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Complexity and Challenges of the Diagnosis and Management of Chronic Bronchiectasis with Recurrent Exacerbations and Anti-synthetase-associated Interstitial Lung Disease

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Abstract

Bronchiectasis is a chronic airway disease that may be underrecognized when its manifestations overlap with pulmonary tuberculosis (TB) and interstitial lung disease (ILD). We report a 45-year-old woman presenting with chronic productive cough, progressive dyspnea, recurrent respiratory infections and weight loss who was initially treated as pulmonary TB despite negative molecular testing and minimal clinical improvement. High-resolution computed tomography (HRCT) revealed extensive bilateral cystic bronchiectasis, ground-glass opacities, centrilobular nodules and honeycombing suggestive of fibrotic ILD. Pulmonary function testing demonstrated a restrictive ventilatory defect, while immunoserological evaluation showed positive anti-Jo-1, anti-Mi-2 alpha and anti-HMGCR antibodies, supporting the diagnosis of anti-synthetase-associated ILD. The clinical course was complicated by recurrent pulmonary exacerbations, with sputum cultures repeatedly isolating *Escherichia coli*, indicating persistent airway infection and bacterial colonization. Management posed a significant therapeutic challenge because immunosuppressive therapy required for ILD control carried the risk of worsening chronic bronchiectatic infection. Therefore, treatment focused on culture-guided antibiotics, bronchodilator therapy, airway clearance, chest physiotherapy, nutritional support and multidisciplinary monitoring before considering definitive immunosuppressive therapy. This case highlights the importance of early recognition of autoimmune-associated ILD in patients with non-resolving bronchiectasis exacerbations to reduce diagnostic delay, prevent progressive pulmonary fibrosis and optimize individualized multidisciplinary management in complex respiratory overlap syndromes, particularly in resource-limited healthcare settings.

Keywords: Anti-synthetase Syndrome, Bronchiectasis, Interstitial Lung Disease, Recurrent Exacerbation.

Introduction

Interstitial lung disease (ILD) comprises a heterogeneous group of diffuse parenchymal lung disorders characterized by varying degrees of inflammation, fibrosis and progressive impairment of gas exchange. ILD may arise from environmental exposures, drug toxicity, connective tissue diseases (CTDs), or idiopathic causes. Among CTD-associated ILDs, anti-synthetase syndrome-associated ILD (ASyS-ILD) represents a clinically important subtype because pulmonary involvement is frequently the dominant manifestation and a major determinant of morbidity and mortality. Delayed recognition may result in progressive pulmonary fibrosis, respiratory failure and reduced survival. ILD represents a significant global health burden due to its progressive nature and association with substantial morbidity and mortality. Among connective tissue disease-associated ILDs, ASyS-ILD remains uncommon but clinically important because pulmonary involvement may occur independently of muscle manifestations, resulting in under recognition and delayed treatment. The clinical intersection of chronic bronchiectasis and Anti-synthetase syndrome-associated Interstitial Lung Disease (ASyS-ILD) presents a profound diagnostic and therapeutic challenge due to the significant heterogeneity of symptoms and the overlapping features of infection and autoimmunity.

ASyS is a rare autoimmune disorder characterized

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by antibodies against aminoacyl-transfer RNA (tRNA) synthetases, manifesting with a classic triad of myositis, arthritis and ILD (1, 2). Importantly, pulmonary involvement may occur as the predominant or isolated manifestation, which contributes to diagnostic delay and under recognition. However, the diagnosis is frequently delayed because patients often present with isolated respiratory symptoms, such as productive cough and fever, that mimic lower respiratory tract infections, leading to initial misdiagnosis as pneumonia or typical bronchiectasis exacerbations (1, 3). This diagnostic uncertainty is exacerbated by the limitations of current diagnostic criteria, which often prioritize syndromic features like myositis over isolated lung involvement (4). The pathogenesis of ASyS-ILD involves autoimmune-mediated injury triggered by abnormal immune responses against aminoacyl-tRNA synthetases, resulting in inflammatory infiltration, alveolar epithelial injury and progressive fibrotic remodeling of the lung interstitium. This immunological process explains why ILD may develop independently of overt muscle involvement in some patients.

Bronchiectasis is a chronic airway disease characterized by irreversible bronchial dilatation, impaired mucociliary clearance, chronic bacterial colonization and recurrent infective exacerbations. Repeated cycles of airway infection and inflammation contribute to progressive structural lung damage, deterioration of pulmonary function, reduced quality of life and increased mortality. Although bronchiectasis may occur secondary to autoimmune diseases, distinguishing primary bronchiectasis from bronchial abnormalities caused by fibrotic ILD remains challenging in routine clinical practice. Furthermore, patients with chronic bronchiectasis frequently present with persistent cough, sputum production, weight loss and recurrent pulmonary infiltrates, clinical features that may overlap with pulmonary tuberculosis, chronic pneumonia, or autoimmune-associated lung disease. The development of bronchiectasis is driven by a self-perpetuating cycle of impaired mucociliary clearance, mucus retention, bacterial persistence and chronic airway inflammation, leading to irreversible bronchial remodeling. In patients with coexisting autoimmune pulmonary disease, this inflammatory environment may further complicate disease progression and clinical interpretation.

