# Mucinous cystadenocarcinoma arising from mucinous cystadenoma of the lung: case report and review of the literature

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**Abstract:** Mucinous cystadenoma is a benign tumor commonly found in the pancreas, the ovaries or the appendix. Only very few cases of these tumors originating from the lungs have been reported worldwide, with even less cases describing malignant transformation. We present the case of a 58-year-old woman with a history of recurrent pulmonary infections who underwent left upper lobectomy for lung abscess and was initially diagnosed with pulmonary mucinous cystadenoma (PMCA). Upon thorough immunohistochemical workup, especially due to carcinoembryonic antigen (CEA) positivity, intramucinous singlet cells were eventually diagnostic for invasive carcinoma, in this case a mucinous cystadenocarcinoma arising from a PCMA. PMCA is a rare benign tumor whose potential for malignant transformation has not yet been fully understood. Due to the low number of cases further studies are needed to evaluate if there is a benefit of complete oncologic resection, provided the general condition of the patient allows it. A review of the currently available literature serves to better understand the clinical, radiological and histological features of this rare tumor.

**Keywords:** Pulmonary mucinous cystadenoma (PMCA); pulmonary mucinous cystadenocarcinoma (PMCAC); rare lung tumor; malignant transformation; carcinoembryonic antigen (CEA)

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#### Introduction

Mucinous cystadenoma is defined as "a localized cystic mass filled with mucin and surrounded by a fibrous wall lined by well-differentiated columnar mucinous epithelium" (1). The benign tumor is commonly found in pancreas and ovaries, as well as in the appendix (2-4). In the lung, however, only a few cases have been reported world-wide (5-7). The usually unilocular tumor can be located in the periphery of any lobe of the lung. Since the first description by Eck *et al.* in 1969 and a report by Sambrook Gowar in 1978, primary pulmonary mucinous cystic neoplasia has been recognized as a separate entity (8-10). Following the classification of Gao *et al.* according to pathologic features there is benign pulmonary mucinous cystadenoma (PMCA), pulmonary mucinous tumor of borderline malignancy [with atypia; postmortem computed tomography angiography (PMCT-A)] and pulmonary mucinous cystadenocarcinoma (PMCAC) (8).

The main differential diagnoses for PMCA and PMCAC are bronchioalveolar carcinoma, solitary metastatic mucinous tumors from other organs and bronchial mucous gland adenoma (11). According to the 2015 WHO classification of tumors of the lung, pleura, thymus and



Figure 1 Smooth margined mass with homogenous density and adjacent inflammatory infiltrate and atelectasis. Mediastinal lymphadenopathy.

heart, the term mucinous cystadenocarcinoma has been discontinued and the entity has been included under the category of colloid adenocarcinoma (12). For simplification, especially with regard to the review we have kept the old term "mucinous cystadenocarcinoma" throughout the manuscript.

#### **Case presentation**

A 58-year old female with a history of recurrent airway infections was admitted to the hospital with cough, dyspnea and pain in the left lower side of the chest. Serum C-reactive protein (CRP) levels were only moderately elevated. The chest X-ray revealed a large opacity in the left upper lobe of the lung. A CT scan was initiated, confirming a 12.0 cm  $\times$  7.5 cm smooth margined homogeneous mass in the left upper lobe with adjacent atelectasis, inflammatory infiltrate and mediastinal lymphadenopathy (*Figure 1*).

Bronchoscopy revealed distortion and partial atelectasis of the segments 1–3 of the left upper lobe and initial occlusion of segment 4 (*Figure 2A*). When probed, a lot of mucous was drained, revealing a rather large necrotic cavern (*Figure 2B,C*). Ample biopsies were taken and endobronchial ultrasound-guided transbronchial fine needle aspiration biopsy (EBUS-TBNA) was performed

