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Original Article

Pulmonary mucoepidermoid carcinoma in Chinese population: a clinicopathological and radiological analysis

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Abstract: Background: Pulmonary mucoepidermoid carcinoma (PMEC) is a rare malignant neoplasm with remarkable resemblance to mucoepidermoid carcinoma of the salivary glands. It constitutes a unique set of patient population. In this study we briefly discussed the current state of knowledge of PMEC and described the clinical presentation and management of 27 PMEC cases. This study aimed to discuss the utility of surgical treatment in the patients with pulmonary mucoepidermoid carcinoma. Methods: We retrospectively studied 27 cases with the diagnosis of PMEC, divided into low grade and high grade based on histopathological characteristics. The clinical symptoms, radiological manifestations, pathological characteristics, treatment strategy and prognosis were systemically analyzed. Results: The tumor could occur in any lobe of the lungs. The treatment included surgical intervention and/or adjuvant therapies. While the sex-age distribution and initial staging was not different between low- and high- grade PMEC, the disease control rate (95%) and 5 year survival (95%) were much higher in low-grade PMEC than the high-grade cases (57.1% and 42.9%, respectively). Conclusion: The clinical, radiographical and pathological features of PMECs were systemically analyzed and summarized, and the utility of pathological grading system as the independent prognostic factor in addition to clinical staging was confirmed.

Keywords: PMEC, clinical features, Chinese population, prognosis

Introduction

PMEC is a rare pulmonary malignant tumor. Its clinical manifestations are diverse and lack of specificity, easily leading to diagnostic confusions. Histologically, PMECs usually arise in the submucosa of the large bronchi and mainly consists of mucous-secreting cell, squamous cell and intermediate cell types [1]. PMECs are classified into low grade and high grade according to their histological characteristics in an attempt to predict malignant potential. These patients typically present with symptoms of airway irritation or obstruction, such as cough, hemoptysis, wheezing, and postobstructive pneumonia. The prognosis of low grade PMECs is significantly better than the high grade ones [2]. In this relatively large scale study we analyzed 27 patients with PMECs with the focus on the clinical outcome with different types of treatment.

Materials and methods

Patients

A total of 27 cases of pulmonary mucoepidermoid carcinoma were identified and recruited at The First Affiliated Hospital of Zhengzhou University from January 2008 to December 2013. The study was approved by the board of Human subject research ethnics committee in Zhengzhou University.

Clinical, pathological and radiological analysis

All histopathological and radiographic diagnoses were consensually reviewed and confirmed at the Department of Pathology and Department of Radiology. Cases with severe cardiac, pulmonary diseases were excluded. Histological features of the tumor were graded according to the standard criteria [3]. Cases were staged following the standard of international TNM staging

Table 1. Clinical and pathological characteristics of patients with PMEC

Characteristic	Low-grade (%)	High-grade (%)
Overall	20 (74.1)	7 (25.9)
Age at diagnosis (years)		
<45	2 (10.0)	1 (14.3)
45-60	11 (55.0)	5 (71.4)
>60	7 (35.0)	1 (14.3)
Mean (± SD)	54.1 (±10.9)	52.2 (±10.3)
Location		
Right upper lobe	5 (25.0)	4 (57.1)
Right middle lobe	2 (10.0)	0 (0)
Right lower lobe	0 (0)	1 (14.3)
Left upper lobe	12 (60.0)	1 (14.3)
Left lower lobe	1 (5.0)	1 (14.3)
Stage		
Early stage (stage I, II)	11 (55.0)	4 (57.1)
Advanced stage (stage III, IV)	9 (45.0)	3 (42.9)
Treatment		
Surgery alone or surgery with any adjuvant therapy	13 (65.0)	5 (71.4)
Adjuvant therapy only (CCRT, RT, CT)	7 (35.0)	2 (28.6)

Abbreviations: SD, standard deviation; CCRT, concurrent chemoradiation therapy; CT, chemotherapy; RT, radiation therapy.

Table 2. Disease control rate and 5 year survival rate according to low-grade or high-grade

Assessment	Low-grade	High-grade	*P*-value
Disease control rate	19 (95%)	4 (57.1%)	0.042
5 year survival rate	19 (95%)	3 (42.9%)	0.09

system (7th edition). The mean follow-up time was 36 months (range 3 to 79 months). Cases were evaluated with physical examination and Thorax CT every 3 months. Further laboratory and radiological tests were requested if there were any other symptoms.