Accurate diagnosis of ASyS-ILD requires a meticulous integration of serological, clinical and radiological findings. Although bronchiectasis and ASyS-ILD are generally considered distinct pulmonary conditions, their coexistence may represent a complex interaction between autoimmune-mediated parenchymal injury and chronic airway remodeling. Fibrotic ILD may result in traction bronchiectasis due to architectural distortion, whereas chronic bronchiectatic infection may amplify inflammatory pathways and contribute to persistent pulmonary injury. High-resolution computed tomography (HRCT) typically reveals patterns such as non-specific interstitial pneumonia (NSIP) or organizing pneumonia (OP) (3, 5). While traction bronchiectasis is a common feature of fibrosing ILD in ASyS, distinguishing this from primary chronic bronchiectasis is critical, as the underlying pathophysiology differs significantly (5). Furthermore, the specific autoantibody profile heavily influences the prognosis; anti-Jo-1 is the most common, whereas non-Jo-1 antibodies (e.g., anti-PL-7, anti-PL-12) and the presence of anti-Ro52 are frequently associated with more severe, isolated, or rapidly progressive ILD (RP-ILD) (4, 6, 7).

An additional challenge arises when recurrent pulmonary infection coexists with autoimmune-mediated lung injury. In bronchiectasis, bacterial colonization and recurrent infection represent important determinants of disease progression. While pathogens such as Pseudomonas aeruginosa are frequently reported in non-cystic fibrosis bronchiectasis, isolation of Enterobacterales including *Escherichia coli* is less commonly emphasized and may create additional therapeutic challenges when immunosuppressive therapy is required. In such circumstances, radiological findings including ground-glass opacities, consolidation, centrilobular nodules, tree-in-bud appearance and cystic bronchiectatic changes may be interpreted as ongoing infection, delaying consideration of an underlying autoimmune process. This diagnostic dilemma is particularly relevant in regions where pulmonary tuberculosis remains prevalent, as patients may initially receive empirical anti-tuberculosis treatment despite negative microbiological investigations.

The management of these coexisting conditions is complicated by the "vicious vortex" of infection and inflammation inherent in bronchiectasis, which accelerates lung function decline (8). Similarly, ASyS-ILD can manifest as life-threatening RP-ILD or Progressive Pulmonary Fibrosis (PPF), with risk factors including elevated serum KL-6 levels and high neutrophil-to-lymphocyte ratios (NLR) (9, 10). Therapeutic strategies must therefore balance aggressive immunosuppression, typically involving high-dose corticosteroids and agents like mycophenolate mofetil or rituximab, with the targeted management of infection risks and airway clearance techniques (2, 6, 8). Early multidisciplinary collaboration involving rheumatologists and pulmonologists is essential, as delayed recognition and insufficient treatment of the autoimmune component can lead to irreversible pulmonary fibrosis and increased mortality (1, 3).

Despite increasing recognition of ASyS-ILD, the clinical overlap between autoimmune-associated ILD and chronic bronchiectasis remains insufficiently characterized, particularly in patients presenting with recurrent infection-like exacerbations. The present case illustrates several uncommon and clinically significant features, including recurrent isolation of *Escherichia coli* from sputum cultures, delayed exclusion of pulmonary tuberculosis despite negative molecular testing, extensive cystic bronchiectasis with concurrent fibrotic ILD features and the coexistence of multiple myositis-related autoantibodies (anti-Jo-1, anti-Mi-2α and anti-HMGCR). These findings created substantial diagnostic uncertainty and complicated therapeutic decision-making, particularly regarding the timing and safety of immunosuppressive therapy in the setting of persistent airway infection. This report aims to highlight the complexity of diagnosing and managing bronchiectasis overlapping with ASyS-ILD and to emphasize the importance of multidisciplinary evaluation in patients with non-resolving respiratory disease.

Case History

A 45-year-old female presented with a chronic productive cough, progressive dyspnea and significant weight loss persisting since May 2024. The symptoms progressively worsened since September 2024, accompanied by decreased appetite, approximately 3 kg weight loss over two months and recurrent respiratory exacerbations requiring repeated medical evaluation. The patient had previously been treated empirically for pulmonary tuberculosis (TB) for approximately two weeks; however, treatment was discontinued due to negative microbiological findings and lack of clinical improvement. Sputum molecular testing (TCM/Xpert MTB-RIF) performed on 29 October 2024 showed MTB not detected and Ziehl–Neelsen staining for acid-fast bacilli was negative. Mycobacterial culture was not available in this evaluation. The absence of microbiological confirmation and limited therapeutic response prompted reconsideration of the initial TB diagnosis. Serial chest radiographs and CT findings demonstrated persistent bronchiectatic changes, cystic abnormalities, ground-glass opacities and fibrotic features rather than a typical pattern of progressive active pulmonary tuberculosis.

