Mucoepidermoid carcinoma of the larynx

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Mucoepidermoid carcinoma of the larynx is an uncommon malignancy. Nearly all cases are found in middle-aged and elderly men. Most cases arise in the supraglottis. Mucoepidermoid carcinoma is classified histologically as low grade and high grade. The prognosis is relatively good for low-grade tumor and poor for high-grade mucoepidermoid carcinoma, which is also referred to as adenosquamous carcinoma. The treatment is primarily surgical, although the efficacy of postoperative radiation, with and without chemotherapy, is presently under evaluation in a National Intergroup Study. The case reported here is nearly classic for high-grade mucoepidermoid carcinoma, both as to clinical presentation and morphology. This report and discussion are offered to familiarize the reader with this uncommon lesion, of which fewer than 80 cases have been reported.

(Key words: Mucoepidermoid carcinoma, larynx, tumor, minor salivary gland stem cell, malignancy)

Mucoepidermoid carcinoma of the larynx is a rare lesion containing mucus-secreting, squamous cell, and intermediate cell types. It is believed to arise from the excretory duct

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stem cell of minor salivary glands. Fewer than 80 cases have been reported. Ninety-five percent of laryngeal carcinomas are squamous cell carcinoma.¹ Less than 1% of laryngeal carcinomas are adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma.²⁻⁴ Mucoepidermoid carcinoma was first described in the American medical literature as a distinct tumor type in 1945 by Stewart and colleagues.⁵ It had been reported originally by Volkman in 1895 in the German medical literature⁶ and by Masson and Berger in 1924 as *epitheliome à double métaplasie* in the French medical literature.⁷ It is the most common malignancy of the parotid gland and accounts for 15% of the malignant tumors of the minor salivary glands.⁸

Gerughty and coworkers,⁹ in 1968, and Damiani and associates,⁶ in 1981, reported cases of laryngeal carcinoma classified as adenosquamous carcinoma or mucoepidermoid carcinoma—adenosquamous carcinomas that are essentially identical to what others have classified as high-grade mucoepidermoid. All cases of mucoepidermoid carcinoma are considered malignant.¹⁰ These tumors have been classified as low and high grades, or low, intermediate, and high grade.¹¹⁻¹⁷

Minor salivary glands are numerous in the upper respiratory tract and upper digestive tract, particularly in the palate, lips, buccal mucosa, nasal mucosa, paranasal sinuses, tongue, pharynx, and larynx. Mucoepidermoid carcinoma has been reported in these sites as well as in the conjunctiva, liver, uterine cervix, anus, and penis.

Report of case

A 71-year-old man had been treated by his general practitioner with antibiotics and supportive therapy for hoarseness and sore throat. There had been no improvement. In April 1987, he had an otolaryngologic consultation. At that time, the patient had been hoarse for 3 months. He admitted to a 100-pack year of cigarette smoking and to drinking two beers daily. One parent and a sibling had died of cancer. As far as is known, both relatives had lung cancer that had metastasized.

Fiberoptic laryngoscopic examination revealed a large tumor in the left supraglottic area and pyriform sinus. A minimally tender solitary, firm mass 1 cm in diameter was palpated in the left side of the neck. The patient had moderate panacinar chronic obstructive pulmonary disease but was otherwise thought to be in good health.

Direct laryngoscopy was performed. A large, friable, exophytic tumor was seen in the left anterior aspect of the epiglottis. The tumor extended along the aryepiglottic fold into the left pyriform sinus. Multiple biopsies demonstrated mucoepidermoid carcinoma.

Laboratory studies, radiographic studies—including computed tomography (CT) scans of the head, neck, and thorax—bronchoscopy, and gastroesophagoscopy showed negative results for tumor. The patient's cancer was classified as stage III with a TMN staging of T3, N2b, M0.

On June 2, 1987, a total laryngectomy with left modified radical neck dissection was performed. The procedure included left hemithyroidectomy and removal of the left submandibular gland. The patient's immediate postoperative course was uncomplicated. Postoperative radiation therapy was planned. The patient was proposed for inclusion in the National Intergroup Study-Southwest Oncology Group (SWOG), which is presently evaluating postoperative radiation therapy with and without combined cis-platinum and 5-fluorouracil (5-FU) chemotherapy.

The patient deferred his decision as to further therapy. In August, gastritis and low-grade anemia developed. In late September, bowel obstruction occurred necessitating an exploratory laparotomy. This procedure demonstrated extensive adenocarcinoma of the colon extending into the mesocolon and mesentery. The malignancy was nonresectable, and palliative gastrojejunostomy and colostomy were performed. The patient deteriorated progressively over the next few months, and died in mid-December. A request for postmortem examination was refused.

Figure 1. Cartilage (C) of epiglottis is distorted and minimally invaded by high-grade mucoepidermoid carcinoma. Note ribbonlike cords and ducts to adenocarcinoma (A) and more solid mass presented by squamous cell carcinoma (S) (hematoxylin-eosin stain, original magnification $\times 40$).

