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A case series of morbid COPD exacerbations during immune checkpoint inhibitor therapy in cancer patients

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ABSTRACT

Background: Immune checkpoint inhibitor therapy is rapidly becoming front line adjuvant or primary therapy in a number of solid cancer types. Since many of these cancers are a result of tobacco smoking, a large number of these patients will have underlying comorbid conditions attributed to smoking such as Chronic Obstructive Pulmonary Disease (COPD). The effect of immune checkpoint inhibitor therapy on COPD is not well documented, and COPD exacerbations are not currently considered a pulmonary associated immune checkpoint inhibitor toxicity in current guidelines.

Case presentation: We describe and summarize here a series of patients with prolonged and severe COPD exacerbations upon the initiation of immune checkpoint inhibitor therapy for cancers of the skin and lung without radiographic evidence of pneumonitis.

Conclusions: COPD exacerbation from immune checkpoint inhibitor is not reported in the literature and is associated with prolonged and severe episodes without radiographic evidence of pneumonitis. Awareness of this potential morbid toxicity and research efforts to understand its etiology are required.

1. Background

Worldwide, 18 million individuals developed solid cancers in 2020 [1]. Nearly two million patients in the U.S. had a solid cancer diagnosed in 2020, and of these solid cancers, immune checkpoint inhibitor (ICI) therapy is approved as treatment in some form for half [2,3]. Since several of the most common solid cancers are smoking associated, an estimated 15–25% of patients who smoke tobacco from cigarettes will develop Chronic Obstructive Pulmonary Disease (COPD) [4], and the prevalence of COPD is increased in patients at highest risk for cancer development [5], a large number of patients undergoing ICI therapy will have co-morbid lung disease. Furthermore, on-going neoadjuvant trials augur a further expansion of immunotherapy utilization [6].

Over the past several years, we have observed some patients that have had persistent, resistant COPD exacerbations upon initiation of ICI therapy. This prompted us to review our center's experience given the lack of information available in the literature on this potential toxicity. We subsequently identified six patients from 2017 to 2020 based on discussions with colleagues and our own internal review of patient

charts that had COPD exacerbations on ICI therapy. We present in depth review of two of these cases below, and we provide summary data of the six in total.

Institutional Review Board (IRB) waiver of consent was approved to publish these data based on the NIH Common Rule and local IRB regulations. All de-identified data regarding the cases reported below were extracted from the electronic medical record at the authors' institutions.

2. Case presentations

An 81 year-old male with stage IIIC melanoma (unknown PDL-1 status) and COPD had nivolumab initiated every three weeks. He developed shortness of breath (SOB) after dose 2 requiring ED evaluation. He was seen in our pulmonary clinic shortly after where more history was elicited regarding his COPD. He was diagnosed 6 years prior to presentation with a 30 pack-year history of cigarette smoking, and he had been on long-acting muscarinic antagonist (LAMA) and as needed albuterol inhalers. He had never experienced an exacerbation since being diagnosed with COPD. He noted that the recent wildfires in the

