The Korean Journal of Pathology 2011; 45: 175-181
DOI: 10.4132/KoreanJPathol.2011.45.2.175

Mucoepidermoid Carcinoma of Tracheobronchial Tree: Clinicopathological Study of 31 Cases

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Received: February 10, 2011
Accepted: March 22, 2011

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Background: All aspects of mucoepidermoid carcinoma (MEC) of the lung including histologic grading, clinical behavior and its differentiation from adenosquamous cell carcinoma are still not fully understood. **Methods:** We reviewed the hematoxylin-eosin stained slides and medical records of 31 cases of MEC of the lungs. The cases were classified as low and high grade according to the quantitative grading system formulated for MEC. High grade tumors were tested for an epidermal growth factor receptor (*EGFR*) mutation. **Results:** Twenty eight cases were classified as low grade and 3 cases as high grade. Histologically, lower glandular component, cellular atypia, necrosis, mitoses >4/10 high power fields, and endolymphatic tumor emboli were typical characteristics of a high grade tumor. Although some tumors showed histologic features mimicking high grade tumors, they were classified as low grade tumors according to this quantitative grading system. Low grade tumors showed no recurrence or metastasis. However, among three patients with a high grade tumor, two had distant metastases and one died of disease. Additionally, an *EGFR* mutation was not detected. **Conclusions:** A high grade MEC was consistently different from a low grade tumor with regard to malignant histologic features and poor prognosis. Therefore, correct histologic grading is important in predicting the prognosis to avoid unnecessary treatment.

Key Words: Lung neoplasms; Bronchi; Carcinoma, mucoepidermoid

Mucoepidermoid carcionoma (MEC) of the tracheobronchial tree is a rare tumor, comprising 0.1 to 0.2% of primary lung tumors, and arising from the bronchial submucosal gland.[1] MEC is defined as a malignant epithelial tumor consisting of squamoid cells, mucin-secreting cells and intermediate cells.[1,2] Although it is histologically identical to the salivary gland tumor of the same name, it is not fully understood, especially with regard to some aspects of histologic grading, clinical behavior, and differentiation from adenosquamous cell carcinoma. There have been no large studies examining pulmonary MEC in Korea. We analyzed 31 cases of MEC of the lung to clarify their clinical and pathological nature. Meanwhile, an epidermal growth factor receptor (*EGFR*) mutation has changed the paradigm for evaluation and treatment of non-small cell lung cancer. One pulmonary MEC study demonstrated an *EGFR* mutation.[3] We performed an *EGFR* mutation analysis in three cases classified as having a poor prognosis.

MATERIALS AND METHODS

Thirty one cases of carcinoma diagnosed as MEC of the lung from 1996 until 2010 were retrieved from the surgical pathology profiles of the Samsung Medical Center, Seoul, Korea. The clinical information including age, sex, presenting symptoms, smoking history, radiologic findings, treatment, and clinical follow up were obtained from a review of the medical records. This study was approved by the Institutional Review Board (2010-12-076-001).

Histopatholgic features

We reviewed all hematoxylin-eosin stained slides of 31 cases, and histopathologically confirmed the diagnosis of MEC. We also evaluated the histologic features including the proportions of glandular and solid components, extent of invasion, degree of necrosis, patterns of mitosis, cellular atypia, neural invasion, and the presence of endolymphatic tumor emboli. The cases were reclassified according to the quantitative grading system of the

Armed Forces Institute of Pathology (AFIP) formulated for MEC in salivary glands, which is based on a point score for each of these five histopathologic features as follows: intracystic component less than 20% (+2); neural invasion (+2); necrosis (+2); mitosis more than 4 in 10 high power fields (HPF, +3); and anaplasia (+4). According to the sum of the points, tumors were classified into low (0-4), intermediate (5-6) and high (7-14) grades.[4]

