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Respiratory Hospitalizations Following Initiation of Nerandomilast: A Case Series

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Case Report

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Title: Respiratory Hospitalizations Following Initiation of Nerandomilast: A Case Series

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Abstract

Nerandomilast is a novel phosphodiesterase-4 (PDE4) inhibitor approved for the treatment of idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF). This case series reports 4 patients with a respiratory hospitalization within 2 weeks of initiation of nerandomilast. Three patients met criteria for interstitial lung disease (ILD) exacerbation with a change in dyspnea, worsening oxygen requirement, and new ground glass infiltrates on chest imaging. The fourth patient had concomitant volume overload and did not definitively meet criteria for ILD exacerbation. This case series suggests that further investigation of respiratory hospitalizations and/or ILD exacerbations following initiation of nerandomilast are warranted.

Introduction

Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are respiratory conditions with a progressive course (1). Despite the available therapies of pirfenidone and nintedanib, the majority of patients continue to worsen, and the only cure is lung transplant.(1-4) Nerandomilast is a novel oral phosphodiesterase 4 (PDE4) inhibitor approved for the treatment of both IPF and PPF. Because nerandomilast has been on the market for less than one year, post-marketing surveillance remains a critical part of drug safety monitoring. This case series reports 4 patients with a respiratory hospitalization following initiation of nerandomilast.

Methods

Four patients with an acute exacerbation of IPF or PPF after starting nerandomilast were identified retrospectively by the pulmonary consult services at Parkland Memorial Hospital and Clements University Hospital in July and August 2026. Clinical characteristics, including the type of ILD, treatment history, pulmonary function testing (PFT), computed tomography (CT) images, bronchoscopy results, and clinical notes and discharge summaries from the respiratory hospitalizations were recorded.

Ethics statement

This study was conducted in accordance with the amended Declaration of Helsinki and was considered exempt by the University of Texas Southwestern Medical Center (UTSW) Institutional Review Board (IRB) (STU20261619). The study was approved by the Parkland Health Office of Research. Consent was waived by the UTSW IRB as only deidentified information was used and the case series involved a small number of patients. Ethnicity was self-reported by study subjects in the medical record. Subjects were not stratified or analyzed on the basis of confounding variables such as socioeconomic status or nutrition; this information was not available in the medical record and was not included. Data for this study was collected in September 2026. Identifying data was not recorded or accessed during or after data collection.

Case 1

Patient 1 is a 56-year-old female with interstitial lung disease due to Systemic Lupus Erythematosus (SLE) and Limited Cutaneous Systemic Sclerosis Overlap. These diagnoses were made with the following serologies: positive antinuclear antibody (ANA) > 1:2560, centromere

pattern, prior positive anti-dsDNA antibody and positive ant-Centromere antibody. Her fibrotic NSIP pattern was identified in 2014 and she was prescribed mycophenolate 1000 mg twice daily, hydroxychloroquine as well as low-dose prednisone. Her disease remained stable until 2017, when she was lost to follow up.

She re-established care in 2022 and at that time she was no longer taking mycophenolate. As her CT chest showed progression of fibrosis, she was restarted on this medication. She was prescribed nintedanib in 2025 which was discontinued due to gastrointestinal side effects.

She was hospitalized in May 2026 for progressive shortness of breath with chest CT showing a new right lower lobe consolidation with cavitation. She underwent bronchoscopy with bronchoalveolar lavage of the right lower lobe on June 3, 2026. The lavage fluid showed predominantly neutrophils, and the fungal culture revealed Histoplasma capsulatum. She was prescribed a six-week course of Itraconazole. Upon outpatient follow up post hospital discharge, she was prescribed nerandomilast 18 mg twice daily.