Outcome and survival analysis

The outcomes of treatments were evaluated by short term responsive rates, such as disease control rate, and long term responsive rates, such as 5 year survival rate and so on. The outcomes of solely medical treatment versus combined surgical resection were compared.

Statistical analysis

All statistical procedures were performed using SPSS version 14.0 software. Categorical variables were expressed as percentages (%) and continuous data as medians with minimum and maximum values. Categorical variables were analyzed with Chi-square test. P<0.05 was considered as statistically significant.

Results

The common clinical presentations of the 27 patients included cough (15 cases, 55.6%), expectoration (11 cases, 40.7%), hemoptysis (7 cases, 25.9%), fever (6 cases, 22.2%), wheezing (6 cases, 22.2%) and dyspnea (2 cases, 7.41%). Two cases (7.41%) were asymptomatic.

All patients underwent CT examination. CT imaging invariably showed a lung mass in all cases. The main radiographic features were well demarcated masses with smooth borders, including 17 cases of round shaped lesions (63%), 6 cases of lobulated tumors (22.2%), and 2 cases with specular signs (7.4%). The complications included atelectasis in 7 patients (25.9%), obstructive pneumonia in 6 patients (22.2%), and pleural effusion in 6 patients (22.2%). Overall the CT findings did not reveal any specific features for PEMC cases.

The final diagnoses and grading of all cases were rendered based on consensual histopathological examinations. The tissues used for diagnosis were obtained by fiber bronchoscopy (16 cases, 59.3%), open thoracic exploration or video-assisted thoracoscopic surgery (VATS) (8 cases, 29.6%), and CT guided percutaneous lung biopsy (3 cases, 11.1%). CT and histopathologic features of PMECs were showed in **Figures 2** and **3**. No specific CT features were associated with either the low or high grade PMECs.

Baseline patient characteristics (demographic, age, radiological, stage, therapeutic, etc.) in overall population were summarized in **Table 1**. Briefly, 20 cases were diagnosed with low grade PMEC and 7 cases with high grade PMEC. The mean ages of the patients were 54.1 and 52.2

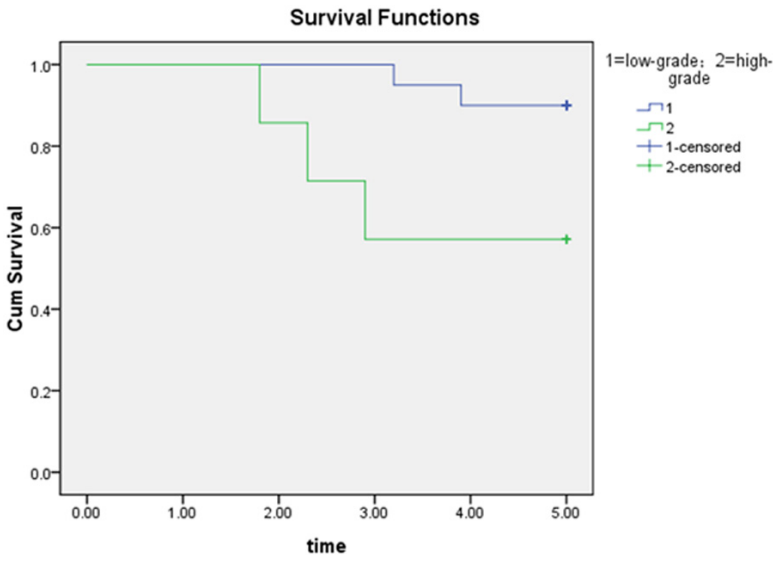

Figure 1. 5 year survival rate according to low-grade and high-grade PMEC.

in low grade PMEC and high grade PMEC groups, respectively. There was no significant difference in the age distribution between these two groups. The tumor could occur in any lobe of the lungs, with relatively higher incidences of low grade PMEC in left upper lobe (60%) and high grade PMEC in right upper lobe (57.1%). 11 cases of low grade PMEC (55%) were diagnosed in early clinical stage (stages I and II), while the rest of 9 cases (45%) were found with advanced clinical stage (stages III and IV). Similarly, 4 cases of high grade PMEC (57.1%) were diagnosed in early clinical stage (stages I and II), while the rest of 3 cases (42.9%) were found with advanced clinical stage (stages III and IV). As for the treatments, 13 patients of low grade PMEC (65% of low grade) and 5 patients of high grade PMEC (71.4% of high grade) underwent surgical resection with or without adjuvant therapy including chemotherapy and radiation therapy. The remaining patients, including 7 cases of low grade PMEC and 2 cases of high grade PMEC, received only adjuvant therapy without surgeries. EGFR gene mutations were examined and negative in all cases (data not shown).