EGFR mutation studies

DNA was extracted from the formalin-fixed, paraffin-embedded samples on unstained slides after deparaffinization using a QIAamp® mini kit (Qiagen, Valencia, CA, USA), according to the manufacturer's directions. The quality of DNA was evaluated using quantification in a spectrophotometer (NanoDrop™ ND-1000, NanoDrop Technologies, Wilmington, DE, USA). DNA samples were amplified with polymerase chain reaction (PCR) for genomic fragments of *KIT* exons 18, 19, 20, and 21. The primer sequences used for PCR were as follows: exon 18 forward 5´-GGCTGAGGTGACCCTTGTCT-3´, reverse 5´-CTGTGCCAGGGACCTTACCT-3´; exon 19 forward 5´-ATGTGGCACCATCTCACAATTGCC-3´, reverse 5´-CCACACAGCAAAGCAGAAACTCAC–3´; exon 20 forward 5´-AGGCACAGCTTTTCCTCCAT–3´, reverse 5´-AGCAGGTACTGGGAGCCAAT-3´; exon 21 forward 5´-ATGAACTACTTGGAGGACCGTC-3´, reverse 5´-TGCCTCCTTCTGCATGGTATTC-3´. The PCR samples contained 50 ng of genomic DNA from each case, 20 mol/L of each primer, and Maxime™ PCR PreMix (i-StartTaq, iNtRON Biotechnology, Seongnam, Korea) in a 20 μL reaction. PCR cycling for exon 18 and 20 was performed at 94°C for 1 minute for one cycle, followed by 40 cycles at 94°C for 30 seconds, annealing temperature at 55°C for 30 seconds, and extension at 72°C for 30 seconds. The final cycle was followed by a 5-minute extension phase at 72°C. PCR cycling for exon 19 and 21 was performed at 94°C for 4 minutes for one cycle, followed by 40 cycles at 94°C for 30 seconds, annealing temperature at 58°C for 30 seconds, and extension at 72°C for 30 seconds. The final cycle was followed by a 5-minute extension phase at 72°C. Distilled water and normal human genomic DNA (Roche Applied Science, Mannheim, Germany) were used for negative and positive controls, and underwent PCR reaction together with genomic DNA from MEC cases. Amplification was confirmed using 2% agarose gel electrophoresis, and the PCR products were purified with a QIAamp® mini purification kit (Qiagen), according to the manufacturer's directions. The purified products were directly sequenced via automated sequencing with fluorescently labeled dideoxy chain-terminating nucleotides using an ABI PRISM BigDye® Terminator ver. 1.1 cycle sequencing ready reaction kit (Applied Biosystems, Foster, CA, USA).

Statistical analysis

The clinicopathological features of low and high grade tumors were compared using Fisher's exact test. Age, tumor size, and cystic component of both grade tumors were compared by way of an independent-samples t-test. The cystic component in the cases, with presence or absence of cholesterol cleft, was evaluated by way of an independent-samples t-test. All tests were two-sided, and p-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using the SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics and clinical manifestations

The clinical characteristics of the patients are described in Table 1. Twenty eight cases were classified as low grade tumors, whereas the remaining three cases as high grade tumors. No case was classified as intermediate grade. Patients classified as low grade tumors were on average younger (mean age, 33.9 years; range, 6 to 65 years) than those with high grade (mean age, 63.0 years; range, 48 to 72 years) ($p = 0.006$). The presenting symptoms including cough, hemoptysis, and sputum were characteristics of patients with MEC. However, 11 of 31 patients did not complain of any symptoms and tumors were found incidentally. Radiologically, tumors were clearly identified by chest computed tomography (CT, 31/31), which contrasts with the poor detection by simple chest X-ray (14/31). Obstructing pneumonia and atelectasis were observed in eight and five cases, respectively. Most tumors were located in the central portion of the respiratory tree: trachea (4), main bronchus (8), lobar bronchus (7), segmental bronchus (12), and periphery (1). Low grade tumors were all classified as stage IA or IB, as opposed to high grade tumors, which were classified as stage IIA or IIIB.

Gross findings

Most low and high grade tumors were well-circumscribed,

Table 1. Clinical data comparing low and high grade mucoepidermoid carcinomas of the tracheobronchial tree