Table 1: Timeline of Radiological Findings During Disease Progression

Date	Imaging Modality	Main Findings	Clinical Significance
4 October 2024	Chest radiograph	Infected bronchiectasis	Supports the diagnosis of bronchiectasis complicated by pulmonary infection.
4 November 2024	Chest radiograph	Pulmonary edema, left pleural effusion and pneumonia	Suggestive of pulmonary infection/pneumonia accompanied by left pleural effusion.
18 December 2024	Chest radiograph	Pulmonary edema, left pleural effusion and pneumonia	Indicates ongoing infectious pulmonary lesions.
24 December 2024	Chest radiograph	Persistent pulmonary edema and left pleural effusion; decreased pneumonic infiltrates	Partial improvement of pulmonary infiltrates, although pleural effusion persisted.
10 January 2025	Chest CT scan (RSSA)	Extensive consolidation predominantly involving the left lower lobe with	Extensive bronchiectasis with secondary infection; radiological

		multiple cystic degenerations; ground-glass opacities (GGO) with mosaic attenuation; centrilobular nodules with tree-in-bud appearance; honeycombing/cystic clustering; multiple mediastinal and axillary lymph nodes <10 mm	findings raised suspicion for interstitial lung disease (ILD) and/or hypersensitivity pneumonitis.
6 April 2025	Chest radiograph	Bilateral paracardiac consolidations suspicious for lung mass versus pneumonia; multiple pulmonary nodules in both lung fields; left pleural effusion	Persistent/progressive lesions requiring CT correlation and further evaluation to differentiate infection from other pathological processes.
9 April 2025	Chest radiograph	Persistent pneumonia; suspicious metastatic pulmonary process	Radiological findings were concerning but not sufficient for a definitive diagnosis without further confirmation.
14 April 2025	Chest CT scan (Panti Nirmala Hospital)	Bronchiectasis involving the right lung, left middle lung and left lower lung with secondary infection/pneumonia; nodules in the medial segment of the right middle lobe and posterior segment of the left upper lobe; left pleural effusion	Bilateral bronchiectasis with concomitant pneumonia and pulmonary nodules requiring follow-up evaluation.
14 April 2025	Abdominal CT scan	Right adnexal cystic mass measuring approximately 4.16 × 5.45 × 3.8 cm; no significant abnormalities in other abdominal organs; no enlarged para-aortic or para-iliac lymph nodes and no ascites	Extrathoracic finding suggestive of an adnexal cyst; no evidence of abdominal metastasis on imaging.
28 December 2024	Abdominal ultrasonography	Bosniak I simple right renal cyst; right adnexal hypoechoic lesion measuring 5.09 × 3.76 cm, suspicious for an endometrial cyst, with pedunculated uterine myoma as a differential diagnosis	Incidental gynecological and renal findings requiring clinical correlation.

Table 1 summarizes the chronological radiological findings observed throughout the patient's clinical course. Serial chest imaging consistently demonstrated persistent bronchiectatic changes with recurrent pulmonary infections despite initial empirical anti-tuberculosis therapy. Subsequent HRCT examinations revealed extensive cystic bronchiectasis, ground-glass opacities, centrilobular nodules and honeycombing, findings that shifted the diagnostic consideration toward fibrotic interstitial lung disease rather than active pulmonary tuberculosis. Incidental abdominal imaging findings, including an adnexal cystic lesion and a simple renal cyst, were unrelated to the patient's respiratory disease but were documented during the diagnostic workup.

