REVIEW

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Clinical Presentation and Treatment Options for Clear Cell Lung Cancer: University of Cincinnati A Case Series and Literature Review of Clear Cell Lung Cancer

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Abstract

Clear cell carcinomas are common finding in renal, ovarian and uterine carcinomas. However, clear cell lung cancer (CCLC), first described by Liebow and Castleman in 1963, is considered an extremely rare variant of lung tumors. The 2011 WHO classification of lung tumors considered CCLC as a rare cytologic feature of squamous cell or adenocarcinomas. It is no longer recognized as a formal subtype, albeit it can be referred to in the pathological diagnosis as "with clear cell features" even with marginal fractions of the tumor cells. Such recognition is needed since the variation in clinical features and outcome in this subset of patients. The disease has a clinically vague natural history, is characterized by slight female predominance and is often seen in the elderly. As frequently encountered with rare diseases, its clinical course and treatment options have many questions still yet to be answered. In this paper, we review both the natural history and treatment options mentioned in literature, in the light of our experience by reporting a case series of four patients diagnosed with CCLC and highlight their aspects.

Keywords: Clear cell- lung cancer- case serious- treatment

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Introduction

Lung tumors with clear cell histology, resulting from intracellular accumulation of glycogen in absence of mucus production, are not an uncommon finding. They are often malignant with renal or ovarian metastases or benign, known as sugar cell tumors(Stopsack et al., 2013a). Primary clear cell adenocarcinoma (PCCA) of lung are very rare tumors and mostly reported as case reports in literature(Xu et al., 2016). The new WHO classification of lung cancers in 2015 reflected 2011 the changes made by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS) classification of lung adenocarcinoma to the 2004 WHO classification. One major change was removal of subtype of clear cell adenocarcinoma and recognizing it as a cytosolic feature of the tumor cells, regardless of the amount present (Travis et al., 2015). This change was made since the lack of evidence that show any clinical significance of recognizing it as a specific histologic subtype, even though there is possible associations with molecular features (Travis et al., n.d.). Studies had shown that some of clear cells features e.g. strong glycogen stain and weak mucin stain are common in all major types of lung carcinoma except for small-cell carcinoma (Katzenstein et al., 1980). Therefore, immunohistochemical and molecular confirmation is needed to diagnose PCCA of lung (Gu et al., 2016). Our knowledge about clinico-pathology, molecular mutations and prognosis of PCCA is not fully understood because most of data are driven from case reports. The incidence is variable, depending on threshold of percentage of clear cell component, but ranging from 1.1%(Edwards and Carlile, 1985) to 2.2 % (Gu et al., 2016). Some reports suggest that clear cell tumors may share certain clinico-pathologic features such as a size >2.5cm, the presence of symptoms, and extensive necrosis or abundant mitoses visible and these features are correlated with more aggressive behavior (Xu et al., 2016). The prognosis of PCCA of lung is controversial due to sacristy of data; while some reported that survival for patients with clear cell adenocarcinoma was not significantly different from those without clear cell changes (Russell et al., 2011), or may have favorable outcome (Edwards and Carlile, 1985). Others reported PCCA as a poor prognostic feature (Katzenstein et al., 1980; Gu et al., 2016). PCCA of lung is associated with gene mutations in G12D in the KRAS gene (Stopsack et al., 2013a) and EGFR mutations (Gu et al.,

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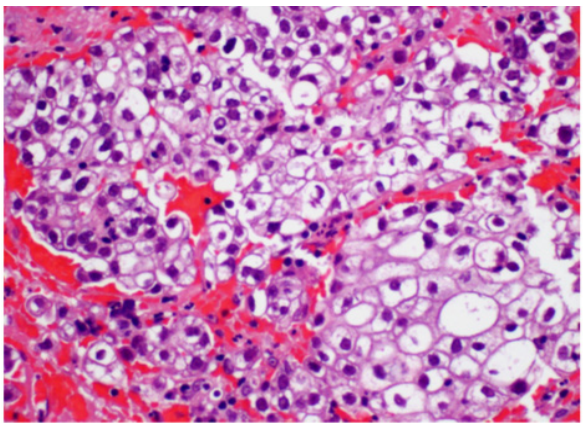

Figure 1. the Figure Illustrates a Hematoxylin and Eosin (H&E) Staining for the Tumor Biopsy of the First Case. Clear cells can be spotted in the lower left corner of the figure.

2016), but the predictive and prognostic value of harboring these mutations is still awaiting further research (Travis et al., 2015). We are reporting four rare cases of clear cell lung cancer patients diagnosed in the cancer center of the University of Cincinnati, representing all cases presented in the same institute with this rare diagnosis.

Patients and methods

We reviewed the charts, pathological diagnosis and imaging studies of 4 rare cases of clear cell adenocarcinoma of the lung that were encountered over the past 5 years at the University of Cincinnati Medical Center.