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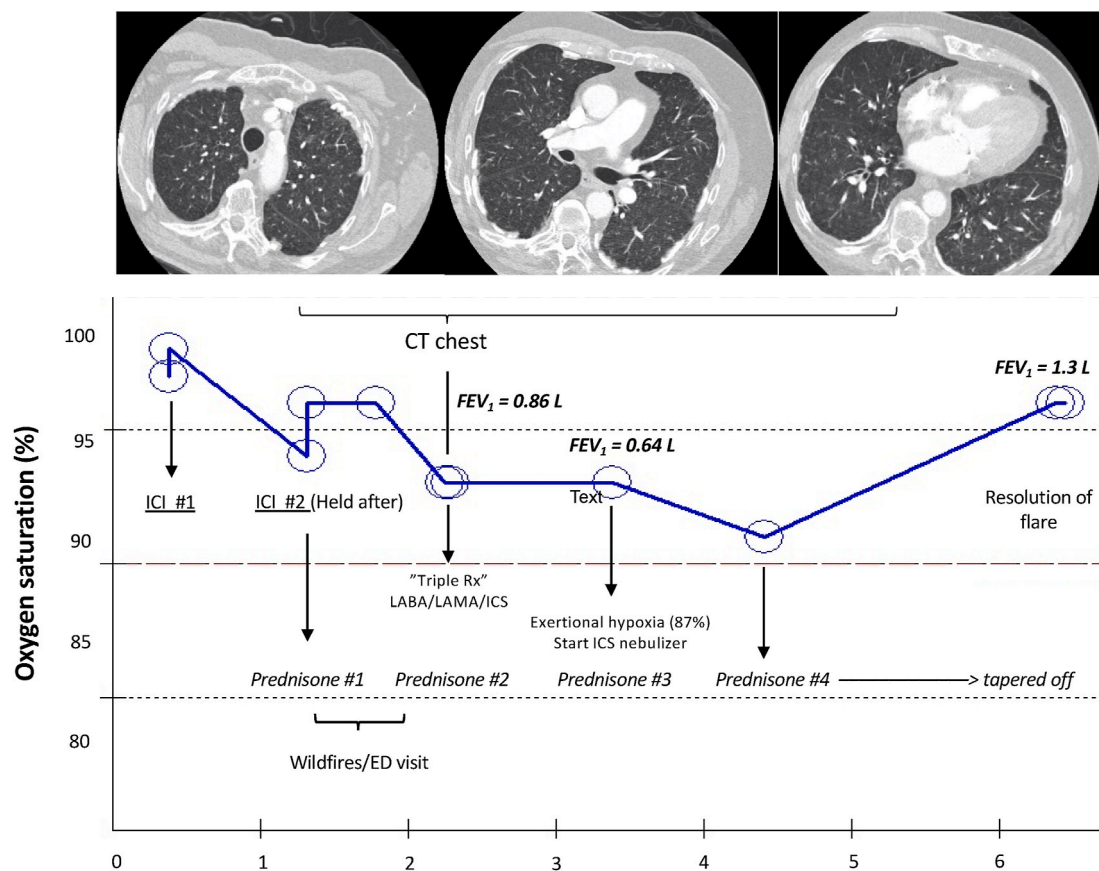


Fig. 1. Timeline of prolonged COPD exacerbation on immunotherapy. Oxygen saturation dropped over time after initiation of immunotherapy for Case 1. Important clinical events and data are illustrated in the timeline for reference to the vignette. ICI = Immune checkpoint inhibitor; FEV₁ = Forced expiratory volume in 1 second; LAMA = Long-acting muscarinic agonist inhaler; LABA = Long-acting beta agonist inhaler; ICS = Inhaled corticosteroid. The red dashed line represents a pathologic oxygen saturation level. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