	Low grade	High grade	p-value
No. of patients	28	3	
Male : Female	14 : 14	3 : 0	0.232[a]
Mean age (median, range)[a]	33.9 (33, 6-65)	63.0 (69, 48-72)	0.006[b]
0-9	3	0	
10-19	2	0	
20-29	9	0	
30-39	1	0	
40-49	9	1	
50-59	1	0	
≥60	3	2	
Smoker	8/28 (29.6%)	2/3 (66.7%)	0.251[a]
Symptoms			
Cough	12	1	
Hemoptysis	11	1	
Sputum	7	0	
Chest pain	2	0	
Dyspnea	2	1	
Myalgia	1	0	
Fatigue	1	0	
Asymptomatic	10	1	
Radiology			
Simple chest X-ray	13/28 (46.4%)	1/3 (33.3%)	1.000[a]
Chest computed tomography	28/28 (100%)	3/3 (100%)	
Bronchoscopy	26/28 (92.9%)	2/3 (66.7%)	0.271[a]
Location			
Trachea	3	1	
Main bronchus	8	0	
Lobar bronchus	5	1	
Segmental bronchus	12	0	
Periphery	0	1	
Stage[c]			
IA	14	0	
IB	11	0	
IIA	0	1	
IIIA	0	1	
Operation			
Lobectomy	14	1	
Sleeve lobectomy	7	0	
Bilobectomy	2	0	
Pneumonectomy	2	1	
Tracheal segmental resection	3	1	
Adjuvant treatment	1/28 (3.6%)	3/3 (100%)	
Follow up (median, range, mo)	57 (1-128)	17 (3-35)	
Recurrence	0/28 (0%)	0/3 (0%)	
Metastasis	0/28 (0%)	2/3 (6.7%)	0.006[a]

[a]By Fisher's exact test; [b]By independent-samples t-test; [c]Four cases of tracheal tumor are excluded in stage.

endobronchial, and polypoid masses that were usually yellow, but occasionally white in color. The cut sections revealed a glistening mucoid appearance with solid and cystic portions (Fig. 1A). Some high grade tumors showed infiltrative growth (Fig. 1B). The size of low grade tumors ranged from 0.7 to 5.5 cm in the greatest dimension (mean, 2.5 cm), and those of high grade tumors ranged from 1.2 to 6.0 cm (mean, 3.6 cm).

Table 2. Histopathologic features comparing low and high grade mucoepidermoid carcinomas

	Low grade (n=28) (%)	High grade (n=3) (%)	p-value
Size (mean, range, cm)	2.45 (0.7-5.5)	3.56 (1.2-6)	0.195[a]
Cystic component (mean, range, %)	46.3 (10-90)	10 (5-15)	0.018[a]
Invasion extent			
Confined within bronchial wall	16 (57.1)	0 (0)	
Invasion beyond bronchial wall	11 (39.3)	2 (66.7)	
Invasion to lung parenchyma	1 (3.6)	1 (33.3)	
Lymph node metastasis	0 (0)	2 (66.7)	0.003[b]
Necrosis	1 (3.6)	3 (100)	0.001[b]
Cellular atypia	2 (7.1)	3 (100)	0.002[b]
Mitosis (≥4/10 HPF)	0 (0)	3 (100)	0.002[b]
Stromal sclerosis, severe	5 (17.6)	3 (100)	0.012[b]
Neural invasion	0 (0)	1 (33.3)	0.097[b]
Endolymphatic emboli	0 (0)	3 (100)	<0.001[b]
Severe sclerosis with infiltrative growth	5 (17.9)	3 (100)	0.012[b]
Calcification	14 (50.0)	0 (0)	0.232[b]
Cholesterol cleft	6 (21.4)	0 (0)	1.000[b]
Clear cell change	3 (10.7)	0 (0)	1.000[b]
Oncocytic change	2 (7.1)	0 (0)	1.000[b]

[a]By independent-samples t-test; [b]By Fisher's exact test.
HPF, high power fields.

Histopathological and molecular findings

Characteristic histopathologic findings are summarized in Table 2. High grade and low grade tumors each revealed distinctive histologic features (Fig. 2A-D). Although most of the tumors were well circumscribed grossly, the microscopic invasion beyond the bronchial wall was observed in 12 out of 28 low grade MEC cases (Fig. 2E). The glandular component was greater in low grade tumors than in high grade tumors ($p=0.018$). Calcifications and cholesterol clefts were only seen in low grade tumors. The portion of the cystic component was larger in the presence of a cholesterol cleft ($65.0\pm16.4\%$) than in its absence ($35.8\pm25.1\%$) ($p=0.012$). The necrosis ($p=0.001$), cellular atypia ($p=0.002$), mitoses greater than 4/10 HPFs ($p=0.002$), and endolymphatic emboli ($p<0.001$) were characteristics of high grade tumors. Lymph node metastases were noted in two cases of high grade tumors ($p=0.003$). Severe sclerosis mimicking highly infiltrative growth was found in 5 low grade tumors and 3 high grade tumors (Fig. 2F). It was more frequently observed in high grade tumors than in low grade tumors ($p=0.012$). Clear cells and oncocytic cells were observed in three and two low grade tumors, respectively. An *EGFR* mutation was not detected in any of the three high grade tumors.