Case 1

A 61-year-old female patient with a history of heavy smoking presented initially with new onset of hemoptysis and unintentional weight loss. Her computed tomography (CT) scans revealed a 7.2cm lung mass with endobronchial extension. Biopsy and pathological analysis revealed a diagnosis of poorly differentiated CCLC. The patient was started on definitive chemo-radiotherapy. One month following completing the treatment course, the patient developed brain metastasis. EGFR mutation was tested and exon 19 and 21 were negative, EML4-ALK and ROS 1 re-arrangements were also negative. She received cranial irradiation and put on a second line systemic therapy but

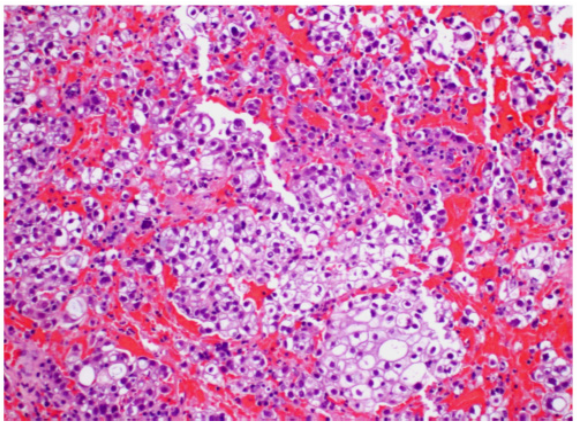

Figure 2. The Figure also Shows the Clear Cell Features for the Second cCase in the Lower Outer Area.

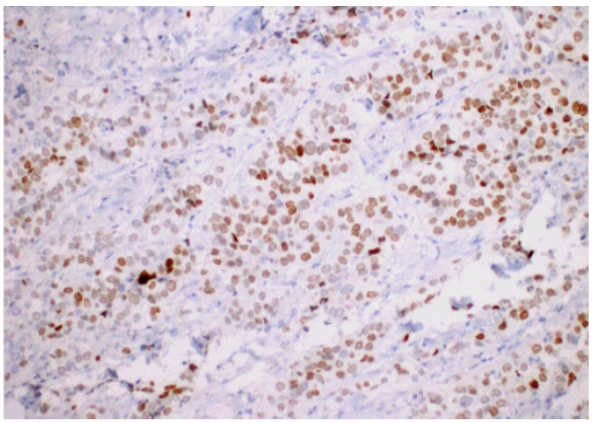

Figure 3. Showing an Illustration of Specimen Obtained from the Third Case

the tumor progressed.

Case 2

The second case 52-year-old female patient. Her history was significant for heavy smoking. She was investigated for unintentional weight loss. Her CT scan of the chest revealed a 1.4cm spiculated nodule. The patient was scheduled for video assisted surgery (VATS) and the pathology confirmed high grade CCLC without lymphovascular or perineural invasion. The patient was managed conservatively.

Case 3

A 71-year-old female smoker had a CT chest scan. It showed a 2.2 cm nodule. Fine needle aspirate (FNA) was done and gave equivocal results. She underwent VATS and pathological analysis showed clear cell adenocarcinoma with no evidence of metastases. No adjuvant therapy was offered.

Case 4

The last case from our records is a 74-year-old female patient. She had a history of orthotopic heart transplantation and on a follow up CT scan an incidental 4cm nodule was spotted. Pathological analysis revealed adenocarcinoma. She underwent VATS and pathology was consistent with clear cell adenocarcinoma without

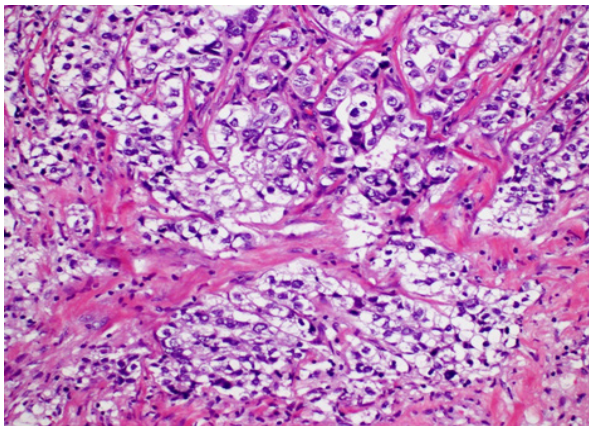

Figure 4. Showing a Stained Section from the Tumor of the Fourth and Last Case.

evidence of infiltration. Her post-operative course was complicated by infection and she passed away due to complications.

Discussion

Though clear cell carcinoma can be more frequent presentation in the ovarian and renal cancers, this entity is very rare in the lung. In 2011, the WHO introduced a classification for lung tumors without listing CCLC. It was considered a rare cytologic feature of squamous cell or adenocarcinomas. However, it still can be mentioned in the pathological report as "with clear cell features" regardless of the fraction they represent in the tumor cells (Travis et al., 2011). So far, about 56 cases of CCLC has been mentioned in reports which reflects the rarity of the disease (Wang et al., 2013). In fact, lung cancer classification has been lacking in the area of categorization of rare presentations such as pulmonary sarcomatoid and large cell neuroendocrine carcinomas (Brambilla et al., 2001; Iyoda et al., 2007; Karim et al., 2018). The presentations of this disease have been so diverse that individualization of tumors according to genatic profiling and molecular classification has been the mainstay of many recent reports (Hassan et al., 2017; Karim et al., 2017; Karim et al., 2017).

