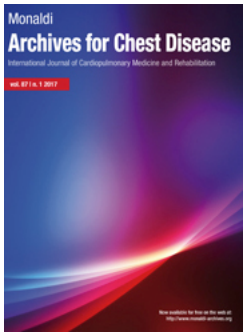

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Bronchoscopically-visible massive central airway cancer cavitation is associated with metastatic disease, lack of actionable mutations and poor prognosis: a case series

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Abstract

Cavitating lung tumors occur in approximately 10-15% of the patients, are more commonly associated with squamous histology, and are typically located in the lung parenchyma. Herein we describe an exceedingly rare series of 5 patients, 4 of whom treatment-naïve, whose tumor caused the disruption of the normal airway anatomy at the level of lobar or segmental bronchi, leading to the formation of an endoscopically-visible cavity which ended up in the lung parenchyma or even into the pleural space. Sex (3 males, 2 females), smoking habit (2 never smokers, 2 former smokers, 1 current smoker), and histology (3 adenocarcinoma, 2 squamous cell carcinoma) were heterogeneous, but the 4 patients treatment-naïve presented with metastatic disease, poor ECOG performance status, similar clinical complaints of long duration, and lack of actionable mutations. The only patient who exhibited a meaningful response to treatment had the lowest symptoms' duration, the smallest size of the cavitated mass, and the best performance status at the time of diagnosis. This series provides the first comprehensive description of a rare presentation of lung cancer characterized by similar clinical complaints, delayed diagnosis and poor prognosis.

Key words: bronchoscopy; cavitated tumor; hemoptysis; immunotherapy; lung cancer; radiotherapy.

Introduction

In the last decade, the awareness towards cavitary lung tumors has increased due to the evidence of an increased risk of cavitation associated with treatment options including antiangiogenetic drugs, immunotherapy, radiotherapy and/or chemoradiotherapy [1-6]. Furthermore, treatment with any of the above treatment options of lung tumors which are already cavitated at the time of diagnosis has been associated with an increased risk of complications, severe hemoptysis and infection being the most feared [7-10].

In most cases, the tumor cavity is located in the lung parenchyma and its characteristics can be studied only at imaging studies [11-13]. To our knowledge, endoscopically-visible, central airway necrosis has been rarely described and exclusively after radiotherapy or chemoradiotherapy [14-16].

The aim of the present manuscript is to provide the first description of the clinical, imaging, pathological and molecular characteristics of an exceedingly rare series of patients exhibiting a centrally located, endoscopically-visible cancer cavity.

Case Presentation

Table 1 summarizes the main demographic, clinical, histological and molecular characteristics of the 5 patients described below in greater detail.

Case #1

A 77-year-old woman, never smoker, presented with a two-months history of hemoptysis and massive weight loss (13 Kg). Her ECOG performance status was 3. A whole-body CT scan showed a 50 x 48 mm cavitated lung mass of the left lower lobe (Figure 1A) and two brain metastases. At bronchoscopy, a single large cavity originating at the level of the lower lobe bronchus orifice and ending up into the lung parenchyma, with complete loss of the regional bronchial anatomy, was evident (Figure 1B; video 1). Histological examination of the bronchial biopsies revealed a TTF1+ pulmonary adenocarcinoma. Culture of bronchial washing performed within the cavity grew *Enterococcus fecium* and *Aspergillius fumigatus*, in the absence of any clinical or laboratory sign of infection. The tumor molecular profiling showed a PD-L1 tumor proportion score (TPS) of 55%, whereas *EGFR, ALK, ROS1, BRAF* were negative. The patient did not receive any specific oncologic treatment due to her poor performance status and died 22 days after the diagnosis.

Case #2

A 74-year-old man, current smoker, presented with cough and hemoptysis of 2 weeks duration. His ECOG performance status was 2. A CT-scan of the chest showed a 28 x 24 mm cavitated lesion of the right upper lobe (Figure 1C), whereas PET demonstrated a marked uptake of the lung lesion and of both the adrenal glands. Bronchoscopy revealed a large cavity originating from the origin of the right upper lobe bronchus, with complete loss of the regional bronchial anatomy (Figure 1D; video 2). Histopathologic analysis of the bronchial biopsies revealed a TTF1+ lung adenocarcinoma with wild-type gene status and a PD-L1 TPS of <1%. *Staphilococcus Aureus* and *Branhamella Catarrhalis* were cultured from the bronchial washing in the absence of clinical or laboratory signs of infection. After a 10-day course of antibiotic treatment with amoxicillin/clavulanic acid, chemo-immunotherapy combination (carboplatin AUC4, pemetrexed 375 mg/mq, pembrolizumab 200 mg

q21) was initiated in August 2020. The treatment allowed to achieve a disease stability until March 2021 when a pulmonary progression was observed. At this point, second line treatment with docetaxel g1q21 was started and 6 cycles were completed. The treatment was well tolerated and the disease remained stable until October 2021 when a thoracic progression (lung, pleura) was noted. In November 2021, a third line treatment with gemcitabine g1,8 q21 was started and is still ongoing. The patient is alive and relatively well (ECOG PS 2) 580 days after the initial diagnosis.