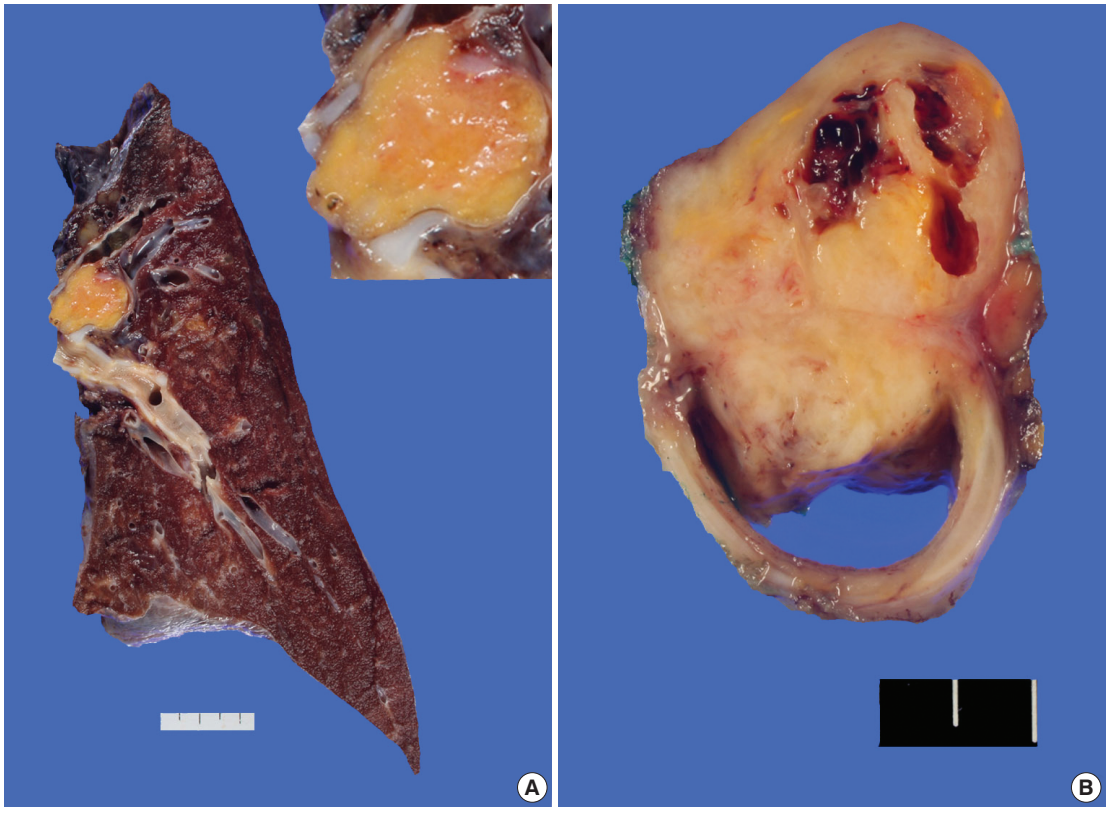

Fig. 1. (A) Most mucoepidermoid carcinomas show a well circumscribed, endobronchial and polypoid mass with a yellow to white glistening mucoid appearance. (B) One high grade mucoepidermoid carcinoma of the trachea reveals more infiltrative growth.

Treatment

All 31 tumors were resected surgically by tracheal resection (4), lobectomy (14), sleeve lobectomy (7), bilobectomy (2), or pneumonectomy (3). Lymph node dissections were performed in all patients. The resection margins were free of tumors in all cases. Adjuvant chemo- or radiotherapy was performed in three high grade tumors and one low grade tumor with a close resection margin.

Prognosis

All twenty eight low grade tumors had no recurrence or metastases during a median follow-up time of 57 months (range, 1 to 128 months). However, three high grade tumors showed more aggressive behaviors. One patient had a brain metastasis 12 months after surgery and adjuvant chemotherapy. He received intracranial chemotherapy and is alive without evidence of disease at 57 months. Another patient had multiple lung metastases following surgery and adjuvant radiotherapy and died 17 months after surgery. The last patient died of a brain infarction 3 months after diagnosis. He suffered a pulmonary embolism postoperatively.