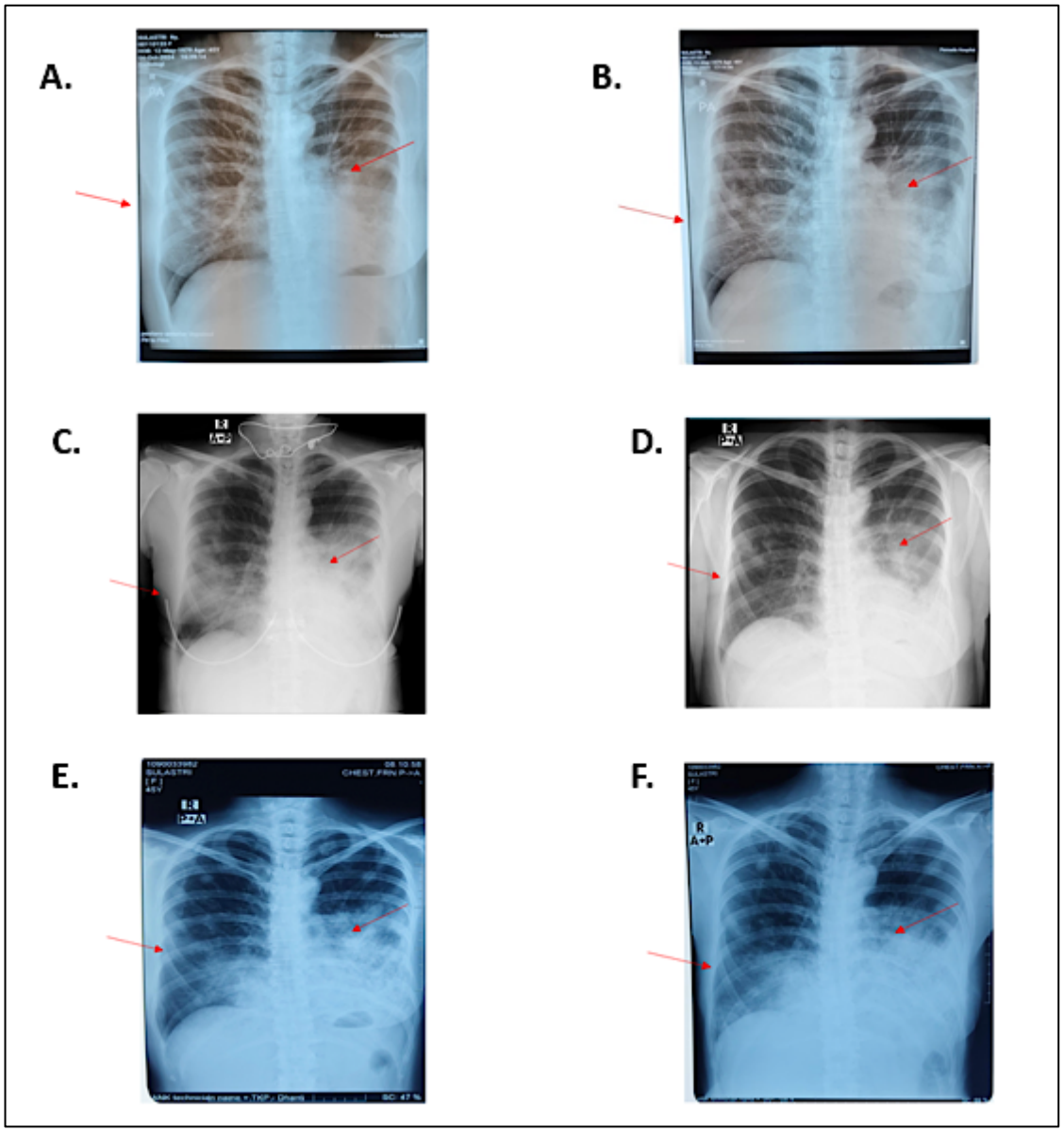

Figure 1: Serial Chest Radiographs Demonstrating Disease Progression from October 2024 to April 2025. (A) Chest radiograph obtained on 4 October 2024 showing findings consistent with infected bronchiectasis, (B) Chest radiograph obtained on 4 November 2024 demonstrating pulmonary edema, left pleural effusion and pneumonia, (C) Chest radiograph obtained on 18 December 2024 showing persistent pulmonary edema, left pleural effusion and pneumonia, (D) Chest radiograph obtained on 24 December 2024 demonstrating persistent pulmonary edema and left pleural effusion with partial improvement of pneumonic infiltrates, (E) Chest radiograph obtained on 6 April 2025 showing bilateral paracardiac consolidations, multiple pulmonary nodules and left pleural effusion, (F) Chest radiograph obtained on 9 April 2025 demonstrating persistent pulmonary abnormalities compared with the previous examination

Figure 1 illustrates the serial chest radiographs obtained during the patient's clinical course, demonstrating persistent and progressive pulmonary abnormalities despite multiple courses of treatment. The radiographs consistently showed recurrent pulmonary infiltrates, left pleural effusion and features of chronic bronchiectatic lung disease without complete radiographic resolution. The persistence of these abnormalities, together with the emergence of bilateral consolidations and pulmonary nodules, prompted further evaluation using high-resolution computed tomography to better characterize the underlying pulmonary pathology. Representative CT findings are shown in Figure 2.

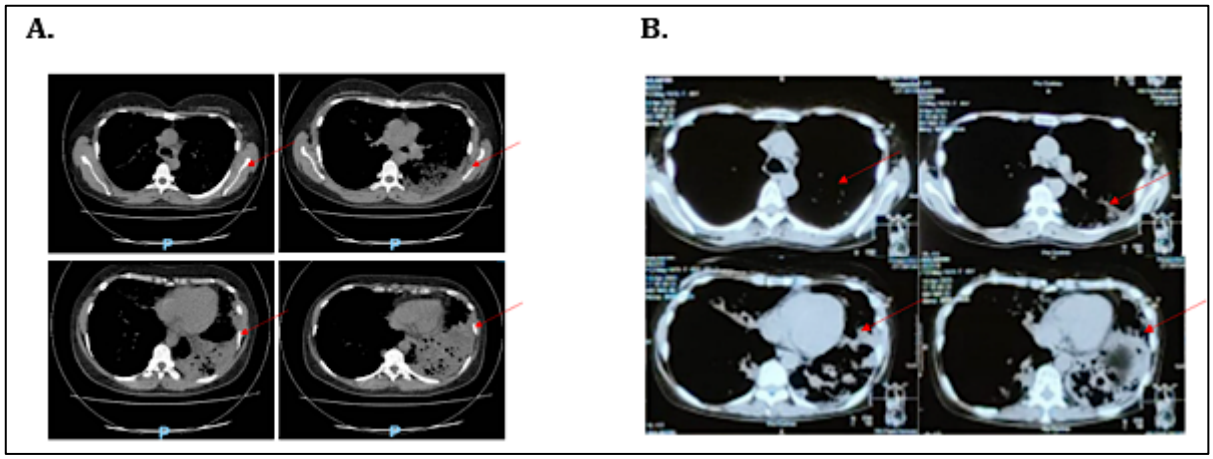

Figure 2: Thoracic CT Findings Demonstrating Bronchiectasis and ILD-Like Abnormalities. (A) Chest CT obtained on 10 January 2025 showing extensive bilateral cystic bronchiectasis, ground-glass opacities with mosaic attenuation, centrilobular nodules forming a tree-in-bud pattern, areas of consolidation and honeycombing-like cystic clustering predominantly involving the left lower lobe, raising suspicion for concurrent fibrotic interstitial lung disease, (B) Chest CT obtained on 14 April 2025 demonstrating persistent bilateral bronchiectatic changes with signet-ring appearance, multiple cystic lesions, pulmonary nodules, secondary infectious changes and persistent left pleural effusion