The Efficacy of treatments was evaluated based on the revised Response Evaluation Criteria in Solid Tumors (RE-CIST) [4]. The follow-up time ranged from 2 to 8 years (median 25 months), and the study endpoints were disease progression, death or cessation of follow-up. There were totally 4 deaths which included one patient of low grade PMEC and three patients of high grade PMEC. Briefly, the first patient with high grade PMEC and brain and bone metastases (stage IV) died three months after a 4-week course of chemo-radiation therapy. The second patient with high grade PMEC (stage IIIb) had pulmonary atelectasis and pleural effusions after 5-week chemotherapy and passed away 5 months later. The third patient with high grade PMEC (stage IV) underwent surgical resection combined with chemotherapy, later on developed brain metastasis and lymph node metastasis and deceased 20 months later. In addition, one patient diagnosed with high stage (IIIa) low grade PMEC also developed widely metastatic disease in spite of surgery and chemotherapy, and died 38 months later.

The disease control rates were evaluated after two months of treatment. 5-year survival rates of the low grade and high grade PMECs were shown in **Table 2** and **Figure 1**. After normalization with age and sex, the disease control rate was much higher in the patients with low grade PMEC (95%) in contrast to the high grade cases (57.1%) (P=0.042) in spite of treatment choices. The same trend was observed in the analysis of the 5 year survival rate, which was much higher in low grade PMEC patients (95%) than the high grade cases (42.9%) (P=0.09).

Discussion

PMEC is a rare pulmonary malignant tumor, which was first described by Smetana in 1952 [5]. Reportedly it accounts for 0.1% to 0.2% of all lung cancers [6-9]. The age distribution of PMEC is wide, ranging from 4 to 78 year old. The average age is around 40 and PMECs in youth and children are not uncommon [7, 10]. In our series, the onset age ranged from 21-79 years, average at 53.6 years. The gender distribution in our study was 2.7:1, with slight male predilection, which was similar to the previous reports by Vadasz P, et al [11].

