Pulmonary Salivary Gland–Type Tumors With Features of Malignant Mixed Tumor (Carcinoma Ex Pleomorphic Adenoma)

A Clinicopathologic Study of Five Cases

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Abstract

We report 5 cases of pulmonary salivary gland–type tumors with features of carcinoma ex pleomorphic adenoma. Patient ages ranged from 44 to 71 years (mean, 53.8 years); 4 patients were men and 1 was a woman. In all 5 cases, the lesions were associated with the bronchial system. None of the patients had a history of a head and neck salivary gland neoplasm. Histologically, the lesions were invasive tumors containing malignant myoepithelial elements and duct-like structures embedded in a benign chondromyxoid stroma. Areas reminiscent of residual pleomorphic adenoma were noted in 2 cases. Follow-up for 3 patients revealed that 2 died 22 and 54 months after diagnosis and 1 was alive 20 months after diagnosis. The cases are characterized by unique morphologic features that, coupled with their immunoprofile, suggest the possibility that these tumors represent carcinoma ex pleomorphic adenoma, an entity that has not been well documented in the bronchopulmonary system.

Pleomorphic adenoma (mixed tumor), a benign tumor of salivary gland type containing epithelial, myoepithelial, and stromal components, is the most commonly diagnosed lesion of the salivary glands. Carcinoma ex pleomorphic adenoma is defined as an epithelial malignancy developing in association with a primary or recurrent benign pleomorphic adenoma. In contrast with the salivary glands, mixed tumors arising in the tracheobronchial system are rare neoplasms, and primary carcinoma ex pleomorphic adenoma has been the subject of only isolated case reports or part of a general description of mixed tumors at this site.

Herein, we describe a series of 5 cases of malignant pulmonary tumors with mixed morphologic features highly suggestive of carcinoma ex pleomorphic adenoma. Histologically, these tumors had striking salivary gland–type features characterized by a malignant epithelial/myoepithelial component set in a prominent chondromyxoid stroma. This histologic finding and the fact that areas reminiscent of residual pleomorphic adenoma were identified in some of the cases were consistent with our interpretation that these neoplasms are salivary gland–type tumors and represent carcinoma ex pleomorphic adenoma. Because none of the patients had prior clinical or radiologic evidence of a head and neck salivary gland neoplasm, these tumors are regarded as primary lung lesions. Carcinoma ex pleomorphic adenoma of the lung is a controversial diagnosis to make, first, because of the rarity of primary pleomorphic adenoma at this site and, second, because of the morphologic variability of the benign and malignant components. To date, a careful analysis of the occurrence of similar tumors in the lung has not been performed.
Materials and Methods

Between 1987 and 2009, 5 cases with the histologic features herein described were identified from the surgical pathology files of M.D. Anderson Cancer Center, Houston, TX, and from the personal consultation files of one of us (C.A.M.). H&E-stained slides were reviewed in all cases. Immunohistochemical studies were performed in 2 cases. Deparaffinized tissue sections were incubated with antibodies directed against CAM5.2 (dilution 1:50; BD Biosciences, San Jose, CA), S-100 (dilution 1:900; BioGenex, San Ramon, CA), smooth muscle actin (SMA; dilution 1:70,000; Sigma, St Louis, MO), calretinin (dilution 1:40; Invitrogen, Carlsbad, CA), thyroid transcription factor 1 (dilution 1:200; DAKO, Carpinteria, CA), pancytokeratin (CK; dilution 1:100; DAKO), cytookeratin 7 (CK7; dilution 1:300; DAKO), synaptophysin (dilution 1:200; DAKO), chromogranin (dilution 1:100; DAKO), desmin (dilution 1:100; DAKO), glial fibrillary acidic protein (GFAP; dilution 1:7,000; BD Biosciences), p63 (dilution 1:200; Santa Cruz Biotechnology, Santa Cruz, CA), myogenin (dilution 1:125; DAKO), cytookeratin 14 (CK14; dilution 1:50; BioGenex), and CD56 (dilution 1:100; Invitrogen) using the polymeric biotin-free horseradish peroxidase method. Appropriate negative and positive control experiments were run for all antibodies tested. Clinical and follow-up information was obtained from the patients’ charts or from referral information, when available.