Pathologic findings

Initially, biopsy specimens were taken from the false cords, left pyriform sinus, and left epiglottic fold. The left pyriform sinus, left epiglottic fold, and samples from the tumor mass demonstrated mucoepidermoid carcinoma. The laryngectomy specimen demonstrated a fungating, moderately soft, yellow-gray tumor distorting and partially replacing the epiglottis and measuring $4.5 \times 4 \times 0.8$ cm. The tumor extended into the left aryepiglottic fold, left ventricular fold, and left pyriform sinus. The radical neck specimen included eight lymph nodes, the largest of which was 1.9 cm in diameter. This tissue was firm, gray, and partially replaced by tumor.

Both the initial biopsy specimens and the supraglottic tumor in the laryngectomy specimen demonstrated moderately well-differentiated adenocarcinoma with low-grade pleomorphism and moderate mitotic activity, as well as squamous cell carcinoma with prominent pleomorphism and giant-

Figure 2. Adenocarcinoma (A) is shown in cords, columns, and tubules and squamous cell carcinoma (S) in large aggregate. Note abundant cytoplasm in large cells (hematoxylin-eosin stain, original magnification $\times 100$).

Figure 3. A review of adenocarcinoma component. Note frequent mitoses (arrows), pale cytoplasm, vesicular nuclei, and significant pleomorphism of columnar cells (hematoxylin-eosin stain, original magnification $\times 430$).

sized cells, very frequent mitoses, intercellular bridging, and rare squamous pearl formation.

The adenocarcinoma component was positive for mucin with periodic acid, Schiff (PAS) and mucicarmine stains. The squamous cell carcinoma component demonstrated keratin with an immunoperoxidase stain. The accompanying photomicrographs illustrate the more significant histopathologic findings (Figs 1 through 6). The grossly positive lymph node demonstrated squamous cell carcinoma only. The left lobe of the thyroid gland included a minute microfollicular adenoma. No other significant pathologic process was noted. The diagnosis was high-grade mucoepidermoid carcinoma.

Gerughty and coworkers⁹ recommended that in order to diagnose a tumor as mucoepidermoid carcinoma, it should demonstrate at least two of the following: intercellular bridging, keratin pearl formation, parakeratotic differentiation, individual cell keratinization, and cellular arrangement showing a pavement or mosaic pattern. The glandular

epithelium component should be confirmed by PAS or mucicarmine staining. This case demonstrated four of Gerughty's criteria for the squamous component and stained positively for mucin.

Discussion

Mucoepidermoid carcinoma of the larynx is an uncommon malignancy in which the initial biopsy is often nondiagnostic or is interpreted as squamous cell carcinoma. Ho and associates¹⁸ reported two cases of mucoepidermoid carcinoma of the larynx and reviewed 66 cases from the literature. Inasmuch as mucoepidermoid carcinoma is less radiosensitive than squamous cell carcinoma and prompt surgical treatment is indicated, early, correct diagnosis is important. With minor salivary gland tumors or adenocarcinoma of the upper respiratory tract, mucoepidermoid carcinoma is classified as to radiosensitivity. Mucoepider-

(continued on page 187)

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dizziness, vertigo or depression during therapy. **Laboratory Tests:** Because serious GI tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients for signs and symptoms of these and inform them of the importance of this follow-up. **Drug Interactions:** Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lithium; beta-blockers; probenecid; or methotrexate. **Drug/Laboratory Test Interactions:** The drug may decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before doing adrenal function tests. The drug may interfere with urinary assays of SHIAA. **Carcinogenesis:** A 2-year rat study showed no evidence of carcinogenicity. **Pregnancy:** Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy. **Nursing Mothers:** Avoid use in nursing mothers. **Pediatric Use:** Single doses of 2.5-5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age. **Adverse Reactions:** In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1500 mg/day than in those on 750 mg/day. In studies in children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults. Incidence Greater Than 1%; Probable Causal Relationship: GI: The most frequent complaints related to the GI tract: constipation; heartburn; abdominal pain; nausea; dyspepsia, diarrhea, stomatitis. CNS: headache; dizziness; drowsiness; light-headedness, vertigo. Dermatologic: itching (pruritus); skin eruptions; ecchymoses; sweating; purpura. Special Senses: tinnitus; hearing disturbances, visual disturbances. Cardiovascular: edema; dyspnea; palpitations. General: thirst. Incidence Less Than 1%; Probable Causal Relationship: GI: abnormal liver function tests; colitis; GI bleeding and/or perforation; hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders; pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia, hemolytic anemia. CNS: aseptic meningitis, cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria. GI: non-peptic GI ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypocalcemia. **Overdose:** May have drowsiness, heartburn, indigestion, nausea, vomiting. A few patients have had seizures. Empty stomach and use usual supportive measures. In animals 0.5 g/kg of activated charcoal reduced plasma levels of naproxen. **Caution:** Federal law prohibits dispensing without prescription. See package insert for full Prescribing Information.