Figure 2 demonstrates representative thoracic CT findings that were pivotal in establishing the final diagnosis. The scans revealed extensive bilateral cystic bronchiectasis accompanied by ground-glass opacities, centrilobular nodules, honeycombing-like changes and persistent pleural effusion, indicating the coexistence of chronic airway disease and fibrotic interstitial lung abnormalities. These findings shifted the diagnostic consideration away from pulmonary tuberculosis and supported further immunological evaluation, which ultimately confirmed anti-synthetase-associated interstitial lung disease.

Upon admission, physical examination revealed a body mass index (BMI) of 19.7 kg/m^2, oxygen saturation of 91–92% on room air and bilateral bronchovesicular breath sound with coarse crackles. Laboratory investigations demonstrated leukocytosis (17,800/µL), supporting the presence of an active inflammatory or infectious process. The patient had a history of minimal smoking exposure (2–3 cigarettes/week during 2004–2005) with cessation since 2005, suggesting that significant smoking-related lung disease was less likely.

Spirometry performed on 25 December 2024 demonstrated a moderately severe restrictive ventilatory abnormality, with pre-bronchodilator forced vital capacity (FVC) of 1.34 L (51% predicted) and forced expiratory volume in 1 second (FEV1) of 1.13 L (51% predicted). Post-bronchodilator testing showed FVC improvement to 1.80 L (68% predicted) and FEV1 of 1.17 L (52% predicted). No serial pulmonary function testing was available for longitudinal assessment. The detailed pulmonary function test results are summarized in Table 2.

Table 2: Pulmonary Function Test Results Before and After Bronchodilator Administration

Parameter	**Pre-bronchodilator (25 December 2024)**	**Post-bronchodilator (25 December 2024)**
Interpretation	Moderately severe restrictive ventilatory defect	Moderately severe restrictive ventilatory defect
Forced Vital Capacity (FVC)	1.34 L (51% predicted)	1.80 L (68% predicted)
Forced Expiratory Volume in 1 Second (FEV_1)	1.13 L (51% predicted)	1.17 L (52% predicted)
FEV_1/FVC Ratio	84.38%	64.78% (77% predicted)
Maximum Mid-Expiratory Flow (MMEF 25–75%)	1.34 L/s (52% predicted)	0.60 L/s (23% predicted)
Maximum Expiratory Flow at 25% of FVC (MEF25)	0.55 L/s (56% predicted)	0.16 L/s (16% predicted)

Table 2 summarizes the patient's pulmonary function test results before and after bronchodilator administration. Spirometry demonstrated a moderately severe restrictive ventilatory defect, which was consistent with the extensive fibrotic changes observed on thoracic CT. Although a modest improvement in FVC was observed following bronchodilator administration, the overall restrictive pattern persisted, suggesting that the patient's respiratory impairment was predominantly related to underlying interstitial lung disease rather than reversible airflow obstruction.

High-resolution computed tomography (HRCT) of the chest revealed extensive bilateral cystic bronchiectasis, predominantly involving the lower lobes, accompanied by ground-glass opacities, mosaic attenuation, centrilobular nodules with tree-in-bud appearance, multiple cystic changes and honeycombing-like features, raising suspicion of concurrent interstitial lung disease (ILD) rather than isolated bronchiectasis alone. Subsequent CT evaluation demonstrated bronchiectatic changes with secondary infection, including multiple cystic bronchiectatic areas, pulmonary nodules and persistent left pleural effusion.

Given the suspicion of an autoimmune component, an immunoserological panel was performed and returned positive for anti-Jo-1, anti-Mi-2 alpha and anti-HMGCR antibodies. Among these findings, anti-Jo-1 positivity was considered the most clinically relevant marker supporting anti-synthetase syndrome-associated ILD (ASyS-ILD), while the additional anti-Mi-2α and anti-HMGCR positivity suggested overlapping autoimmune features requiring clinical correlation. No definitive histopathological confirmation was obtained because lung biopsy was not performed; therefore, the diagnosis was established based on the integration of clinical presentation, radiological findings, pulmonary function impairment and autoimmune serology. The final diagnosis was established through multidisciplinary integration of pulmonology, radiology, microbiology and autoimmune serological findings.