Results

Clinical Features

The main clinical features are summarized in Table 1. Of the patients, 4 were men and 1 was a woman. The age range was from 44 to 71 years (mean 53.8 years). The patients had shortness of breath, cough, hemoptysis, chest pain, or pleural effusion. In 1 case, the tumor was found incidentally in a routine chest radiograph. In 4 cases, the tumors were found in an endobronchial location. None of the patients had a history of head and neck neoplasm or previous surgery for salivary gland tumors. Treatment consisted of complete surgical excision in 4 cases (3 lobectomies; 1 pneumonectomy) and endobronchial debulking in 1 case. In 3 cases, chemotherapy and/or radiation therapy was given; 2 patients were lost to follow-up.

Gross Features

The lesions ranged in size from 2.3 to 5 cm. Grossly, they were well-demarcated, lobulated tumors with a fleshy to firm whitish gray cut surface and focal areas of hemorrhage. In all cases, the tumors were associated with a major or secondary bronchus.

Histologic Features

The histologic features in the 5 tumors consisted of a biphasic arrangement with varying proportions of epithelial/myoepithelial and stromal elements. The overall histologic features of all cases were strongly reminiscent of salivary gland-type neoplasms displaying varying proportions of glandular or duct-like structures, myoepithelial cells, and a chondromyxoid stroma.

On low magnification, some of the tumors protruded into the bronchial lumen and were covered by normal bronchial epithelium [Image 1]. All 5 tumors showed a diffuse infiltrative growth pattern into the surrounding bronchial wall structures and lung parenchyma. Two tumors had a prominent multinodular architecture. On higher magnification, the myoepithelial component ranged from highly cellular sheet-like or solid proliferations to islands, gland-like structures, and trabecular strands of tumor cells [Image 2]. The individual tumor cells were small to medium-sized and displayed mild to moderate pleomorphism. A common finding was a vesicular nuclear chromatin pattern with inconspicuous nucleoli and scant eosinophilic to clear cytoplasm [Image 3]. In 1 case, the tumor cells had a more spindled appearance with finely granular nuclear chromatin, small nucleoli, and clear to eosinophilic cytoplasm. Scattered duct-like epithelial structures were noted in 4 cases [Image 4]. Common to all tumors was a benign mesenchymal
component composed of a myxochondroid stroma. This stroma contained scattered small spindle- and stellate-shaped cells with bland cytologic features. Well-developed cartilage, however, was not identified in any of the cases.

In 2 cases, small areas of hyalinization containing a more bland-appearing myoepithelial cell proliferation could be seen. This myoepithelium was closely associated with small duct-like epithelial structures. Overall, these findings were reminiscent of small residual areas of pleomorphic adenoma.

The mitotic activity ranged from 2 to 64 mitoses per 10 high-power fields. Necrosis was seen in 3 cases amounting to 10% to 25% of the tissue examined, and vascular invasion was prominent in 1 case. A single tumor showed a peculiar pattern of pagetoid spread into the overlying bronchial epithelium. It is important to note that no malignant mesenchymal elements were noted in any of the tumors.

Immunohistochemical Features

Immunohistochemical studies were performed on 2 of the tumors. The neoplastic cells showed immunoreactivity for CK, CK7, CAM5.2, SMA, and CD56 and were focally positive for S-100, CK14, synaptophysin, and calretinin. No staining was identified for chromogranin, desmin, myogenin, thyroid transcription factor 1, GFAP, or p63.
Clinical Follow-up

Follow-up information available for 3 patients showed that 2 had died of disease, 1 patient 22 months after diagnosis with metastasis to the bone and liver and the other 54 months after diagnosis with metastasis to the opposite lung and mediastinum. One patient was alive with disease 20 months after diagnosis with metastasis to the contralateral lung and kidney.

Discussion

Malignant mixed tumors of the salivary glands classically encompass 3 distinct tumors: carcinoma ex pleomorphic adenoma, carcinosarcoma, and metastasizing pleomorphic adenoma.7 Carcinoma ex pleomorphic adenoma, the most common member of this group, is defined as an epithelial malignancy arising in association with a benign pleomorphic adenoma or developing as a recurrent neoplasm at the site of a previous pleomorphic adenoma excision.2,8 Most commonly, the carcinoma component in carcinoma ex pleomorphic adenoma is a poorly differentiated adenocarcinoma followed in frequency by salivary duct carcinoma and other typical salivary gland carcinoma subtypes.7 Carcinoma ex pleomorphic adenoma is a notoriously difficult diagnosis to make based on several peculiarities: First, the benign pleomorphic adenoma component may be small and is easily overlooked; second, the carcinoma component may be extremely variable and is often difficult to classify; and last, the malignant elements may completely replace any benign pleomorphic adenoma parts.8 As a reflection of the often high-grade malignancy, the prognosis is rather poor with an overall survival rate of only 30% at 5 years.2