DISCUSSION

Since first described in 1952 by Smetana *et al.*,[5] there has been debates about the clinical behavior of pulmonary MEC. Earlier studies regarded MEC as a benign neoplasm which was included under the category of bronchial adenoma together with carcinoid tumor and adenoid cystic carcinoma.[6] However, a definitely malignant type of MEC was reported in later studies and the distinction of low and high grade MEC was suggested by gross, microscopic, and ultrastructural criteria.[7-9] That is, the low grade tumor presents as an exophytic mass confined mainly to the bronchus and consists of well formed mucous glands with no or few mitoses and no necrosis. In contrast to the low grade tumor, a high grade tumor is less polypoid more frequently invasive[7] and consists of more atypical and pleomorphic cells with fewer well formed mucous glands as well as numerous mitoses and necrosis.[7] Klacsmann *et al.*[8] supported these differences with

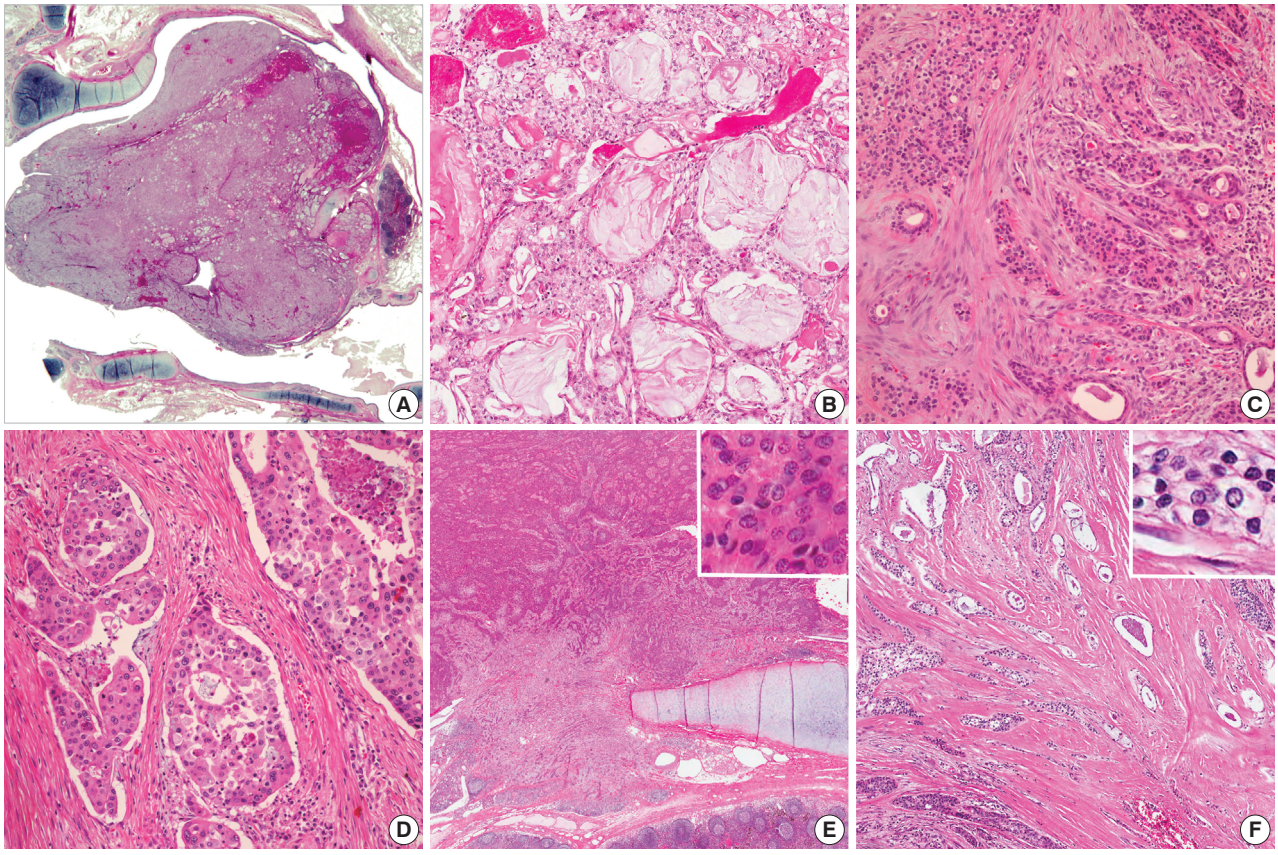

Fig. 2. (A, B) Low grade mucoepidermoid carcinomas present as an endobronchial mass composed of a dominant glandular component containing mucin with a solid portion of squamoid cells. (C, D) High grade mucoepidermoid carcinomas have less glandular component than low grade tumors. Transition from the glandular component to the solid portion is characteristic. Necrosis, nuclear atypia and mitoses greater than 4/10 high power fields are found. (E) Focal invasion beyond the bronchial wall is observed even in low grade mucoepidermoid carcinoma. However, these tumor cells do not reveal nuclear atypia, mitosis or necrosis (inset). (F) Severe sclerosis with highly infiltrative growth is noted in low grade mucoepidermoid carcinoma. However, these tumor cells do not show any high grade features (inset).

ultrastuctural studies. Because of its value in predicting behavior in several large studies, this classification is now well accepted.[10-12] Although the criteria for discriminating between low and high grade tumors are not definitely established, the distinction is similar to the previous studies. Heitmiller *et al.*[11] divided pulmonary MEC on the basis of mitotic activity, cellular necrosis, and nuclear pleomorphism, and also provided a correlation of histologic grading with prognosis. Yousem and Hochholzer[12] separated the two grades using the criterion of severe cellular atypia characterized by pleomorphism, hyperchromatism, and irregularity of chromatin distribution, and also showed clinical and prognostic differences depending on the grade. In addition, they found that necrosis and mitosis (average 4/10 HPF) were restricted to high grade tumors. In our study, we used an AFIP weighted MEC grading criteria for the salivary gland,[4] because it covers all of the components previously mentioned. The classification by these criteria divided the two groups very clearly. Twenty eight low grade tumors were all stage IA or IB and did not show any recurrence or metastasis during follow up. However, among three patients with high grade tumors, two patients had lymph node metastases at the time of diagnosis. With a clinical follow-up of a median 17 months (range, 3 to 57 months), two patients had distant metastases and one of them died of the intercurrent disease.