Table 3: Summary of Clinical Findings Supporting the Diagnosis

Component	Case Data	Interpretation for Manuscript
Patient epidemiology	Female, 45 years old, residing in Malang; occupation: bank marketing staff; BMI 19.7 kg/m^2; history of very light smoking (2–3 cigarettes/week) in 2004–2005, ceased since 2005.	The case occurred in a middle-aged female with minimal smoking exposure. Clinically notable due to the development of chronic bronchiectasis with recurrent exacerbations and radiological features overlapping with pulmonary tuberculosis (TB) and interstitial lung disease (ILD).
Main symptoms	Productive cough since May 2024, worsening since September 2024; exertional dyspnea; decreased appetite; 3 kg weight loss over 2 months.	Suggestive of chronic respiratory disease with recurrent infectious exacerbations.
Clinical criteria of bronchiectasis	Chronic productive cough, progressive dyspnea, recurrent exacerbations and multiple hospital admissions.	Consistent with active chronic bronchiectasis.
Radiological criteria of bronchiectasis	Chest CT showing extensive consolidation, multiple cystic degeneration/cystic bronchiectasis, signet-ring/cystic changes, ground-glass opacities, mosaic attenuation, centrilobular nodules/tree-in-bud pattern and left pleural effusion.	HRCT findings are consistent with bronchiectasis complicated by secondary infection; however, imaging also demonstrates features suggestive of interstitial lung disease (ILD) or hypersensitivity pneumonitis, warranting differential evaluation.
Main differential diagnoses	Pulmonary tuberculosis, connective tissue disease-associated ILD (CTD-ILD)/anti-synthetase syndrome-associated ILD, hypersensitivity pneumonitis, recurrent pneumonia and opportunistic/non-tuberculous mycobacterial infection.	The main diagnostic challenge lies in differentiating recurrent infective bronchiectasis from TB and ILD due to overlapping clinical and radiological features.

Component	Case Data	Interpretation for Manuscript
Microbiology	Sputum cultures grew Escherichia coli; previous isolates included Streptococcus mitis (normal flora), Streptococcus viridans and coagulase-negative Staphylococcus.	Findings support secondary bacterial infection and airway colonization as triggers of exacerbations.
Main treatment	Culture- and sensitivity-guided intravenous antibiotics, bronchodilators for dyspnea, long-term mucolytic agents and airway clearance physiotherapy.	Management focused on infection control, mucus clearance optimization and supportive therapy. Antibiotic therapy for exacerbations was recommended for 14 days and adjusted according to culture results.
Immunosuppression	Mycophenolate mofetil was initiated due to suspicion of autoimmune disease, then temporarily discontinued due to recurrent infectious exacerbations.	Immunosuppressive therapy was withheld due to the risk of worsening active infection and because autoimmune evidence was not yet definitive or consistent.

Table 3 summarizes the key clinical, radiological, microbiological and immunological findings that contributed to the final diagnosis. The integration of chronic respiratory symptoms, characteristic HRCT abnormalities, restrictive pulmonary function and positive autoimmune serology supported the diagnosis of anti-synthetase syndrome-associated interstitial lung disease coexisting with chronic bronchiectasis. The table also highlights the principal differential diagnoses and therapeutic considerations, emphasizing the complexity of distinguishing chronic infection from autoimmune-related pulmonary disease in this patient.

Despite these findings, the patient experienced recurrent pulmonary exacerbations. Sputum cultures demonstrated changing bacterial profiles during the disease course, including *Streptococcus mitis*, *Streptococcus viridans* and *coagulase*-negative *Staphylococcus*, followed by *Escherichia coli* isolation on 23 December 2024. The E. coli isolate showed resistance to amoxicillin-clavulanate, ampicillin and ampicillin-sulbactam, while remaining susceptible to piperacillin-tazobactam, meropenem and other selected antibiotics. The repeated detection of bacterial organisms was interpreted as airway colonization with superimposed infectious exacerbations, considering the presence of worsening respiratory symptoms, leukocytosis and clinical deterioration. Although *Pseudomonas aeruginosa* is more commonly reported in bronchiectasis, persistent isolation of *Escherichia coli* in non-cystic fibrosis bronchiectasis is less frequently described and may represent an important factor complicating antimicrobial selection and immunosuppressive decision-making.

Consequently, the patient was managed with culture-directed intravenous antibiotics, bronchodilator therapy, mucolytic treatment and intensive airway clearance strategies including chest physiotherapy. The patient required close multidisciplinary monitoring, including clinical assessment of exacerbation frequency, sputum microbiology surveillance, evaluation of inflammatory markers and repeated radiological assessment before reconsidering long-term immunosuppressive therapy. Mycophenolate mofetil was considered/initiated due to suspicion of autoimmune-related ILD but was temporarily discontinued because of recurrent infectious exacerbations and concern that immunosuppression could aggravate bacterial airway infection. Definitive immunosuppressive therapy for the anti-synthetase-associated ILD was carefully withheld due to the high risk of aggravating the ongoing bacterial infection within the bronchiectatic airways, highlighting the therapeutic dilemma in managing this complex overlap syndrome. Future management was planned to include reassessment for initiation of steroid-sparing immunomodulatory therapy once adequate infection control was achieved, with continued airway clearance strategies and regular pulmonary follow-up.