One week after initiating nerandomilast, she was admitted progressive dyspnea and pleuritic chest pain. CT chest revealed increased ground glass opacities (Figure 1). She underwent bronchoscopy with BAL of the LLL with 41% lymphocytes in the lavage fluid. Microbiology studies of the BAL do not show any fungal or bacterial growth. She was discharged with a six-week prednisone taper with improvement of her dyspnea and pleuritic chest pain at time of discharge. A CT chest was performed three days after initiating steroids which showed slight improvement of the ground glass opacities.

Case 2

Patient 2 is a 65-year-old female with unclassifiable ILD initially diagnosed in 2022. Her laboratory evaluation revealed a positive ANA 1:320, homogenous pattern, a positive CCP > 250.00 and a positive Ha antibody. A HRCT was performed at the time of her diagnosis with findings consistent with fibrotic ILD, indeterminate for UIP, as well as mediastinal adenopathy. An initial bronchoscopy was notable for a neutrophil predominant bronchial alveolar lavage and transbronchial biopsies showing alveolar and bronchial mucosa with acute and chronic inflammation. The patient was started on low-dose prednisone and mycophenolate 1500mg twice daily. An outpatient evaluation by rheumatology did not show identifiable rheumatologic disease. PFTs at that time were significant for mild restriction and moderately reduced DLCO. She had multiple admissions in 2026 for acute on chronic dyspnea for which she was treated with extended courses of prednisone. She was started on pirfenidone in 2026, and within 1 month of initiating the medication she had two admissions - the first admission with acute on chronic dyspnea and CT imaging notable for pneumomediastinum. She was treated with steroids and discharged home. Her second admission was due to an upper respiratory infection with parainfluenza and left-sided pyelonephritis resulting in sepsis and *E.coli* bacteremia. She was discharged home on a prescribed steroid taper.

Her recurrent hospitalizations with acute on chronic hypoxic respiratory failure were suspected to be due to worsening of her underlying ILD, and nerandomilast was added to her pirfenidone. She presented to the hospital one week after she began taking nerandomilast 18mg

twice daily due to acute nausea, vomiting, worsening dyspnea and acute on chronic hypoxic respiratory failure. Upon admission, she had tachycardia and increased oxygen requirement of up to 50% FiO2 on high flow nasal cannula. Her work up was notable for a negative respiratory viral pathogen panel, normal NT-proBNP, and negative blood cultures. A CT of the chest was performed which was negative for pulmonary embolism, showed chronic interstitial lung disease with an increase in ground glass and fibrosis compared to her CT scan 3 months prior (Figure 2). She was treated initially with broad spectrum antibiotics but due to a negative infectious evaluation these were discontinued after 72 hours. She was started on intravenous methylprednisolone 60mg every 6 hours with significant improvement in her symptoms and she was placed on an extended steroid taper upon discharge. Nerandomilast was discontinued.

Case 3

Patient 3 is a 59-year-old female with anti-synthetase syndrome with features of scleroderma as diagnosed via skin biopsy in 2006 and SSA (Ro) Antibody positivity complicated by ILD. Her chest imaging had shown evidence of fibrotic changes beginning in 2007, and she was on oral prednisone until 2016 when she transitioned to mycophenolate. Her immunosuppression was escalated to hydroxychloroquine and rituximab by 2025 per rheumatology. She was also diagnosed with pulmonary arterial hypertension in 2021 for which she is currently receiving macitentan/tadalafil and inhaled Treprostinil. She had tried nintedanib in 2024 which she did not tolerate due to gastrointestinal side effects. Nerandomilast 18 mg twice daily was prescribed in 2026 due to progression of chest imaging and pulmonary function testing.

She presented to the hospital three days after beginning to take nerandomilast with report of increased shortness of breath. She was found to have acute worsening of her oxygen requirement and was notably tachycardic. CT chest revealed an increase in ground glass opacities (Figure 3). She received intravenous methylprednisolone as well as diuretics with improvement in her dyspnea and she returned to her baseline oxygen requirement. Her infectious work-up was unrevealing and a right heart catheterization prior to discharge showed similar hemodynamics to catheterization performed two months prior. She was discharged with an oral steroid taper and discontinuation of nerandomilast.