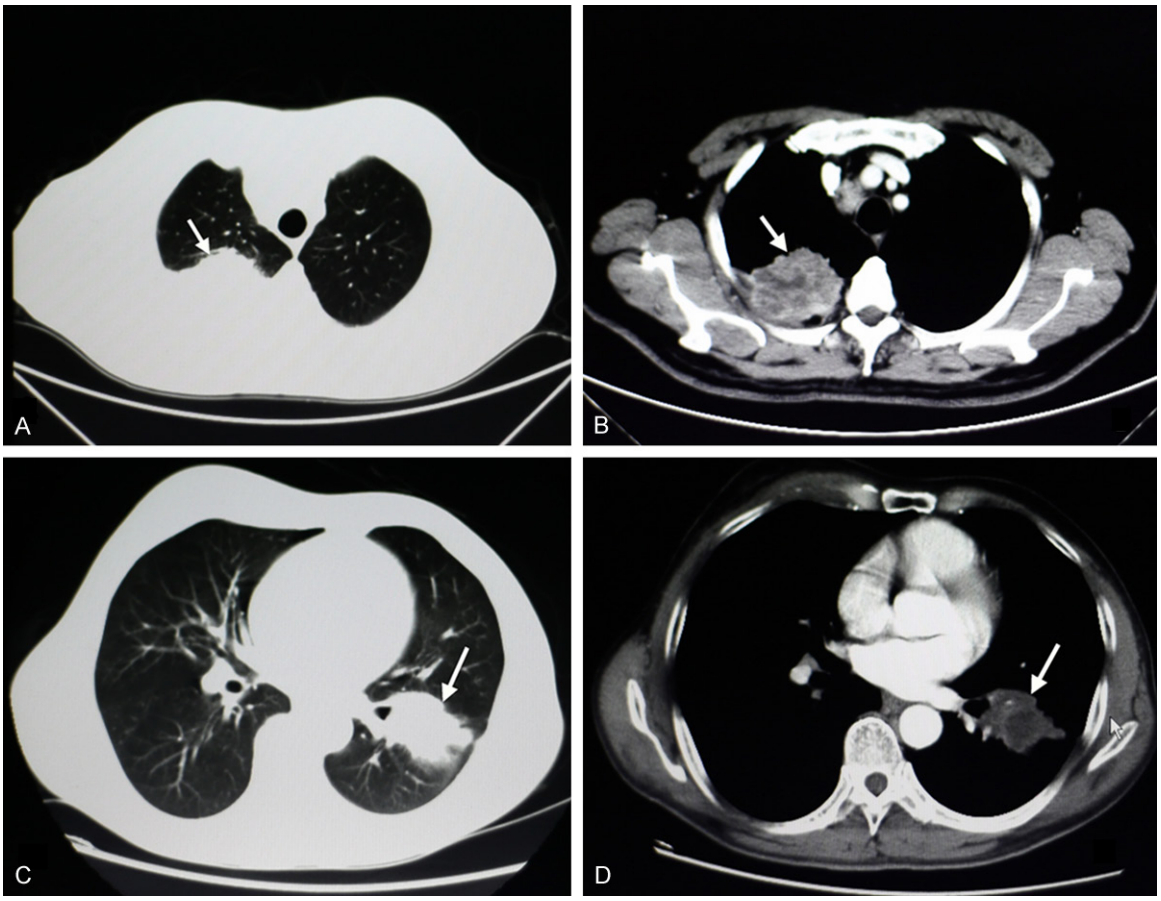

Figure 2. Computed tomography (CT) features. A and B: CT revealed a mass in the right upper lobe of representative case 1 (arrowhead). C and D: CT revealed a mass in the left hilum of representative case 2 (arrowhead).

Because the tumor tends to grow slowly, many patients may be asymptomatic for a long time, especially in the elderly, which was demonstrated in two of our patients. As the disease progresses, symptoms of airway irritation or obstruction will appear at variable stages, presenting as cough, expectoration, haemoptysis, wheezing, and dyspnea, etc., which are no different than the other bronchial lung cancers [12].

PMECs are commonly found in the segmental or lobar bronchi [13, 14], hence bronchoscopic examination is critical in establishing diagnosis. The CT image findings are similar to other types of benign and malignant bronchial nodules and rather non-specific, therefore the value of CT study in PMEC diagnosis is limited.

Because the clinical and radiographic manifestations of PMEC are non-specific, the diagnosis mainly relies on the histopathology. PMECs are mainly composed of mucous-secreting, squamous and intermediate cell types, and conventionally classified into low grade and high grade groups based on certain specific pathological features. This classification has been regarded as an independent factor in predication of level of malignant behavior of this tumor and long term prognosis [15]. In our study we confirmed the finding that high-grade PMEC cases had much worse disease control rate and 5 year survival, and served the only independent prognosis determining factor besides the clinical stage. These findings are consistent with the previous reports [16, 17].

The ideal mainstream treatment is to completely remove the tumor surgically if possible [18]. The common surgical procedures for PMEC include lobectomy, sleeve resection, local resection, segmental resection, or even endoscopic removal when the disease is limited. The efficacy of radiation therapy and chemotherapy is still debatable [19]. A few groups reported