Case #3

An 85-year-old, never smoking female patient, was referred to the interventional pulmonology outpatient clinic complaining of cough, hemoptysis and weight loss (6 kgs in 12 months). Her ECOG performance status was 3. A CT-scan performed on hospital admission showed a 61 x 47 mm, massively cavitated lesion of the left upper lobe and an ipsilateral pleural effusion. Bronchoscopy showed a large, endoscopically visible cavity that could be explored from the apical segment of the left upper lobe bronchus and ended up directly into the lung parenchyma. Biopsies from the lesion allowed us to diagnose a squamous cell carcinoma, which had a PD-L1 TPS of 30-40%. No pathogens were cultured from the bronchial washing. The patient was considered unfit for any oncologic treatment due to her age and poor performance status and died 132 days after the diagnosis.

Case #4

A 50-year-old man, former smoker, presented to the emergency room with a history of weight loss (7 Kg in the previous 4 months), cough and recent hemoptysis. His ECOG performance status was 2. A contrast-enhanced CT-scan showed a large cavitated mass (87 x 68 mm) of the right upper lobe associated with an ipsilateral massive mediastinal lymph node involvement. A PET scan demonstrated a marked uptake of the pulmonary lesion, the mediastinal lymph nodes, and the left adrenal gland. Bronchoscopy revealed a large cavity which originated at the level of the right upper lobe bronchus outlet, was almost completely occupied by fibrin, and disrupted the normal bronchial anatomy ending up directly into the lung parenchyma. Histopathologic and molecular analysis of bronchial biopsies revealed a TTF1+ lung adenocarcinoma with a *KRAS* mutation (p.G13D) and a PD-L1 expression of <1%. No pathogens were isolated from the bronchial washing. The patient underwent treatment with pemetrexed/cisplatin doublet chemotherapy (4 cycles), but neither clinical nor radiological significant response were obtained, and he died 156 days after the diagnosis.

Case #5

A 57-year-old male, former smoker, underwent a diagnostic work-up for a dry cough which had worsened progressively over a 5-month period. Contrast-enhanced CT of the chest showed a right upper lobe solid mass which was surrounded by lymphangitic carcinomatosis, infiltrated the right upper lobe bronchus, the mediastinal fat and, partially, the superior vena cava. Furthermore, markedly enlarged lymph nodes were evident in stations #4R, #7, #8R, #10R and #11Rs. Histologic examination of bronchial biopsies taken from the right upper lobe and of EBUS-TBNA samples obtained from lymph node #4R revealed a squamous cell carcinoma with a PD-L1 TPS of 70%. A first-line treatment with pembrolizumab (200 mg q 21) was initiated but after the 3rd cycle the patient showed frank signs of mediastinal syndrome and a CT revealed a local progression of the tumor, which almost completely obstructed the superior vena cava, as well as signs of interstitial lung disease. At this point, steps were taken to perform a palliative radiotherapy, which led to a rapid regression of the signs of mediastinal syndrome. However, 1 month after radiotherapy and shortly after 4th pembrolizumab administration, the patient was admitted to hospital for fever not responsive to ciprofloxacin treatment and progressive respiratory failure. A new CT of the chest showed a marked worsening of the interstitial changes and a massive cavitation (89 x 60 mm) of the right upper lobe mass (Figure 1E). At bronchoscopy (video 3), the anterior and apical segments of the right upper lobe bronchus were replaced by a large cavity (Figure 1F) which led into to the pleural space through a large opening located at the bottom of the cavity (video 3). Bronchial washing performed into the lesion grew *Stenotrophomonas Maltophilia* and *Candida Albicans*. Despite antibiotic and antifungal treatment, as well as non-invasive ventilation delivered through a helmet the patient died 38 days after the hospital admission.

Discussion

Herein we have provided the first organic description of a series of lung cancer patients whose primary tumor caused the disruption of the normal airway anatomy at the level of lobar or segmental bronchi, leading to the formation of an endoscopically-visible cavity which ended up in the lung parenchyma or even into the pleural space.