Case 4

Patient 4 is a 71 year-old male with familial PPF. He initially presented 3 months prior to admission and was initiated on 4 iters per minute supplemental oxygen at that time. His family history was notable for a sister with fibrotic hypersensitivity pneumonitis. His serologic evaluation for connective tissue disease was negative. He reported home mold exposure due to a water leak that had not yet been remediated. At his initial clinic visit, his forced vital capacity was 34% predicted and DLCO 59% predicted. In clinic he was initiated on a 12-day prednisone taper as well as nerandomilast 18mg twice daily.

He received the nerandomilast after he had completed the prednisone taper. Three days after starting nerandomilast he endorsed increased shortness of breath and increased time to recover from desaturation. He scheduled an urgent clinic visit and desaturated to 55% in clinic despite using his home oxygen and was admitted. He denied any change in cough. CT scan revealed a marked increase in ground glass compared to 3 months prior to admission (Figure 4). Inferior vena cava caliber was not well visualized on echocardiogram on admission; right heart catheterization revealed a pulmonary capillary wedge pressure of 3. He was treated with intravenous methylprednisolone and an expedited lung transplant evaluation was initiated. He underwent bilateral lung transplantation 3 weeks after hospital admission. Explant revealed a heterogeneous pattern of chronic fibrosing interstitial pneumonia with microscopic honeycombing and fibroblastic foci as well as acute lung injury characterized by alveolar septal edema, reactive fibroblastic foci, and pneumocyte hyperplasia.

Table 1. Physical examination findings and laboratory values on presentation for ILD exacerbation.

	Patient 1	Patient 2	Patient 3	Patient 4
Temperature (°C)	36.8	36.7	37.7	36.6
Lower extremity edema (Yes/No)	No	No	Yes	No
Lung auscultation findings	Bilateral crackles	Bilateral crackles left > right, rare inspiratory squeaks	Bilateral crackles	Bilateral crackles
Jugular venous distension (Yes/No)	No	No	Yes	No
Nt-pro BNP pg/mL	289	123	13,276	299
White blood cell count (x10(9)/L) Neutrophils (x10(9)/L) Immature granulocytes (x10(9)/L)	18.52 15.99 0.13	7.99 7.32 0.2	9.56 8.17 0.04	9.53 6.69 0.03
Respiratory viral panel result	Negative	Negative	Negative	Negative

Sputum culture result	Not performed (BAL cultures negative)	Not performed	Not performed	Not performed (sputum culture rejected due to excessive oral contamination)
Echocardiogram inferior vena cava (IVC) caliber and collapsibility	Normal IVC caliber and collapsibility	Normal IVC caliber and collapsibility	Dilated with <50% inspiratory collapse (unchanged from 2 months prior)	Difficult to visualize IVC; right heart catheterization with pulmonary capillary wedge pressure 3

Discussion

This case series describes 4 patients who had respiratory hospitalizations 2 weeks of initiation of nerandomilast. An exacerbation of ILD is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality in a patient with a previous or concurrent diagnosis of IPF or PPF, acute worsening of dyspnea typically < 1 month in duration, new bilateral ground glass abnormality superimposed on a background of ILD, and not fully explained by heart failure or fluid overload.(7) Patients 1, 2, and 4 in this series met this definition clearly. In addition, patient 1 had a lymphocyte-predominant bronchoalveolar lavage during the respiratory hospitalization, which is supportive of a diagnosis of ILD exacerbation.(8) Patient 4 had an explant confirming diffuse alveolar damage, suggestive of an ILD exacerbation. Patient 3 had concomitant volume overload during the admission and it is difficult to confidently assess whether her hospital admission was due to volume overload exclusively or whether ILD exacerbation was also present.