Discussion

This case report underscores the considerable diagnostic and therapeutic challenges posed by the overlap between bronchiectasis and anti-synthetase syndrome-associated interstitial lung

disease (ASyS-ILD) (11, 12). In such cases, chronic airway infection and autoimmune interstitial inflammation may occur simultaneously, influence one another and produce overlapping clinical and radiologic features, thereby delaying recognition of the full disease process. The uniqueness of this case lies in the coexistence of extensive cystic bronchiectasis, persistent bacterial airway involvement with *Escherichia coli,* previous empirical anti-tuberculosis therapy despite negative microbiological evaluation and the presence of multiple autoimmune-associated antibodies (anti-Jo-1, anti-Mi-2α and anti-HMGCR), which collectively created substantial diagnostic uncertainty.

The patient presented with chronic cough, dyspnea and weight loss and was initially managed as pulmonary tuberculosis. However, negative TCM findings and the absence of clinical improvement should have prompted early reconsideration of the diagnosis, as these findings suggested that infection alone was insufficient to explain the clinical course. Although tuberculosis remains an important differential diagnosis in patients presenting with chronic respiratory symptoms and abnormal chest imaging, persistent radiological abnormalities characterized by bronchiectatic changes, ground-glass opacities, cystic abnormalities and fibrotic features without microbiological confirmation should raise suspicion for alternative inflammatory or autoimmune lung disorders (13). Recurrent exacerbations, repeated episodes of presumed pneumonia and variable chest radiograph abnormalities further contributed to diagnostic uncertainty.

An important lesson from this case is the need to identify an atypical clinical course in patients with known bronchiectasis. In routine practice, persistent respiratory symptoms are often attributed to recurrent infective exacerbations, particularly in settings where infectious diseases are common. Nevertheless, coexisting ILD should be considered when patients demonstrate ongoing or progressive dyspnea despite appropriate antimicrobial treatment, especially when this is accompanied by restrictive ventilatory patterns on spirometry, persistent bilateral ground-glass or fibrotic abnormalities on HRCT and/or positive autoimmune serology. Autoimmune-associated ILD may therefore remain underrecognized because its pulmonary manifestations frequently overlap with chronic infection, particularly when patients present without classical extrapulmonary manifestations such as myositis or arthritis (12, 14).

In this patient, the combination of bronchiectatic and interstitial changes on HRCT, together with positive anti-Jo-1 and anti-Mi-2α antibodies, supported the diagnosis of ASyS-ILD overlap and clarified the limited response to treatment directed solely at infection. Radiologically, the coexistence of extensive cystic bronchiectasis, ground-glass opacities, mosaic attenuation, centrilobular nodules with tree-in-bud appearance and honeycombing-like changes contributed substantially to the diagnostic complexity. While several of these findings may occur in chronic infection, the presence of diffuse interstitial and fibrotic abnormalities raised concern for concomitant autoimmune-associated ILD rather than isolated bronchiectasis alone. The coexistence of anti-Jo-1, anti-Mi-2α and anti-HMGCR antibodies is uncommon and may represent an overlapping autoimmune profile requiring careful clinical interpretation. Although anti-Jo-1 is strongly associated with ASyS-ILD, the additional antibody positivity may reflect broader immune dysregulation within the inflammatory myopathy spectrum; however, false-positive results cannot be completely excluded without longitudinal clinical correlation.

Once ILD is suspected, evaluation should follow a structured, multidisciplinary approach (11, 15, 16). This includes detailed HRCT pattern assessment, pulmonary function testing (with serial FVC and DLCO monitoring when available) and focused autoimmune work-up, while concurrently performing microbiological investigations to detect active infection and guide antibiotic selection (17). In overlap syndromes such as this, infection control is not only a primary therapeutic goal but also a necessary condition before immunosuppressive treatment can be introduced safely. In the present case, repeated sputum cultures demonstrated different bacterial profiles during the disease course, eventually identifying *Escherichia coli.* While airway colonization is common in bronchiectasis due to impaired mucociliary clearance (18), the clinical deterioration, leukocytosis and recurrent exacerbations suggested that bacterial persistence was associated with clinically significant infectious

episodes rather than simple colonization alone. Although *Pseudomonas aeruginosa* is more frequently reported in bronchiectasis, persistent isolation of *Escherichia coli* in non-cystic fibrosis bronchiectasis represents a less commonly described finding and may complicate antibiotic selection and long-term management.

Previous reports have described ASyS-ILD presenting predominantly with respiratory manifestations before the development of overt myositis or other systemic features (6, 11, 12). Similarly, the present patient initially manifested chronic respiratory symptoms and recurrent pulmonary infections, resulting in delayed recognition of the underlying autoimmune process. This observation reinforces the need for early autoimmune evaluation in patients with unexplained bronchiectatic and interstitial abnormalities that fail to respond to conventional antimicrobial therapy. Although histopathologic confirmation was not obtained because lung biopsy was declined, the diagnosis remained clinically justifiable based on convergent clinical, radiologic and serologic evidence. The absence of tissue confirmation represents an important limitation of this case and should be considered when interpreting the diagnostic conclusion. Nevertheless, invasive biopsy may not always be feasible in patients with significant respiratory impairment or ongoing infection risk and multidisciplinary clinical-radiological assessment remains essential in complex ILD cases.

