Signet-Ring Cell Adenocarcinoma of Sinonasal Tract
An Immunohistochemical Study of the Mucins Profile

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- Context.—Adenocarcinomas of the sinonasal tract are classified into 4 categories: salivary-type, intestinal-type, nonintestinal-type, and metastatic. Signet-ring cell carcinoma is the rarest form of intestinal-type adenocarcinoma. Only isolated cases have been reported in the literature.

- Objective.—To evaluate clinical attributes, morphology, and immunohistochemistry in signet-ring cell carcinoma of the sinonasal tract.

- Design.—Seventy-three cases of primary sinonasal adenocarcinomas were retrieved from the files. Only 5 signet-ring cell adenocarcinomas (tumors composed of more than 90% signet-ring cells) were identified. In all cases, clinical data and histologic slides were available and were reviewed. Consecutive tissue sections were immunostained with monoclonal antibodies against MUC2, MUC5AC, MUC5B, MUC6, p53 protein, and MIB-1.

- Results.—Four of our 5 patients were woodworkers. They were treated by surgical excision and radiotherapy.

- Conclusions.—The mucin profile is similar to the profile described in digestive tract adenocarcinoma. It is not useful to differentiate between metastatic adenocarcinoma and primary intestinal-type sinonasal adenocarcinoma. Clinical data and immunohistochemistry with p53 protein and MIB-1 confirm that sinonasal signet-ring cell carcinoma is a high-grade and aggressive tumor.

(Arch Pathol Lab Med. 2007;131:961–964)

MATERIALS AND METHODS

Patients Selection

Seventy-three cases of primary sinonasal non–salivary gland-type adenocarcinomas were electronically retrieved from the files of the Department of Pathology at Lille University Hospitals (Lille, France) between January 1996 and February 2005. An adenocarcinoma metastatic to the sinonasal tract was excluded by imaging studies (digestive endoscopy and abdominal computed tomography). All cases with histologic documents were available. We identified 5 consecutive cases by using a strict microscopic criterion: tumor composed of more than 90% of signet-ring cells.

Histologic Study

Specimens were fixed in 10% buffered formalin and then embedded in paraffin. Slides and paraffin blocks were available for each case (from 1 to 14 blocks). Sections 4 µm thick were routinely stained with hematoxylin-eosin and saffron. All histologic slides were reviewed independently by 2 pathologists. Clinical data and follow-up information were obtained from patient charts and referring clinicians for all cases.

Immunohistochemical Study

Immunohistochemistry was performed by using an avidin-biotin-peroxidase complex method on an automated immunostainer (Benchmark XT, Ventana, Strasbourg, France). Primary antibodies used were p53 protein (D07, dilution 1:100; Dako, Trappes, France), MIB-1 (Ki-67, dilution 1:50; Immunotech, Marseille, France), MUC2* (LUM2-3, dilution 1:5), MUC5AC (CLH2, dilution 1:2; Novocastra, Newcastle, United Kingdom), MUC5B* /H11545, MUC5B /H11002, and MUC6 /H9262. Eighty percent of cells were immunostained by p53 protein antibody and 60% cells with MIB-1 antibody.
Table 1. Clinical Findings and Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y/sex</td>
<td>66/M</td>
<td>71/M</td>
<td>78/M</td>
<td>67/M</td>
<td>80/M</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Nasal obstruction</td>
<td>Nasal obstruction</td>
<td>Nasal obstruction-epistaxis</td>
<td>Nasal obstruction-epistaxis</td>
<td>Nasal obstruction</td>
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<tr>
<td>Occupation</td>
<td>Woodworker</td>
<td>Unknown</td>
<td>Woodworker</td>
<td>Woodworker</td>
<td>Woodworker</td>
</tr>
<tr>
<td>Location</td>
<td>Ethmoid</td>
<td>Ethmoid</td>
<td>Nasal cavity</td>
<td>Ethmoid</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Dead of disease (40 mo)</td>
<td>Dead of disease (32 mo)</td>
<td>Alive with metastatic disease (16 mo)</td>
<td>Dead of disease (84 mo)</td>
<td>Alive without evidence of disease (11 mo)</td>
</tr>
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Results

Clinical Features

Table 1 summarizes the clinical findings. All patients were men, and ages ranged from 66 to 80 years (mean, 72 years). Four patients were woodworkers for more than 15 years. Clinical symptoms were nonspecific: unilateral nasal obstruction in the 5 cases and epistaxis in 2 cases. Imaging and endoscopic studies revealed tumor masses developed in sinonasal cavities. In 3 cases, computed tomography and magnetic resonance imaging revealed ethmoid osteolysis.

The tumors were located in the ethmoid sinus in 3 cases and in the nasal cavity in 2 cases. In all cases, the treatment included surgical resection with adjuvant radiation therapy.

Patient follow-up ranged from 11 months to 84 months (mean, 36.6 months). Three patients presented a pejorative evolution and died of the disease associated with local recurrence, cervical regional lymph node metastasis, and distant pulmonary metastasis (32 to 84 months). The 2 last patients are still alive at last follow-up, 16 and 11 months, respectively. The first one presented with regional lymph node metastasis treated by radiation therapy, and the other one had no evidence of disease.