Limitations of this case series include absence of a control group and inability to control for confounding factors. Patients were treated according to standard of care rather than a research protocol, so no investigation of the mechanism of nerandomilast-associated respiratory hospitalizations was not conducted.

This case series suggests that further investigation of respiratory hospitalizations and/or ILD exacerbations following initiation of nerandomilast are warranted.

Figures:

Legend to figures.

Figure 1A. Patient 1 CT 3 months prior to initiation of nerandomilast.

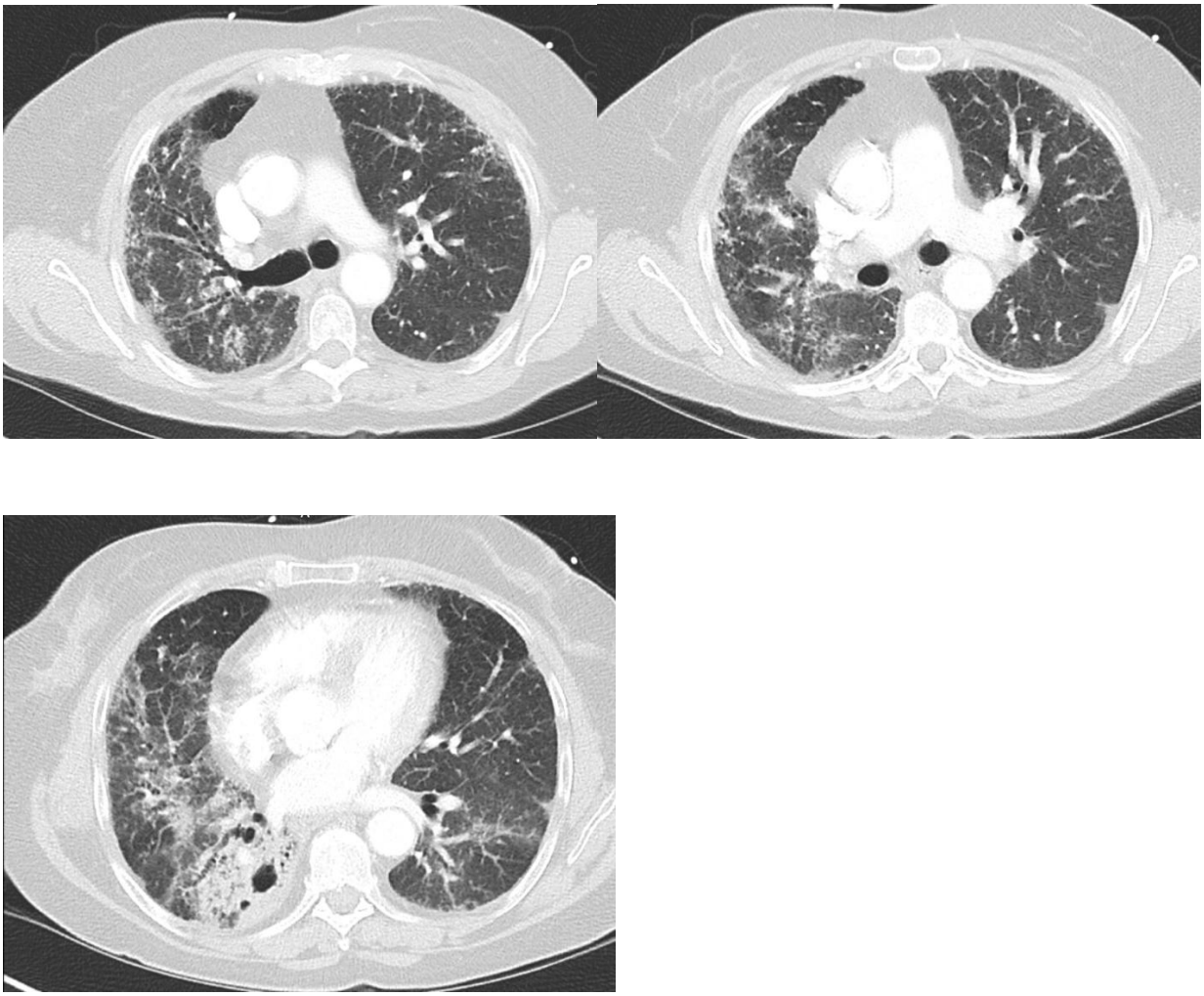
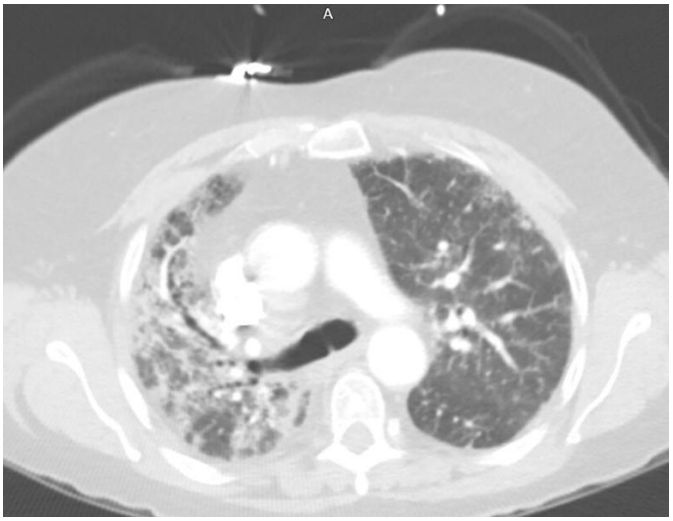