Salivary gland–type tumors are of ubiquitous distribution and have been described in many anatomic sites outside the head and neck area. However, their presence in the lower respiratory tract is rare. Nevertheless, reports on the more conventional types of these tumors have been presented in the literature, including mucoepidermoid carcinoma, acinic cell carcinoma, epithelial myoepithelial carcinoma, adenoid cystic carcinoma, and pleomorphic adenoma.4,9-13 Malignancy in association with a primary pleomorphic adenoma (carcinoma ex pleomorphic adenoma) of the lung has been reported only infrequently. Moran et al,4 in a general description of 8 primary “mixed tumors” (pleomorphic adenomas) of the lung, described 2 tumors that were designated as malignant owing to the presence of angioinvasion, infiltration of adjacent lung parenchyma, necrosis, mitotic activity, and, ultimately, aggressive clinical behavior. Similarly, Nicholson et al14 reported 2 cases of a “malignant myxoid endobronchial tumor,” which may be part of the spectrum of tumors that are herein described. In addition, sporadic case reports comment on the presence of primary carcinoma ex pleomorphic adenoma occurring in the trachea. These tumors consisted of polypoid submucosal lesions that, on a histologic level, showed biphasic morphologic features composed of malignant high-grade epithelial elements and a benign stroma showing myxoid, hyaline, or osteoid differentiation.3,5,6

A series of cases addressing the issue of malignant salivary gland–type tumors of the lung reminiscent of carcinoma ex pleomorphic carcinoma, however, is lacking, not only because of the rarity of such tumors primarily occurring in...
the lung but also because there are no definitive criteria to diagnose the tumors when they occur in this site. Herein, we report 5 such cases in which the histologic features, namely a malignant myoepithelial proliferation associated with duct-like structures and a chondromyxoid stroma, were reminiscent of a malignant salivary gland–type neoplasm, and we propose that these tumors are best classified under the designation of carcinoma ex pleomorphic adenoma.

One important aspect with the cases herein presented is the fact that the “benign” component present in some of the cases, by itself, is clearly similar to the histologic features that benign pleomorphic adenomas show. However, it is the malignant component that may also show a wide spectrum of histologic differentiation and that needs to be recognized as such to not dismiss the case merely as a non–small cell carcinoma or poorly differentiated carcinoma. The malignant component in our experience clearly shows myoepithelial differentiation, yet not adenocarcinoma or salivary duct carcinoma as commonly seen in the tumors arising in the salivary glands. In some cases, this may pose a problem in interpretation; however, the presence of more benign areas of residual pleomorphic adenoma may be of help in providing a better classification for these tumors.

In this setting, the list of malignant primary lung tumors that may show mixed morphologic features with heterologous components is rather short. The most notable tumors of this group would include carcinosarcoma and pulmonary blastoma.15-17 In the former, the presence of a malignant epithelial component, most commonly in the form of squamous cell carcinoma, and the presence of a mesenchymal neoplasm in the form of chondrosarcoma, rhabdomyosarcoma, or any other conventional sarcoma should facilitate correct interpretation. In pulmonary blastoma, the presence of a type of glandular embryonic-like component with areas of undifferentiated sarcoma should be of help in separating this tumor from the embryonic-like component with areas of undifferentiated conventional sarcoma should facilitate correct interpretation.

We believe that a diagnosis of pulmonary carcinoma ex pleomorphic adenoma should primarily be based on the morphologic features; however, the use of immunohistochemical markers may support classification of these tumors as such. Carcinoma ex pleomorphic adenomas are known to display an immunohistochemical phenotype that consists of variable expression of markers like CK, CK7, carcinoembryonic antigen, vimentin, S-100, SMA, and GFAP in salivary gland and tracheal locations.3,5,7 These findings are in accordance with those in our own cases in which the neoplastic cells were positive for CK, CK7, CAM5.2, SMA, and CD56 and in which focal reactivity was seen for S-100, CK14, synaptophysin, and calretinin.

Our follow-up information shows that 2 patients died of their tumor after 22 and 54 months and 1 was alive with metastatic disease, indicating a similarly aggressive behavior to that in the salivary glands.

We have described 5 cases in which the findings of histologic and immunohistochemical studies are in keeping with a salivary gland–type malignancy and one that we would designate as malignant biphasic neoplasm of salivary gland derivation, probably representing carcinoma ex pleomorphic adenoma. The recognition of more of these neoplasms can provide more meaningful insight into their behavior, thereby allowing comparison in outcome with their counterparts in the head and neck area.

References