In 4 of the 5 patients described, the central tumor cavity was already present at the time of the initial diagnosis, before any specific treatment. Although pathogenic organisms were cultured in the bronchial washing obtained from the cavity in 2 out of these 4 patients (*Enterococcus Faecium* and *Aspergillus Fumigatus* in Case #1; *Staphylococcus Aureus* and *Branhamella Catarrhalis* in Case #2),

none of them had clinical or laboratory signs of infection and we hypothesize that these organisms were simple colonizers. More likely, the pathogenesis of cavity formation in these patients was related to a check-valve mechanism secondary to bronchial obstruction and/or to ischemia secondary to vascular invasion or excessive tumor growth outpacing neoplastic vascularization. Furthermore, as most of these cases (3 of 4) were diagnosed between June and July 2020, we believe that the diagnostic and consequent treatment delays observed during the first wave of the Covid pandemic might have contributed significantly to the occurrence of the massive lesion necrosis [17-19].

In the remaining patient, the primary tumor presented as a solid mass at the time of diagnosis and cavitated after first-line treatment. We believe that the *primum movens* towards the necrotic evolution in this case was the palliative radiotherapy of tumor and massive right paratracheal lymphadenopathy aimed at relieving a clinically evident mediastinal syndrome secondary to obstruction of the superior vena cava. However, it is likely that a secondary infection of the lesion contributed to worsening the process. In fact, the patient complained of fever not responsive to antibiotics in the 10 days before referral to the emergency room and bronchial washing performed in the cavity grew *Stenotrophomonas Maltophilia* and *Candida Albicans*.

Unlike cavitated tumors of the lung parenchyma, which are more frequently of squamous histology [5], we did not find such a preferential association in our series. In addition, the clinical presentation of the 4 treatment-naïve patients was strikingly similar. All of them, in fact, presented with metastatic disease, poor ECOG performance status, similar clinical complaints, and lack of actionable mutations. As for the symptoms, hemoptysis was present in all of them and 3 complained also of clinically important weight loss. Among the 3 patients with adenocarcinoma, 2 had a wild type gene status and 1 had a KRAS p.G13D mutation.

Although the limited number of cases does not allow us to draw definitive conclusions, the prognosis associated with central cavitary tumors seems very poor. The only patient who had a meaningful response to treatment and is still alive 19 months after the initial diagnosis is the one (Case #2) who presented with the lowest duration of symptoms, the smallest size of the cavitated mass, and the best performance status. This emphasizes the importance of not underestimating hemoptysis, which is invariably present in these patients, in order to identify them early during the disease course when they are still fit enough to receive a treatment.

In conclusion, our series suggests that endoscopically-visible, central cavitary tumors can be found even at the time of initial diagnosis and tend to have similar clinical (advanced disease, poor

performance status, hemoptysis) and molecular (lack of actionable mutations) characteristics which portend a poor prognosis.

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Table 1. Demographic, clinical, histological and molecular characteristics of the 5 patients.

	Sex/Age	Smoking	Timing of diagnosis*	Symptoms	Histology	Cultures	TNM v.8 (stage)	Genotyping	PDL1 (TPS)	Treatment (line)	Survival[#]
#1	F / 77	Never	Onset	Hemoptysis Weight loss	Adeno	*E. faecium* *A. fumigatus*	T4N0M1c (IV)	Wild type	55%	None	22
#2	M / 74	Current	Onset	Hemoptysis	Adeno	*S. Aureus* *B. Catarrhalis*	T3N2M1c (IV)	Wild type	<1%	CDBCA-Pem-Pembro (I); CDDP-Doc (II); Gem (III)	580°
#3	F / 85	Never	Onset	Hemoptysis Weight loss	SqCC	No growth	T4N0M1a (IV)	Not indicated	40%	None	132
#4	M / 50	Former	Onset	Hemoptysis Weight loss	Adeno	No growth	T4N2M1c (IV)	KRAS p.G13D	<1%	CDDP-Pem	156
#5	M / 57	Former	After IO-RT	Fever Hypoxemia	SqCC	*S. maltophilia* *C. albicans*	T4N2M1a (IV)	Not indicated	70%	Pem-RT	38

*Referred to diagnosis of the central airway disruption; [#]days after the diagnosis of the airway disruption; °patient still alive; F, female; M, male; Adeno, adenocarcinoma; SqCC, squamous-cell carcinoma; CDBCA, carboplatin; Pem, pemetrexed; Pembro, pembrolizumab; Doc, docetaxel; Gem, gemcitabine; CDDP,: cisplatin; IO, immunotherapy; RT, radiotherapy.