Figure 1B. Patient 1 CT on admission after starting nerandomilast.



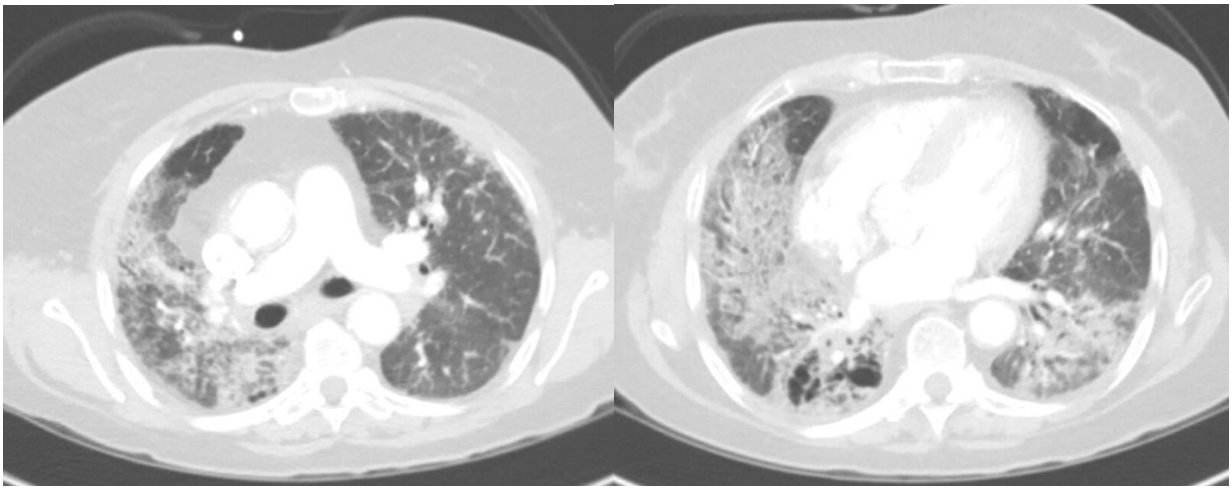


Figure 2A. Patient 2 CT 5 months prior to initiation of nerandomilast.