Table 2. Immunohistochemical Results*

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
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<tr>
<td>MIB-1</td>
<td>80%</td>
<td>70%</td>
<td>70%</td>
<td>-†</td>
<td>60%</td>
</tr>
<tr>
<td>p53</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MUC2</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>MUC5A/C</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>MUC5B</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>MUC6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Staining: – indicates 0%; +, 1% to 10%; ++, 11% to 50%; ++++, 51% to 75%; +++, +++, 75% or more.
† Immunostaining could not be properly estimated because of extensive tumor necrosis.
Pathologic Features

Grossly, tumors were composed of many fragments of gelatinous or mucoid masses measuring up to 3 cm. In 3 cases, the tumor was locally aggressive with bone infiltration and osteolysis.

Microscopically, tumors produced abundant mucin deposits forming large extracellular pools. Tumor cells were predominantly signet-ring cells floating in the pools of mucin (Figure 1). Tumor cells were large and round to oval, with an eosinophilic or pale cytoplasm and a vacuole of intracellular mucin (Figure 2). Nuclei were eccentric, distorted by intracellular mucin vacuole, irregular, and hyperchromatic. On average, more than 11 mitoses for 10 high-power fields with abnormal mitotic figures were noted. Large areas of necrosis were frequently observed. The background was highly vascularized. There was no vascular invasion. In 3 cases, tumors invaded bone structures.

Immunohistochemical Findings

The immunohistochemical study (Table 2) showed a strong and diffuse immunoreactivity against MUC2, MUC5AC, and MUC5B antibodies. In 1 case (case 4), extensive areas of tumor necrosis limited the immunohistochemical investigation. Staining was cytoplasmic with MUC5AC and MUC5B antibodies. Intracellular and extracellular mucin was stained with MUC2 antibody (Figure 3). No tumor cells were stained with MUC6 antibody.

Nuclear immunostaining for p53 was observed in 80% to 100% of tumor cells in 4 cases (Figure 4) and was negative in 1 case (case 4). The percentage of MIB-1–positive tumor nuclei ranged from 4% to 80% but was heterogeneous (mean, 60%) (Figure 5).

COMMENT

Signet-ring cell adenocarcinoma is an unusual subtype of sinonasal adenocarcinoma rarely reported in the literature (about 3% in our institution). As with the other variants, this subtype is also strongly associated with an occupational exposure to wood dust (4/5 patients in our series). A strong male predilection is observed because of this exposure. Sites of origin and clinical presentation are nonspecific.¹

The main diagnostic difficulties concerning this histologic subtype are represented by mucocele and metastasis from digestive tract. Mucocele is a benign pseudotumor that can simulate a malignant neoplasm because of its local aggressiveness. It corresponds to a cystic expansion of a paranasal sinus by retention of mucoid secretions. Microscopically, the cyst wall epithelial lining is of the respiratory type, without cellular atypia or mitotic figures. Submucosal fibrosis and chronic inflammation may be observed.¹ An intraosseous myxoma is composed of bland spindle cells in an abundant myxoid background, and no epithelial tumor cells are observed.⁹,¹⁰ The other main differential diagnosis is represented by metastatic adenocarcinoma from the gastrointestinal tract.¹¹ When the occupational context and the clinical presentation are discordant, the referring physician must exclude a primary digestive tumor using digestive endoscopy because microscopic examination is nonspecific. The immunohistochemical study with cytokeratin (CK) 7 and CK20 antibodies is sometimes advocated for the differential diagnosis. However, immunohistochemical staining for CK7 and CK20 does not help distinguish a metastatic colorectal...
adenocarcinoma from a primary sinonasal intestinal-type adenocarcinoma. Moreover, immunohistochemical staining for CDX2 was previously studied but did not discriminate both tumors. Human mucins are high-molecular-weight glycoproteins expressed in specialized normal epithelial cells and often in colorectal tumors. Secreted mucins (MUC2, MUC5AC, MUC5B, and MUC6) are expressed in mucus-secreting cells. In all our cases, we observed a strong and diffuse immunoreactivity with MUC2, MUC5A/C, and MUC5B antibodies and no staining with MUC6 antibody. These results are similar to gastric and colorectal adenocarcinomas immunophenotype. In a recent study, Nguyen et al showed that gastric and colorectal signet-ring cells adenocarcinomas were mainly stained with MUC1, MUC5AC, and MUC5B. Thus, as with CDX2, CK7, and CK20, secreted mucins are not useful for differentiating between metastatic adenocarcinoma and primary intestinal-type sinonasal adenocarcinoma. In fact, we hypothesize that mucins' gene expression is associated with the cellular differentiation specialization and not with the origin.

It is important to differentiate a metastatic adenocarcinoma from a primary sinonasal adenocarcinoma because metastatic digestive adenocarcinomas composed of signet-ring cells are associated with a very poor prognosis. Primary sinonasal signet-ring cell carcinomas are aggressive, but the prognosis is better. The treatment for the two forms differs, consisting of surgical resection with or without radiotherapy for primary sinonasal adenocarcinoma and palliative chemotherapy with or without surgical resection for metastatic adenocarcinoma. In our study, 3 cases with a long follow-up died of the disease. Two patients are alive, one with regional lymph node recurrence. In all cases, we observed a strong and diffuse immunoreactivity with p53 antibody without evident differences between the cases. The MIB-1 index was high, from 60% to 80% in all cases.

In conclusion, the present study confirms that sinonasal signet-ring cell adenocarcinoma is a high-grade and aggressive tumor with a poor prognosis. Mucin immunostaining is not helpful in distinguishing primary sinonasal signet-ring cells adenocarcinomas from gastrointestinal tract adenocarcinomas.

The authors thank Dallas Swallow, PhD (Galton Laboratory, University College, London, United Kingdom), and Ingemar Carlstedt, PhD (Lund University, Sweden), for kindly providing antibodies against mucins.

References