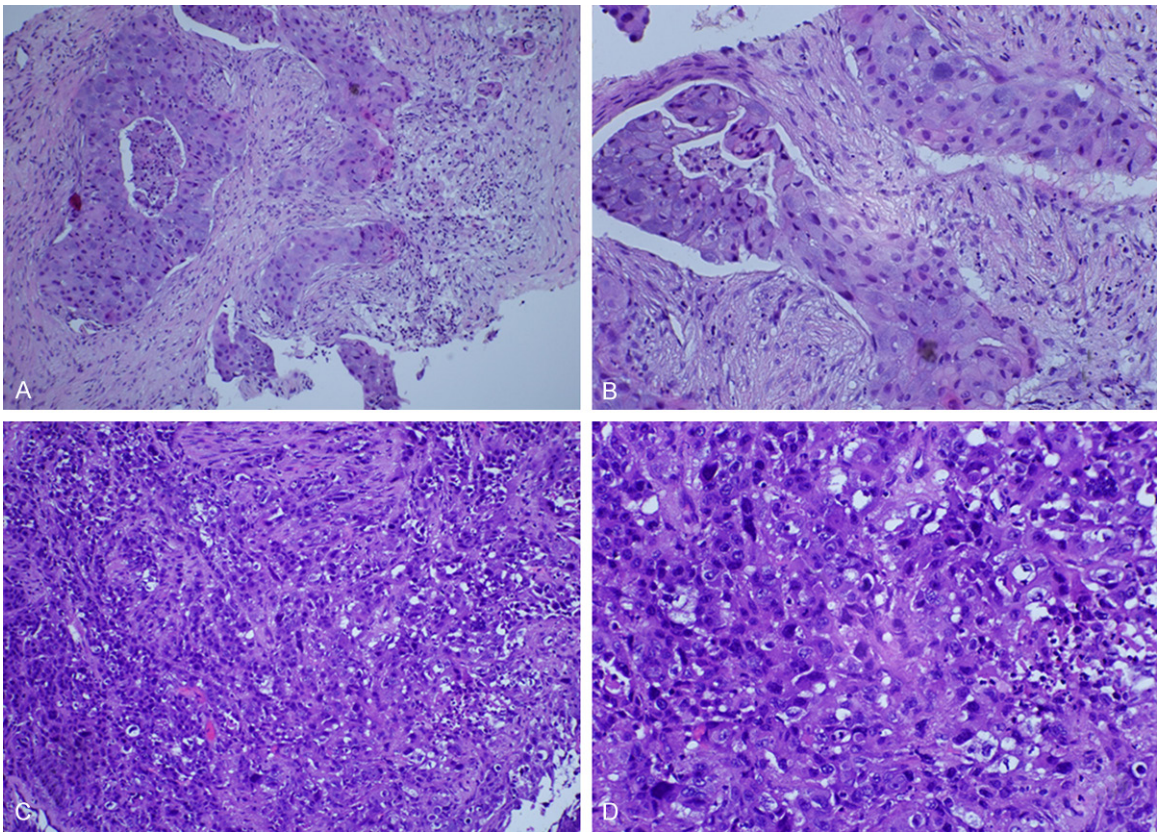

Figure 3. Histopathology of the representative cases of PMEC. A (low power at 4×) and B (high power at 20×) showed the features of a case of low grade PMEC, including mild cytologic atypia, evident cystic component, low mitotic activity and lack of necrosis. C (low power at 4×) and D (high power at 20×) showed the features of a case of high grade PMEC, including high grade cytologic atypia, relatively solid architecture, high mitotic activity and patchy necrosis.

PMEC cases [20, 21] that were successfully treated with bronchoscopic neodymium-yttrium aluminum garnet laser surgery. Those were interesting attempts because the laser surgery was much less invasive than conventional surgical intervention, however long-term follow-up information is needed for validating the effects of these treatments.

For high grade PMEC patients, the mortality rate still remains high [22, 23]. Reports [24, 25] have shown that if EGFR(epidermal growth factor receptor) mutation of the tumor is detected, tyrosine kinase inhibitors gefitinib may improve the prognosis in advanced PMEC patients. Macarenco et al. [26] reported that 92% (11/12) of PMEC specimens were positive for EGFR expression. In MEC of salivary glands, EGFR expression is correlated with histological grade but not with patient outcome [27]. Lee et al [28] reported a patient with aggressive high-grade MEC treated with the TKI erlotinib who also showed radiographic evidence of partial response. However, EGFR gene mutation was not detected in any of our cases, raising a question for further elucidation of the underlying mechanism for the difference of mutation distribution among the studies. Furthermore, the status of MAML2 gene translocation as a confirmation modality in PMEC [29-31] and its association with clinical and radiological features would be studied in detail in the future work.

Overall, our study systemically analyzed the clinical, radiographical and pathological features of a large series of 27 PMEC patients. Although significance the pathological grading system for MEC in salivary glands has been well established, its usefulness in pulmonary MEC was only explored in handful studies because of the rarity. Here we provided solid reassuring evidences that the same grading system can be reliably used in PMECs as the most important prognostic factor in addition to clinical stages, which was in accordance with two other

recent series of PMEC studies [16, 32]. Together with the other preceding studies in PMEC, our study would serve as a foundation for further studies in this rare lung malignancy as for early awareness, timely diagnosis, and appropriate treatment strategy and prognosis assessment.

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Disclosure of conflict of interest

None.

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