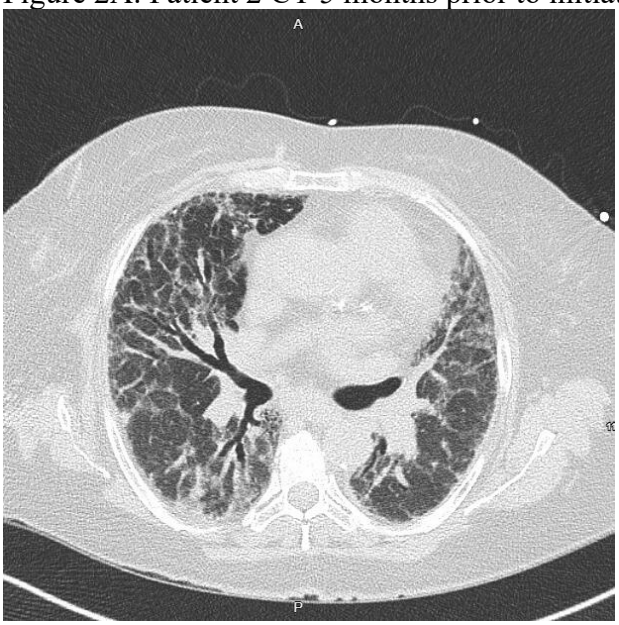


Figure 2B. Patient 2 CT on admission after starting nerandomilast.

