. If one applies these scoring systems to the reported cases of columnar cell carcinoma, 8 of the 10 fall into high-risk, low-survival categories in the preceding scoring systems. Only those two cases of columnar cell carcinoma that are small and encapsulated (case nos. 3 and 6; Table 2) are low risk by Cady's classification. It is not clear whether columnar cell morphology alone is a predictor of poor survival independent of such other factors as age or size. There does not appear to be an increased incidence of aneuploid DNA content in columnar cell carcinoma, although the authors examined only two cases.

Columnar cell carcinoma is associated with a high
incidence of distant metastasis (8 of 10 cases) and a relatively low incidence of cervical lymph node metastasis (5 of 10 cases). Although the tumors appear to concentrate radioactive iodine, this does not appear to be a particularly effective treatment. The presence of thyroglobulin expression immunohistochemically does not appear to be related to the response to radioactive iodine.

Evans, in his original report, speculated that columnar cell carcinoma might be related to follicular carcinoma, and Sobrinho-Simoes echoed his thoughts. The presence of areas of classic papillary carcinoma associated with one of the cases in this study, coupled with rare psammoma bodies found in areas of columnar cell carcinoma, as well as the nuclear features of grooving clearing and rare cytoplasmic invaginations support the contention that these are variants of papillary carcinoma.

The differential diagnosis of columnar cell carcinoma includes usual papillary carcinoma, the tall cell variant of papillary carcinoma, and metastatic carcinoma, particularly adenocarcinoma of the colon or endometrium. Metastatic carcinoma can be readily excluded by use of immunohistochemistry for thyroglobulin because this antibody is specific for thyroid tumors and should not be expressed in metastatic lesions. Immunohistochemistry for CEA may be helpful in this regard because all columnar cell carcinomas have been negative for this antibody, whereas metastatic carcinomas may be CEA positive.

The tall cell variant of papillary carcinoma has some features in common with columnar cell carcinoma. Both are often of large size, commonly show extrathyroidal extension, and are associated with a more aggressive clinical course. The tall cell variant is defined histologically by cells that have a height of at least twice the width. The nuclei in the tall cell variant are usually basally oriented and show the typical nuclear features of papillary carcinoma. This contrasts with columnar carcinoma, where the nuclei are typically pseudostatified and may show some nuclear grooving, but the classic papillary carcinoma nuclei are not predominant. Additionally, tall cell carcinomas typically have a granular or eosinophilic cytoplasm, whereas the cytoplasm of columnar cell carcinoma is often clear. A rare example of a tumor showing both features of tall cell variant and columnar cell carcinoma has been reported. This patient developed lung metastases and died of disease 5.5 years after diagnosis.

The distinction of columnar cell carcinoma from usual papillary carcinoma is based primarily on the presence of pseudostratification of the nuclei, which is present in columnar cell carcinoma but absent in usual papillary carcinoma. Additionally, colloid is absent or sparse in columnar cell carcinoma but often prominent in usual papillary carcinoma. Psammoma bodies are seen in about 40% to 50% of cases of usual papillary carcinoma but have been observed in only rare cases of columnar cell carcinoma.

In summary, the authors describe the clinicopathologic features of three additional cases of columnar cell carcinoma.

**REFERENCES**


**TABLE 2.** Prognostic Scoring and Risk-Group Systems Applied to Columnar Cell Carcinoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>MACIS Score</th>
<th>EORTC Score</th>
<th>Cadby Risk Group</th>
<th>Sloan-Kettering Risk Group</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>10.76</td>
<td>102</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>2</td>
<td>9.93</td>
<td>98</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>3</td>
<td>3.98</td>
<td>46</td>
<td>Low risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>4</td>
<td>8.9</td>
<td>86</td>
<td>High risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>5</td>
<td>10.76</td>
<td>99</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>6</td>
<td>3.55</td>
<td>21</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>7</td>
<td>10.2</td>
<td>112</td>
<td>High risk</td>
<td>High risk</td>
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<td>8</td>
<td>11.14</td>
<td>88</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>9</td>
<td>10.68</td>
<td>83</td>
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<td>High risk</td>
</tr>
<tr>
<td>10</td>
<td>9.9</td>
<td>69</td>
<td>High risk</td>
<td>Intermediate risk</td>
</tr>
</tbody>
</table>

Abbreviations: MACIS, metastasis, age, completeness of surgery, extrathyroidal invasion, and size; EORTC, European Organization for Research into the Treatment of Cancer.

*With scores of 8+, 20-year survival is 24%.
†EORTC score based on age, sex, tumor type, T stage, and distant metastases. With scores of 84 to 100, 5-year survival is 33%; with scores of 101 to 120, 5-year survival is 5%.
‡Cady prognostic system based on age, size, metastasis, and extrathyroidal extension. Tumors are separated into low and high risk groups.
§Sloan-Kettering risk group based on age, histology, size, extrathyroidal extension, distant metastases, histological grade, and neck nodal metastases (in age > 45 years). Tumors are separated into low, intermediate, and high risk groups.
in papillary thyroid carcinoma: Development of a reliable scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 114:1050-1058, 1993