to evaluate the mediastinal lymph nodes. Malignancy could not be excluded by histopathological findings alone, so the patient underwent surgical therapy. Anterolateral thoracotomy was performed with resection of the left upper lobe and systematic mediastinal lymphadenectomy. Macroscopic examination showed a well-circumscribed cystic mass filled with mucus and a maximum diameter of 12 cm. Histologically the cyst was lined by tall mucinous epithelium, while nuclear atypia was mild and polarity was still conserved. Thus, the tumor was initially interpreted as mucinous cystadenoma (Figure 3A) Immunohistochemical analysis of the mucin producing epithelial cells showed expression of CEA and CK7. In pneumocytes and respiratory epithelium CK7 staining was also positive. However, further analyses revealed focal singlet cells within the mucus, which were diagnostic of cystadenocarcinoma arising from the cystadenoma (Figure 3B,C,D). All lymph nodes were found to be cancer free. There weren't any postoperative complications. Antibiotic therapy was started with cefuroxime right after surgery and later changed to moxifloxacin following the identification of the pathogen as Klebsiella pneumoniae. There was a gradual decrease in serum inflammatory parameters.

About 1 year after initial surgery the patient is doing well



Figure 2 Left segment B4 was initially completely occluded (A). Once probed a large mucous-filled cavern was revealed (B,C).



**Figure 3** Histological work-up. (A) The cyst is lined by tall mucinous epithelium, while nuclear atypia was mild and polarity was still conserved, leading to the initial interpretation as mucinous cystadenoma (HE staining); (B) intramucinous singlet cells, diagnostic for invasive carcinoma (HE staining); (C,D) immunohistochemical analysis of the mucin producing epithelial cells showed expression of CK7 (C) and CEA (D). In pneumocytes and respiratory epithelium CK7 staining was also positive. Further analyses revealed focal singlet cells within the mucus, which were diagnostic of cystadenocarcinoma arising from the cystadenoma. CEA, carcinoembryonic antigen.

and is undergoing regular follow-ups including CT-scans and bronchoscopy.

# Discussion and review of the current literature

We conducted a systemic search for "PMCA", "pulmonary

mucinous cystadenoma", "PMCAC", "pulmonary mucinous cystadenocarcinoma" and "PMCT-A" in Medline and the Cochrane Library. To our knowledge, 14 cases of PMCA have been reported in the English literature so far with one being describes as unusual mucinous cyst (5-8,10,13-16). Patients' age ranges from 32–75 years (median 61 years)

and the tumor seems to be more common in females (10 females vs. 5 males). They were located in the periphery of any lobe of the lung, with a preference towards the right side (11 vs. 4 cases). The median size was 5 cm (range, 0.8–15 cm), which makes our case one of the largest tumors diagnosed so far. In some cases, the cystadenoma could be reached via bronchoscopy, yet a definite diagnosis could never be established by endoscopic biopsy alone (Table 1). Preoperative diagnosis is challenging because more than 90% of the tumor bulk consist of mucin (5), leaving only a small number of cells. Radiographically PMCA appears as a well-defined, homogeneous lesion. In one case of pediculate PMCA, the tumor proved to be difficult to distinguish from a pleural tumor due to its location close to the chest wall in the right upper lobe (16). Inflammation and adjacent atelectasis only seem to be present after a certain enlargement of the lesion due to compression and distortion of the surrounding tissue. Patients then develop recurrent pneumonia, cough and chest pain. Except for one patient presenting with hemoptysis originating from a 5-cm PMCA, the other lesions were detected incidentally. Aside from other malignant and benign tumors originating from the lungs, solitary metastatic mucinous tumors from other organs, especially from the ovary and pancreas, are important differential diagnoses. Thorough clinical and radiologic evaluation is, as always, mandatory (17).

Thoracotomy was performed for tumor resection for all but two cases (video-assisted thoracoscopy), followed by lobectomy in eight cases and wedge resection in seven cases. A benign lesion confirmed in intraoperative frozen section led to the surgery being finished after wedge resection. In our case enlargement of the mediastinal lymph nodes was present in addition to a large tumor of unclear dignity, therefore complete oncological resection was performed.