Management of this overlap phenotype requires concurrent attention to both disease components, with careful sequencing of therapy. Treatment of bronchiectasis should prioritize airway clearance, culture-directed antibiotics and strategies to reduce exacerbation frequency (19). At the same time, the ASyS-ILD component requires timely immunomodulatory therapy once infection has been adequately controlled. The major therapeutic dilemma in this patient was balancing the need for immunosuppression to prevent progression of autoimmune-mediated lung fibrosis against the risk of worsening chronic airway infection (20). Initiation of immunosuppressive therapy should therefore be individualized based on infection status, severity of ILD progression, respiratory function and multidisciplinary risk-benefit assessment (21).

In this context, mycophenolate mofetil (MMF) is an appropriate steroid-sparing agent for long-term management of ASyS-ILD, particularly when prolonged immunosuppression is anticipated (15, 22, 23). However, in patients with coexisting bronchiectasis, MMF or other immunomodulatory agents should be introduced cautiously with continuous surveillance for infectious complications, including recurrent exacerbations, sputum microbiological changes and radiological progression. Ongoing follow-up is essential to evaluate infection recurrence, treatment tolerance, radiologic progression and decline in pulmonary function.

Future management of this patient requires continued multidisciplinary follow-up involving pulmonologists, rheumatologists, infectious disease specialists and radiologists to determine the appropriate timing of immunosuppressive therapy while maintaining infection control (24). Long-term strategies should include optimization of airway clearance, vaccination, prevention of exacerbations, serial pulmonary function assessment and reassessment of autoimmune disease activity (25).

Conclusion

Overall, this case emphasizes that early consideration of ILD in patients with “non-resolving bronchiectasis exacerbations” is essential to prevent diagnostic delay and to improve outcomes through coordinated multidisciplinary care. Although limited by the nature of a single case report and the absence of histological confirmation, this case highlights the need for increased awareness of autoimmune-associated ILD in patients with persistent infectious-like respiratory disease and provides insight into the complex decision-making required in respiratory overlap syndromes.

This case highlights the diagnostic and therapeutic complexity of chronic bronchiectasis overlapping with anti-synthetase-associated interstitial lung disease (ASyS-ILD). Persistent respiratory symptoms and recurrent exacerbations despite appropriate antimicrobial therapy should prompt clinicians to consider underlying autoimmune-related ILD, particularly when accompanied by restrictive ventilatory defects, characteristic HRCT abnormalities and positive myositis-associated autoantibodies. Early recognition is essential to

prevent diagnostic delay and progressive pulmonary fibrosis. Management remains challenging because immunosuppressive therapy required for ILD control may aggravate chronic airway infection and bacterial colonization in bronchiectatic lungs. Therefore, treatment strategies should prioritize infection control, airway clearance and careful multidisciplinary evaluation before initiating definitive immunomodulatory therapy. This case is limited by the absence of histopathological confirmation and the lack of longitudinal pulmonary function monitoring, which may restrict definitive assessment of disease progression and treatment response. Future management should include continued multidisciplinary follow-up, serial radiological and pulmonary function assessment and reassessment of immunomodulatory therapy once adequate infection control has been achieved. This case emphasizes the importance of individualized and multidisciplinary management in achieving optimal outcomes in complex respiratory overlap syndromes.

Abbreviations

ASyS: Anti-synthetase syndrome, ASyS-ILD: Anti-synthetase syndrome-associated interstitial lung disease, DLCO: Diffusing capacity of the lungs for carbon monoxide, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, HRCT: High-resolution computed tomography, ILD: Interstitial lung disease, MMF: Mycophenolate mofetil, PPF: Progressive pulmonary fibrosis, RP-ILD: Rapidly progressive interstitial lung disease.

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Author Contributions

Geraldi Kusuma Wijaya: Conceptualization, Study Design, Definition of Intellectual Content, Literature Search, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review, Susanthy Djajalaksana: Conceptualization, Study Design, Definition of Intellectual Content, Literature Search, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review, Iin Noor Chozin: Conceptualization, Study Design, Definition of Intellectual Content, Literature Search, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review, Perdana Aditya Rahman: Conceptualization, Study Design, Definition of Intellectual Content, Literature Search, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review, Dini Rachma Erawati: Conceptualization, Study Design, Definition of Intellectual Content, Literature Search, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review. All authors reviewed and approved the final version of the manuscript and take full responsibility for the integrity and accuracy of the work

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data availability

The data supporting the findings of this case report are available from the corresponding author upon reasonable request. However, due to patient confidentiality and ethical restrictions, the complete clinical data and identifiable patient information are not publicly available.

Declaration of Artificial Intelligence (AI) Assistance

During the preparation of this manuscript, the authors used generative AI and AI-assisted technologies solely to improve the readability, grammar, language structure and clarity of the manuscript. After using these tools, the authors carefully reviewed and edited the content as needed and take full responsibility for the final content of the published article.

Ethics Approval

Ethical approval was not sought because this manuscript is a single-patient case report and does not constitute a formal human subject research study. The report was prepared retrospectively for educational and scientific purposes using de-identified clinical data, with no intervention performed specifically for research. No personally identifiable information is disclosed in the manuscript. Written informed consent for

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