We noted several interesting histologic features, as follows. First, severe sclerosis mimicking highly infiltrative growth can be observed in low grade tumors. Although 5 of the 28 low grade tumors showed this feature, there was no necrosis, mitosis or cellular atypia, suggesting an excellent prognosis (Fig. 2F). Second, focal invasion beyond the bronchial wall or lung parenchyma is not by itself a poor prognostic feature (Fig. 2E). Although focal invasive tumors were found in 12 out of 28 low grade tumors, none had a poor prognosis. Third, a high glandular component is not mandatory for the diagnosis of low grade tumors.

As mentioned earlier, it is commonly accepted in the aspect of tumor biology that low grade tumors consist of well formed glands. In our study, five low grade tumors had a glandular component less than 20% and did not satisfy the criteria to be classified as a low grade tumor in the quantitative grading system of the AFIP formulated for MEC in salivary glands,[4] which was used in this study. However, they did not show any other high grade histologic features and were ultimately classified as a low grade tumor. The patients of these five tumors showed an excellent prognosis. It should not be misunderstood that the glandular component is higher in low grade tumors than in high grade tumors. Fourth, focal cellular atypia can be found in low grade tumors. But other high grade features, such as mitosis or necrosis, were not observed and these cases demonstrated a good prognosis despite cellular atypia. These third and fourth points clarify the usefulness of the AFIP weighted MEC grading criteria used in this study because it utilizes a point value system. Fifth, calcification or ossification was observed only in low grade tumors (14/28). It was not associated with size or a glandular component. Sixth, cholesterol clefts with a focal granulomatous reaction were observed only in low grade tumors (6/28), especially when the glandular component was high. This might be the result of mucus extravasation. Seventh, clear cell or oncocytic cell changes and peritumoral lympocytic infiltration were noted in several cases, but they did not appear to have prognostic significance. Several studies reported these features with the same interpretation.[2,12] Although Shilo *et al.*[13] insisted that prominent lymphocytic infiltration expands the differential diagnostic considerations from the lymphoma or lymph node metastasis, that was not seen in our study.