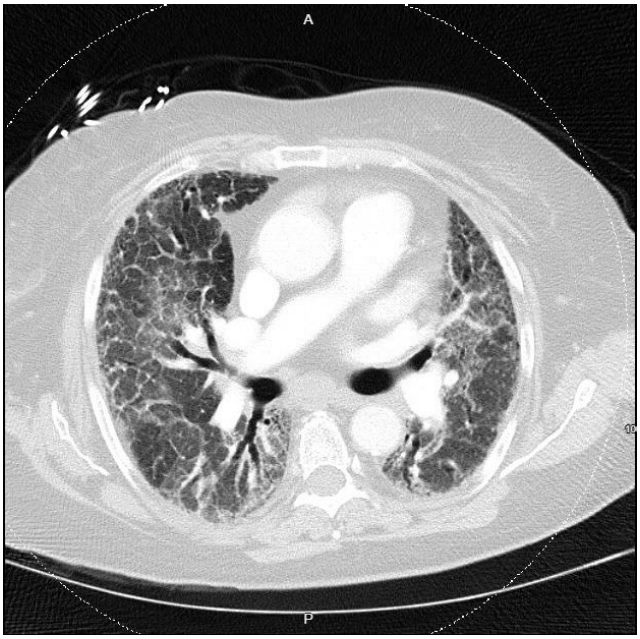


Figure 3A. Patient 3 CT 2 months prior to initiation of nerandomilast

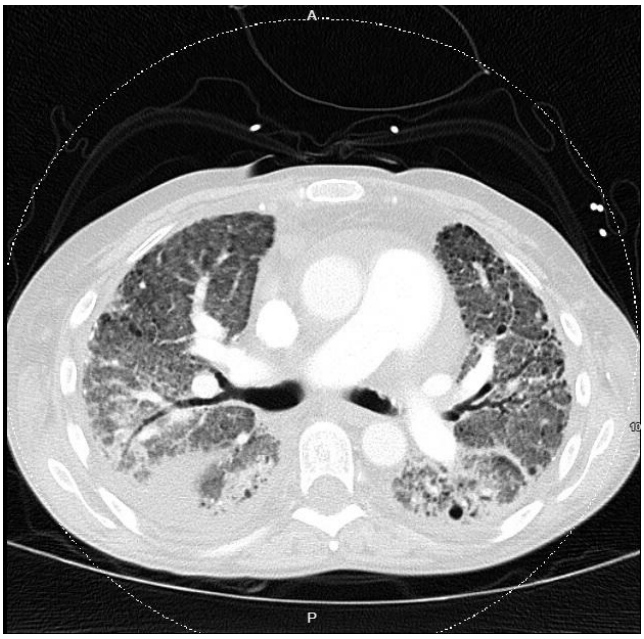


Figure 3B. Patient 3 CT on admission after starting nerandomilast

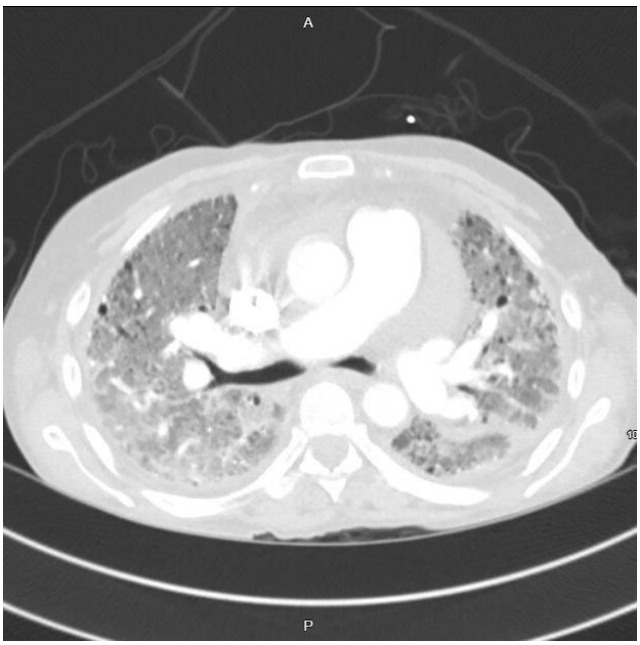
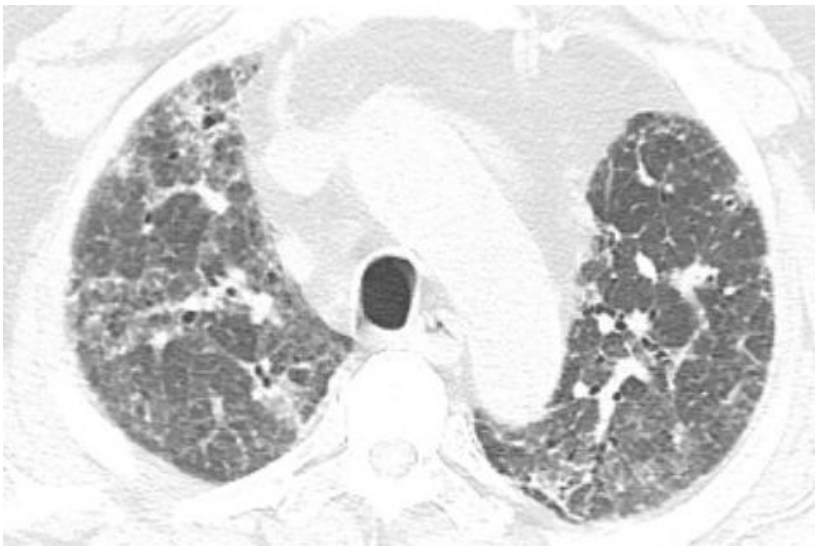


Figure 4A.

Patient 4 CT 3 months prior to initiation of nerandomilast.