The first case required further investigations to increase her treatment options. EGFR mutation was tested and exon 19 and 21, and were negative, EML4-ALK and ROS 1 re-arrangements were also negative. That goes with other reported cases were these tumors demonstrated negative results to EGFR gene mutations associated with gefitinib or erlotinib sensitivity. There was no translocation of the ALK gene (2p23). however, this case KRAS exons 2–4 was sequenced and revealed point mutation G12D (Stopsack et al., 2013b).

Our four cases had a presentation that escalated from indolent disease to rapidly progressive disease. The first case presented in an advanced stage. She had not had much clinical improvement on treatment, albeit stable, and did not maintain a sustained response. The rest of the cases underwent VATS without need for adjuvant treatment due to early stages. Later these cases progressed rapidly at different time points with poor responses to treatment. Other reported cases showed close patterns. Stopsack et al reported a female case with early stage CCLC (stage IIIA). The patient underwent tumor resection followed by adjuvant chemotherapy with cisplatin and pemetrexed for four cycles. The patient was alive with no signs of recurrence 9 months after surgery (Stopsack et al., 2013b). It is worth mentioning that our three cases that underwent VATS showed progression within this time frame. Case 2 and 3 were diagnosed at an earlier stage of the disease and were not offered chemotherapy in the adjuvant setting. Case 4 questions if these lesions could be followed without surgery in high-risk patients to avoid unnecessary morbidity and mortality associated with surgery. In previously mentioned cases, however, the CCLC cases were offered surgery without major complications (Stopsack et al., 2013b; Wang et al., 2013).

Our 4 cases were all clear cell adenocarcinoma of the lung confirmed by immunohistochemistry. All of which showed sheets polygonal cells arranged in irregular trabeculae. They had clear watery cytoplasm with foamy appearance in some cells. The abundant cytoplasm was positive to periodic acid Schiff (PAS). The cells have large eosinophilic nuclei. Scanty stroma infiltrated by lymphocytes. Necrosis was less pronounced in all specimen, and mitosis was moderate. Immunostains done on the tumor tissue samples for these patients were positive for CAM5.2, TTF-1 and CK7 and negative for CK20, p63, S-100 and PAX-8. Several case reports shared same histopathlogical description of their cases.

Edwards C et al, described cases of CCLC as large polygonal cells with rich cytoplasmic material. The authors also mentioned the moderate mitosis as well as positivity to periodic acid Schiff stain. However, these cases were reported in the eighties and immunostains were not available (Tsai and Giddens, 1985). In a report about a 59-year-old woman with incidentally discovered lung nodule, turned to be CCLC, the tumor tissue sample was tested for several immunomarkers. The results were close to the outcome of our patients with pan cytokeratin positivity, CK7 positive tumor and TTF-1 positive. The tumor was also negative to S-100 and CK20 (Stopsack et al., 2013b). Another case report revealed a close but rather diagnostic immunomarkers stains for CCLC. The tumor was strongly immunoreactive for HMB-45 and showed a positive reaction to vimentin, CD34, and S-100 protein but no reactivity for cytokeratin, desmin, CD68, EMA, RCC, and TTF-1 (Wang et al., 2013). Lung cancer cases which have vimentin overexpression were reported to have decreased survival compared to lung cancer cases (Karim et al., 2017). So, reported vimentin positivity might need to be related with this rare entity to define it more. Since clear cell histology is part of adenocarcinoma or squamous histology, scanty biopsy material might be not enough and underdiagnose such cases as seen in case 3. Other reports also based their diagnosis on needle biopsies (Wang et al., 2013) or surgical resection (Stopsack et al., 2013a).

Cases diagnosed in our institute were females. The CCLC, is known to show slight female predominance (Travis et al., 2015). This emphasize the importance of running a panel of markers to exclude more frequent presentations such as endometrial and ovarian cancers in females. Renal cancer added for both genders.

Cases 1 and 2 highlight the lack of established treatment guidelines for CCLC. As in many cases of rare aggressive lung tumors, such as sarcomatoid pulmonary cancer, surgical intervention is seen as seen as the best treatment modality regarding the outcome (Karim et al., 2018). Currently, same chemotherapy regimens are used as for non-clear cell adenocarcinoma. One studies held mammalian target of rapamycin hyperactivation as a driver for the disease (Kenerson et al., 2007). But these findings still in early stage and far from clinical application (Lee et al., 2005). Another reported KRAS as driver mutation, which, if established, could lead to future therapeutic options (Yousem, 2013). However, the latter option might not be applicable to all CCLC patients as is of higher

incidence in CCLC cases, but report absent mutations. Our cases received radiotherapy in the context of local palliation or for brain metastases.

In conclusion, CCLC is a rare tumor and more studies are needed to establish management and guidelines. Genetic mutations could be potential therapeutic targets. Risks and benefits of treatment should be considered in high-risk patients.

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