*Incidence of reported reaction 3%-9%. Where unmarked, incidence less than 3%.

U.S. patent nos. 3,904,682, 3,998,966 and others.

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Figure 4. Note prominent granules (G) in cytoplasm of adenocarcinoma component (mucin stain, original magnification $\times 430$).

moid carcinoma, like other malignancies of the larynx, occurs mainly in middle-aged and elderly men. The mean age is 62 years. Men predominate over women by a 7.1 ratio. Although squamous cell carcinoma has been associated with alcohol and tobacco use, no such association has been shown with mucoepidermoid carcinoma. Binder,⁴ reporting 15 cases of laryngeal mucoepidermoid carcinoma by location, noted that 10 occurred in supraglottic, 2 in glottic, and 3 in subglottic locations. The location correlates with the distribution of laryngeal seromucous glands that are concentrated largely in the supraglottic structures. Our patient's presentation is nearly classic.

The histogenesis of mucoepidermoid carcinoma is not fully established. It is generally believed that the tumor arises from the excretory duct stem cell of minor salivary glands. Other theories as to origin include the intercalated duct of seromucous glands,¹⁸ and, according to a letter from D. K. Hefner, MD, (June 17, 1987), surface mucosal epithelium. The three basic cellular elements of mucoepidermoid carcinoma are mucous, intermediate, and

squamous cells. All are readily seen with light microscopy. With electron microscopy, six types of neoplastic cells can be seen. They represent various stages of differentiation of the intermediate cells toward mucus-secreting, keratin-forming, and lumen-lining cells.

Mucoepidermoid carcinoma may be classified as low, intermediate, or high grade, depending on morphology and the dominant cell type. Stewart⁵ considered cases with marked squamous cell predominance and scattered mucin-positive glandular cells to be high grade. Gerughty and colleagues⁹ prefer to classify these as adenosquamous carcinoma, but the prognosis and response to treatment are essentially identical. According to several authors and to Dr Hefner in the aforementioned personal communication, the 5-year survival rate for low-grade mucoepidermoid carcinoma has been reported at 91% to 100% and that for high-grade mucoepidermoid carcinoma at 29% to 50%.¹⁹⁻²¹ Reporting on 15 cases of laryngeal mucoepidermoid carcinoma with 4-year follow-up, Binder and associates⁴ found 1 death due to mucoepidermoid carcinoma, 5 patients with regional metastasis; 6 patients were lost to follow-up. Metastasis to the lung, as well as to lymph nodes, has been reported.

The prognosis is poorer with lymph node metastasis. Ferlito²² believes that the presence of lymph node metastasis is the most important factor in the choice and success of treatment in laryngeal carcinoma. Okinaka and Sekitani²³ believe that other important factors are the time interval between the onset of symptoms and final diagnosis and the tendency for mucoepidermoid carcinoma to show noncontiguous spread.

Damiani and colleagues,⁶ reporting a series of 21 cases, found hoarseness to be the presenting symptom in 18 cases. Our patient had had hoarseness for 3 months. Other less frequent findings included hemoptysis, foreign body sensation, dysphagia, and neck mass. The average duration of symptoms was 9 months. Tumor size in the Damiani series varied from 0.6 cm to 6 cm. Our patient's tumor was 4.5 cm.

The treatment of mucoepidermoid carcinoma is based in part on grade and anatomic

Figure 5. Review of squamous cell carcinoma component. Note significant pleomorphism, frequent mitoses (M), intercellular bridging (BR), and giant cell with huge, atypical nucleus in mitosis (GC) (hematoxylin-eosin stain, original magnification $\times 430$).

Figure 6. Note dark granules in cytoplasm of tumor cells (GR) in the squamous cell carcinoma component (immunoperoxidase stain for keratin, original magnification $\times 430$).

location. Partial laryngectomy is indicated for small, low-grade supraglottic tumors. Total laryngectomy is necessary for larger low-grade supraglottic tumors and low-grade subglottic tumors. Total laryngectomy with modified radical neck dissection is indicated for high-grade mucoepidermoid carcinoma, particularly in the presence of palpable lymph nodes.^{4,22,23} Forastieri and coworkers²⁴ treated one patient with laryngeal mucoepidermoid carcinoma with intra-arterial cis-platinum and 5-FU as adjuvant therapy. The patient had a partial response lasting 11 months. Study of this treatment continues. In the Damiani series the patients were treated with subtotal or total laryngectomy. The overall recurrence rate was 38%.

Comment

Although radiation is effective in treating squamous cell carcinoma of the larynx, it is

of limited value in high-grade mucoepidermoid carcinoma. Inasmuch as the biologic behavior of tumor oncotypes found in the larynx varies, appropriate therapy must be based in large part on histopathology. It is hoped that the SWOG protocol for laryngectomy, followed by postoperative radiation therapy with cis-platinum and 5-FU, will lessen recurrence and improve survival rates.

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