The clinical features were not different from previous studies. In the largest previous study, Yousem and Hochholzer[12] reported a mean age of 34.8 years in 45 low-grade tumors, as well as a mean age of 44.5 years in 13 high grade tumors.[12] Also they found that the ratio of men to women was 18:27 in low grade tumors, and 6:7 in high grade tumors. In our study, the patients with high grade tumors (median, 63 years; range, 48 to 72 years) were older than those with low grade tumors (median, 34 years; range, 6 to 65 years). The ratio of men to women was 14:14 in low grade tumors, and 3:0 in high grade tumors, with no significant difference between the two groups. Another point to consider is that pulmonary MEC can occur in young patients, especially in the pediatric population. There have been several reports of MEC in the pediatric population[1] and one study suggested that 4 cases of MEC occurred among 22 primary lung neoplasms in children.[14] In our study, 5 out of 31 patients were less than 20 years old. The symptoms were not uncommon, mainly due to bronchial irritation and obstruction. It should however be noted that eleven of all 31 patients were asymptomatic and the duration of symptoms was long (more than six months) in six patients, particularly in younger patients. It is not easy to think that common symptoms such as cough and sputum in young patients might originate from lung cancer, especially in Korea where the incidence of tuberculosis is high. The diagnosis was confirmed by chest CT (31/31), in contrast to plane film chest X-ray (14/31) or bronchoscopy (28/31). These findings suggest that patients with persistent respiratory symptoms despite symptomatic treatment should undergo a chest CT regardless of age.

The differential diagnosis of high grade MEC from adenosquamous cell carcinoma is important because it is known that adenosquamous cell carcinoma has a poorer prognosis. The differential criteria have been the subject of controversy. Klacsmann *et al.*[8] suggested the criteria for high grade MEC: exophytic endobronchial growth, surface epithelium lacking changes of in situ carcinoma, absence of individual cell keratinization and squamous pearl formation, and transitional areas to low grade MEC. In our study, all three cases of high grade tumors fulfilled these criteria. Although one tumor was located peripherally, it demonstrated mainly endobronchial growth. In addition, the immunohistochemical stains in all three cases were negative for thyroid transcription factor-1 (TTF-1), which is positive in adenosquamous cell carcinoma. The p63 staining revealed variable positivity. According to Choi *et al.*,[15] immunoreactivity for TTF-1 is not detected in salivary gland type carcinomas such as MEC or adenoid cystic carcinoma, which is in contrast to adenocarcinoma which was positive for TTF-1 in 90% of cases. Shilo *et al.*[13] also showed negativity for TTF-1 and cytokeratin 20 in bronchial MEC. These previous studies support our data.

Yousem and Hochholzer[12] insisted that low grade tumors with complete resection do not require further therapy except for clinical follow-up and high grade tumors should be treated as exophytic bronchogenic carcinomas of low stage. Based on our study, with an absolute distinction of low grade and high grade tumors related to prognosis, we suggest that surgical excision is sufficient for treatment of low grade tumors. However, since several cases involving aggressive behavior in histologically low grade tumors have been reported,[7] careful clinical follow-up is required. In high grade tumors, the treatment should be performed according to stage, as with any other lung cancer. Further studies concerning the role of adjuvant chemo- or radiotherapy are necessary.

Introduction of EGFR tyrosine kinase inhibitors (EGFR-TKI) such as gefitinib or erlotinib have changed the paradigm for treatment of non-small cell lung carcinoma. It is well known that the response to EGFR-TKI is expected to be good in the presence of the *EGFR* mutation, which is common in Asian women and non-smokers.[16,17] Han *et al.*[3] reported a patient with pulmonary MEC who showed a good response to EGFR-TKI. They also reported three cases of pulmonary MEC with *EGFR* mutation. However, subsequent studies by other groups have so far failed to demonstrate the *EGFR* mutation in pulmonary MEC.[18,19] In our study, an *EGFR* mutation was not detected in all specimens of three patients with high grade tumors. Further studies are needed since we examined only three cases, and patients with multiple metastases would get a chance to try EGFR-TKI if the *EGFR* mutation is detected.

In conclusion, MEC of the lung usually occurs in the central tracheo-bronchial tree. It is divided into low grade and high grade tumors which are absolutely different groups with regard to histology and prognosis. Mitotic figures greater than 4/10 HPF, tumor necrosis, and severe nuclear atypia are important histologic features in high grade tumors. Because the low grade tumors have an excellent prognosis while high grade tumors do not, exact histologic grading is very important to predict prognosis and avoid unnecessary treatment. The differential diagnosis from adenosquamous cell carcinoma with a poorer prognosis should be kept in mind.

ACKNOWLEDGEMENTS

We thank So Young Kang for her generous help in the EGFR mutation study.

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