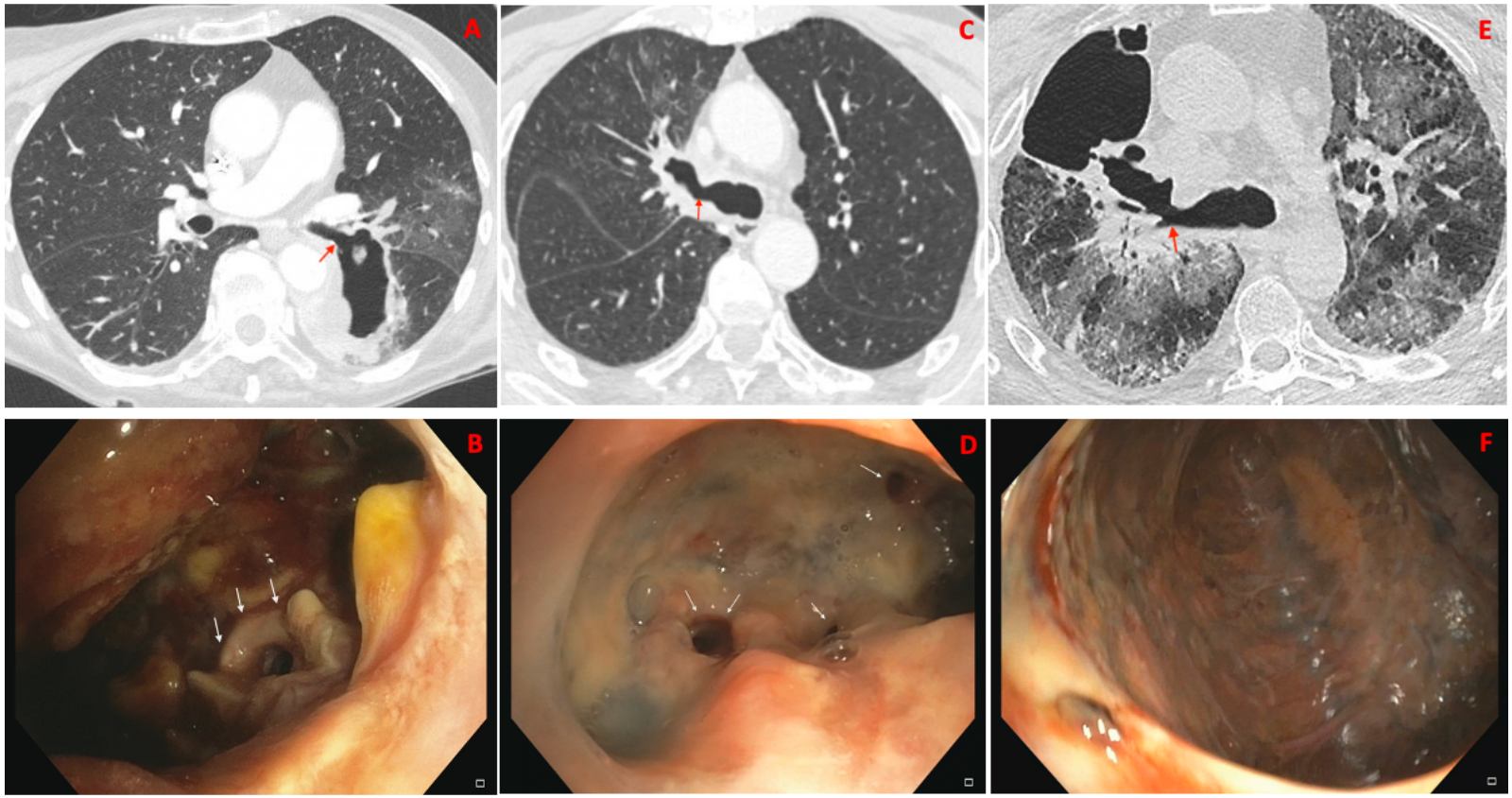

Figure 1. Bronchoscopically-visible central airway disruption in 3 patients of the present series. A) CT of the chest showing a large cavitated mass of the left lower lobe bronchus (arrow). B) Corresponding videobronchoscopy image from the orifice of the left lower lobe bronchus showing the large cavity. The arrows highlight a severed segmental airway (see also video 1). C) CT of the chest showing a cavitary lesion of the right upper lobe with direct communication with the origin of the right upper lobe bronchus (arrow). D) Corresponding videobronchoscopy image showing the cavity, whose walls are largely covered with fibrin/necrotic tissue. Three severed segmental airways can be seen (arrows) (see also video 2). E) Chest CT showing a large cavitary lesion of the right upper lobe (arrows), as well as extensive bilateral ground glass opacities and traction bronchiectasis/bronchiolectasis. F) Corresponding videobronchoscopy image showing the inner aspect of the thoracic wall, clearly visible from a large opening located at the bottom of the cavity (see also video 3).