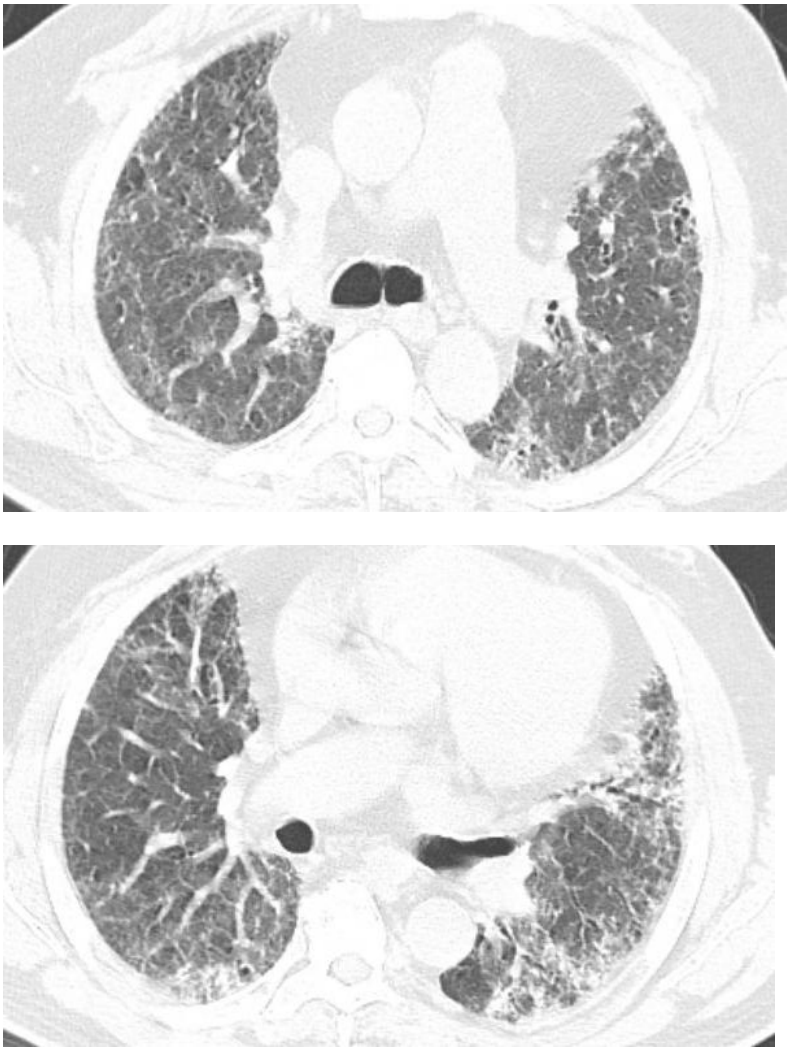
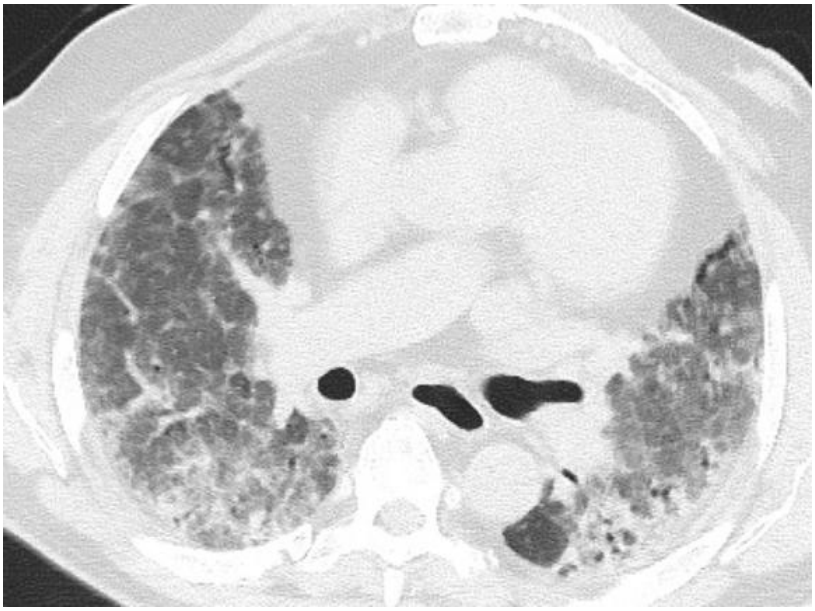


Figure 4B

Patient 4 CT on admission after starting nerandomilast







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