Immunohistochemical studies usually show positivity for pan-cytokeratin (CK) and in some cases CEA (5), in accordance with the findings from our case. Stains for thyroid transcription factor-1 (TTF-1) are usually negative. In our case initial interpretation was difficult due to the fact that most lining epithelial cells showed only mild atypia, which is in agreement with PCMA. Upon thorough immunohistochemical workup, especially due to CEA positivity, intramucinous singlet cells were diagnostic for invasive carcinoma, in this case a mucinous cystadenocarcinoma arising from a PCMA. Rigorous and precise sampling and microscopic evaluation including the intracystic mucinous masses are therefore pivotal for the assessment of malignancy in PCMA. *KRAS* point mutations have been suggested to be associated with tumor development in mucinous neoplasms originating from the ovary, appendix or pancreas (4,5). In the literature, there has been only one case of mucinous cystadenoma in the lung that was analyzed for *KRAS* and *EGRF* mutations and both were negative.

We prepared micro dissection of the tumor and extracted DNA from the cancer cells, which were then analyzed for 15 different well-known driver mutations using next-generation sequencing (TruSight Tumor 15, Illumina, USA). We found a driver mutation typical for carcinomas in exon 12 of the *KRAS* gene (p.G12V). In concordance with this finding, *EGFR* exons 18–21, as well as *BRAF* exons 11 and 15 revealed wild type sequences. Furthermore, two more polymorphisms that have been documented in the dbSNP (database of Single Nucleotide Polymorphism; PIK3CA exon 9 p.R524K; TP53 exon 4 p.P72R) were identified. On the basis of our molecular pathological investigations with detection of a typical *KRAS* mutation the transformation into a mucinous cystadenocarcinoma could be further verified.

#### Conclusions

PMCA is a rare benign tumor that should be kept in mind as a differential diagnosis when investigating patients with solitary, radiographically well-defined, mucinous lesions in the lung. Most patients are not experiencing any symptoms. There are, however, cases like ours where the lesion has grown to cause distortion in the surrounding tissue and inflammation and atelectasis are present.

Although the prognosis for patients with PMCA is usually good, this is the third case reporting a focal adenocarcinoma arising from a mucinous cystadenoma (13). Moreover, there is another case reporting focal atypia in PMCA consistent with adenocarcinoma (14) and one case reporting recurrence of PMCA 20 years post initial surgery despite initial complete (R0) resection (6).

Due to a very limited number of cases reported so far, the biology of this tumor and the underlying pathogenesis of malignant transformation remains unclear but our molecular analyses reveal that driving *KRAS* mutations, which are typical for mucinous carcinomas of the lung, may as well be one mechanism for the development of mucinous cystadenocarcinoma arising from PCMA. To further corroborate those findings and to determine if complete oncologic resection might be beneficial, more studies are needed.

Table	1 Clinical det	tails of rep	ported cases of <b>F</b>	oulmonary mi	ucinous cyst	tadenoma						
No. of cases	Authors (year)	Age (years), gender	Symptoms	Location	Size (cm)	CT scan	FDG- PET	Bronchoscopy	Smoking	Molecular markers/ histology	Treatment	Follow-up/ outcome
2	Kragel <i>et al.</i> (1990)	62, M/62,F	NA	RML/RML	1.5/0.8	NA	NA/NA	NA	AN	NA	Wedge resection/ lobectomy	3/1 year(s)/ without recurrence
<del></del>	Davidson <i>et al.</i> (1992)	69, F	Neck pain and arthritis/ incidental	RML	2.5	NA	AN	NA	Yes	Small adenocarcinoma detected (0.2 cm × 0.3 cm)	THT, wedge resection	6 months/ without recurrence
N	Roux <i>et al.</i> (1995)	53, M/32, F	Incidental/ incidental	RUL/RLL	5.0/5.0	Round homogeneous mass of tissular density/ well defined rounded mass, no lymph node enlargement	NANA	Macroscopically normal/NA	Yes/no	MIB-1 <10%/<5%, both CEA negative	Mediastinoscopy (negative), THT upper lobectomy/THT wedge resection	2 years without recurrence (died from a stroke)/ 15 years without recurrence
<del>.</del>	Guimaraes et al. (2004)	75, M	2-cm mass detected incidentally on chest radiograph, 6.4 cm 2 years later	RLL	6.4	Smooth margined mass with homogeneous density, no adjacent atelectasis	Υ Υ Ζ	Distorsion of the anterior and lateral basilar segments of the RLL, no endobronchial lesion	Ч Z	Multiple foci of adenomatous lining with mild atypia	Thoracoscopic evaluation followed by THT + lobectomy	Approximate 3 months/ without recurrence
<del>.</del>	Matsuo et al. (2005)	56 [36] * F	Palpitations (atrial fibrillation)/ incidental	1	5.0	Heterogeneous mass in the LLL without lymph node enlargement	Υ Υ Ζ	No evidence of malignant cells	Ч Z	Previous suture line on the tumor surface, no mitotic figured, CEA negative, no cancerous cells	Wedge resection for a lung tumor 20 years ago. THT + 2nd wedge resection	2 years/ without recurrence
-	lgai <i>et al.</i> (2008)	60, M	Incidental	RUL	Q	Homogenous D-shaped opacity, growth from 4 to 6 cm over time (15 years)	NA	Computed tomography- guided needle aspiration, no bronchoscopy performed	AN	No mitotic figures were detected	VATS, wedge resection	3 months/ without recurrence
Table	1 (continued)											