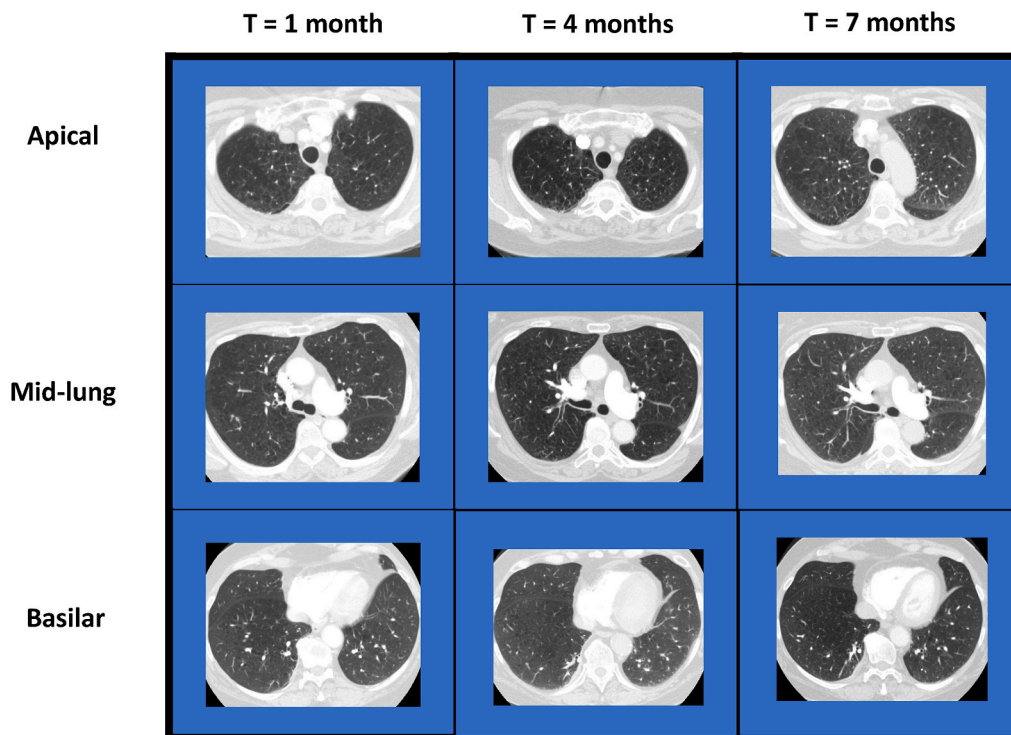


Fig. 2. Serial imaging of COPD exacerbation on immunotherapy. Representative apical, mid and basilar lung fields are shown by timepoint in columns for Case 2. There was no evidence of pneumonitis or another pulmonary cause of this patient's breathing difficulties and a cardiac evaluation was negative.

Pacific Northwest of the United States had caused him breathing difficulty and thought he responded to a prednisone burst but then deteriorated off of it and was using his rescue inhaler daily. In clinic, his resting oxygen saturation was 93%, his exam was notable for some tripodding without wheezing or respiratory distress, and a CT scan demonstrated emphysema without evidence of pneumonitis and severe pleural calcifications from asbestos. COVID testing was negative. The patient was restarted on 10 days of prednisone and prescribed an inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) inhaler. Nivolumab was held.

One month later, the patient reported his breathing improved on prednisone but deteriorated off it. His Forced Expiratory Volume in 1 second (FEV₁) had decreased from 0.86 L to 0.64 L (L) in one month (Fig. 1). His exam now demonstrated wheezing in addition to tripodding and he desaturated to 87% with minimal exertion on room air. He was placed back on a prednisone burst and given nebulized ICS. Exercise oximetry was performed while the patient was on prednisone with a marked improved in exercise tolerance and desaturation to 90% on room air.

One month later, the patient remained SOB off of prednisone despite maximal inhaler therapy and was now using oxygen at home with activity. He was placed back on a slow taper of prednisone over 4 weeks. After 2 months, the patient weaned off of prednisone, was off of oxygen with an FEV₁ of 1.3 L (from 0.64 L prior), and he had a CT scan that showed no evidence of pneumonitis. Nivolumab remains on hold indefinitely. A diagnosis of prolonged exacerbation from ICI therapy was invoked.

2.1. Case 2

A 76 year-old female with COPD and stage IV lung adenocarcinoma (PDL-1 15%) is seen by the pulmonary clinic for progressive respiratory failure. She had a 30 pack-year history of cigarette smoking and quit 4 months prior to initiating immunotherapy. She reported having had yearly COPD exacerbations on a LABA/LAMA with a documented FEV₁

of 1.1 L prior to therapy. She began pembrolizumab therapy for four months. During her 1st month she was admitted with a COPD exacerbation. Viral swabs for common respiratory viruses and COVID were negative. She continued to have SOB at month 3 with response to prednisone. She became hypoxic during her 4th month and developed ICI associated diabetes mellitus at which point ICI therapy was held. She was admitted again at month 7 for SOB and was seen by an outside pulmonologist at that time. Her echocardiogram showed normal left ventricular function and elevated pulmonary systolic pressures. Over the course of the next two months, she had progressive symptom deterioration and was placed on a slow prednisone taper for one month by our pulmonary team. She subsequently developed pneumonia and atrial fibrillation and was placed on hospice at month 12. Her CT scans prior to ICI initiation and at months 1, 4, and 7 demonstrated no evidence of pneumonitis (Fig. 2). A diagnosis of refractory COPD exacerbation from ICI therapy was invoked. She expired 15 months after ICI initiation from metastatic lung cancer and COPD.

3. Discussion

T cell activation is required for an effective immune response to lung cancer. Studies of human lung cancer specimens in COPD patients demonstrate a polarized CD4 Th₁ response and blunted cytotoxic CD8 response in this group that may be rescued or enhanced by immunotherapy [7,8].