#### Journal of Thoracic Disease, Vol 10, No 4 April 2018

E247

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No. of case	Authors (year) s	Age (years), gender	Symptoms	Location	Size (cm)	CT scan	FDG- PET	Bronchoscopy	Smoking	Molecular markers/ histology	Treatment	Follow-up/ outcome
-	Haruki <i>et al.</i> (2010)	71, F	Incidental	RUL	2.5	Well circumscribed rounded tumor mass	No uptake	NA	°Z	CK and CEA positive, TTF- 1 and SP-A negative, MIB- 1 Index <1%, no KRAS or EGFR mutation	VATS, wedge resection	8 months/ without recurrence
<del></del>	Sambrook Gowar (1978)	68, F	Acute pain under right lower ribs	BLL	15.0 (7.0, 5.0)**	NA, chest radiograph only	AN	Granulations in right apical lower segment bronchus, bluish cystic lesion in the lumen	АА	AN	THT, left lower lobectomy + removal of 2 more masses, R2	5 years/ without recurrence
-	Dixon et al. (1993)	59, M	Chest radiographs only, over 11 years	LUL	4.5	ΨN	NA	Complete occlusion of the anterior segmental bronchus	NA	Focal marked glandular atypia described, classified as MCT	THT, resection	5 years/ without recurrence
က	Gao <i>et al.</i> (2005)	50, F/61 F/61, F	Hemoptysis/ incidental/ incidental	LUL/ RML/RUL	5.0/2.5/3.0	Solitary, soft tissue density, no evidence of calcification	AN	A	yes yes	CK7 positive, CEA negative, TTF-1 intermed./ CK7 and CEA positive, TTF- 1 negative/ CK7 and CEA positive, TTF- 1 negative. All 3 cases Ki-67: 0%	Lobectomy + lingula resection/ lobectomy / upper bilobectomy	10/6/1 year(s)/ without recurrence
-	Our case	58, F	Recurrent pneumonia, acute pain under the left ribs	LUL	15.0	Homogenous mass with adjacent atelectasis, inflammatory inflitrate and mediastinal LAD	AN	Occlusion of the left segment B4, after probing, a large cavern was revealed	Yes	Positive for CK7 and CEA, negative for TTF-1	EBUS-TBNA of the subcarinal lymph node, THT + lobectomy + systematic lymp <sup>+</sup> node dissection	Bronchoscopy revealed a new polyp in the LLL, no tevidence of recurrence of PMCA
*, the refer right transe	e patient had μ to the dimens upper lobe; Rl cription factor	previously sions of t LL, right 1 1; SP-A,	/ received a par wo more lesior lower lobe; LLL surfactant prot	rtial resectio is removed , left lower l ein A; EBUS	in of the lunc from the par lobe; CEA, ci	g for a pulmonary r tient in that report. arcinogenic embry obronchial ultrasou	mucinou . M, mal- onal anti ind-guid	s cystadenoma 2( e; F, female; NA, r gen; VATS, video- ed transbronchial	) years ag not availab assisted th needle asp	o when she was 34 le; RML, right mid toracoscopy surge viration; PMCA, pul	6 years old; **, dat ddle lobe; THT, tho sry; CK, cytokeratir ilmonary mucinous	a in parenthesis racotomy; RUL, i; TTF-1, thyroid cystadenoma.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Informed Consent:* Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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