Clinical studies have confirmed this observation in lung cancer [9]. Interestingly, immunotherapy influences progression free survival in lung cancer more than overall survival when stratified by COPD status, suggesting that competing risks of death such as from COPD may reduce the overall survival benefit [10]. Since it is biologically plausible for immunotherapy to aggravate a patient's COPD, immune related adverse events (irAE's) specific to this condition are also plausible. Thus, we suggest here that COPD may not only be a biomarker of immunotherapy response for patients with cancer [11], but it may also portend irAEs.

Based on the success of immunotherapy to present, its increasing use,

Table 1

Review of center's experience of potential COPD exacerbations on immunotherapy.

ID	Age (years)	Sex	Smoking Status	Cancer Type	ICI Therapy	PDL ₁ IHC	CT features	FEV ₁ (L) Pre-	FEV ₁ (L) Post-	Blood Eosinophilia†	Summary
1	81	M	past	Melanoma	2 doses, Nivolumab	*	COPD	*	0.86	Y	See text, Case 1
2	76	F	past	Lung AC	6 doses, Pembrolizumab	15%	COPD	1.1	1.02	Y	See text, Case 2
3	80	M	past	SCLC	3 doses, Nivolumab/Ipilumimab	*	COPD/ILD	*	2.83	N	Developed oxygen requirements after 2 doses of ICI that increased from 3 to 5 L per minute (LPM). Prednisone courses twice, now oxygen dependent. Serial CTs show severe para-septal emphysema. Cardiac function evaluated and normal during this course. NED at 15 months from ICI initiation.
4	75	F	current	Lung SCC	13 doses, Pembrolizumab	0	COPD	0.52	*	N	Treated for cT ₂ disease by radiation, with early recurrence. Received chemotherapy followed by ICI resulting in multiple exacerbations and one admission for COPD. Expired from disease progression and comorbidities 21 months after ICI initiation.
5	80	M	past	Lung AC	9 doses, Pembrolizumab	80%	COPD	0.89	*	N	cT ₂ disease treated with radiation with early recurrence. COPD exacerbation after 3 months of ICI resulting in 1 year drug holiday between dose 6 and 7. Dies from disease progression 18 months after ICI initiation.
6	85	M	past	Lung AC	4 doses, Pembrolizumab	0	Pneumonia/COPD	*	*	Y	Underwent ICI for recurrent disease after radiation for clinical stage I disease. Multiple COPD exacerbations and pneumonia following. Dies 1 year after ICI initiation from COPD with NED.

† Defined as Absolute Eosinophil Count (AEC) \geq 0.5.

* Data not available.

M = Male, F = Female.

ICI = Immune checkpoint inhibitor.

IHC = Immunohistochemistry.

FEV₁ = Forced expiratory volume in 1 second.

AC = Adenocarcinoma, SCLC = Small cell lung cancer, SCC = Squamous cell carcinoma.

NED = No evidence of disease.

and the lack of reporting on COPD irAE's in the literature, it is likely that only a minority of patients with COPD suffer more adverse consequences from therapy than benefit. However, it is unclear what proportion of patients with COPD will experience morbid exacerbations with immunotherapy and whether severity of underlying lung disease, age or other clinical variables are associated with COPD irAEs (Table 1). We report these data here as a call to recognize and study this problem further.

4. Conclusions

We show here previously unreported cases of prolonged and severe COPD exacerbations without imaging evidence of pneumonitis in patients with cancer undergoing ICI treatment. Further recognition of this emerging irAE and research is required to understand the predictors of this potentially morbid irAE and to identify appropriate management algorithms in the clinic.

Declaration of competing interest

The authors declare no conflicts of interest.

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List of abbreviations

COPD	Chronic Obstructive Pulmonary Disease
ICI	Immune Checkpoint Inhibitor
IRB	Institutional Review Board
NIH	National Institutes of Health
PDL-1	Programmed Cell Death Ligand - 1
LAMA	Long-Acting Muscarinic Antagonist
LABA	Long-Acting Beta Agonist
ICS	Inhaled Cortico-Steroid
FEV₁	Forced Expiratory Volume in 1 second
L	Liters
CT	Computed Tomography
irAE	Immune Related Adverse Events

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Authors' contributions

VSN conceived of the study concept and write-up. KE and AMH participated in study design and review of the manuscript. All authors have read and approved the manuscript.

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