Literature Review

Diagnosis and Management of Interstitial Lung Abnormalities (ILA): An Article Review

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Abstract

Interstitial lung abnormalities (ILA) are radiological findings on chest computed tomography (CT) scans that occupy more than 5% of the lung area across upper, middle, and lower lung fields. Interstitial lung abnormalities manifest through several imaging features, including ground-glass opacities (GGO), reticular patterns, diffuse centrilobular nodules, non-emphysematous cysts, honeycombing, and traction bronchiectasis, while emphysema is excluded from its definition. Although global prevalence data for ILA are limited, epidemiological studies report a prevalence ranging from 3% to 10% in various populations. The ILA shares a similar pathological pathway with ILD. Histologically, the structural alterations are caused by a series of inflammations in the parenchyma, the part of the lung that is involved in gas exchange (bronchioles, alveolar ducts, and alveoli). Numerous proteins and pro-fibrotic components reside in this compartment. Connective tissue builds up because of these proteins' recurrent activation cycles. Identified risk factors for developing ILA include advanced age, cigarette smoking, exposure to inhaled substances such as dust and air pollution, and genetic predispositions. The ILA is further categorized into three subtypes: non-subpleural, nonfibrotic subpleural, and fibrotic subpleural, which reflect different radiological characteristics. Currently, there is no definitive treatment for ILA, and management strategies primarily involve clinical assessment, regular radiological follow-ups, and control of risk factors to mitigate disease progression. Given the potential implications of ILA on respiratory health, ongoing research is essential to elucidate its natural history and inform future therapeutic approaches.

Keywords: interstitial lung abnormalities (ILA), prevalence, risk factors, treatment

INTRODUCTION

The identification of pre-clinical interstitial lung disease (ILD) has introduced a term known as Interstitial Lung Abnormalities (ILA), characterized by incidental radiologic findings on computed tomography (CT) scans affecting over 5% of each lung zone. While ILA has emerged as a relatively new concept in imaging diagnostics, its clinical significance remains uncertain. Compounding the issue is the lack of comprehensive global data on the

prevalence of ILA, with estimates from limited epidemiological studies suggesting a prevalence range between 3% and 10% in select populations. This gap in data highlights a pressing need for further research to understand its implications, particularly as ILA may represent the early stages of more severe lung diseases, creating challenges in early detection, management, and patient outcomes.

Both authors did a systematic search of the published literature using Google as the primary search engine to access the Google Scholar and PubMed databases. The search included studies from the inception of these databases up to June 2024 that were written in English. An additional update to the search was carried out in August 2024.

During the screening process, all retrieved titles and abstracts were carefully evaluated by the authors to ensure accuracy and minimize bias. This review emphasized topics of clinical importance to pulmonologists, with a particular focus on the identification, diagnosis, management, and evaluation of patients diagnosed with ILA.

In instances where multiple studies addressed the same topic, the selection process prioritized the most pertinent study, which was determined based on its recency or the significance of its findings in the field. To maintain relevance, the inclusion criteria were restricted to studies published within the last decade.

Consequently, 19 studies were identified and included in this review. Despite employing a systematic and structured approach to the literature search and selection process, the overarching aim of this review was to present a narrative synthesis.

INTERSTITIAL LUNG ABNORMALITIES

Definition

Interstitial Lung Abnormalities are incidental radiologic findings in over 5% of the lung area across upper, middle, and lower zones on thoracic CT scans. Typically found in asymptomatic individuals without prior suspicion of ILD, ILA can potentially progress to more severe forms of ILD, highlighting the need for careful monitoring and risk factor assessment.[1]

Thoracic CT scans in ILA often reveal characteristic features, including ground-glass opacities (GGO) or reticular patterns, indicating early interstitial changes. Common findings also include diffuse centrilobular nodules, non-emphysematous cysts, and more advanced signs like honeycombing, which suggests lung fibrosis, and traction bronchiectasis, where airways are widened due to surrounding fibrosis. These features exclude emphysematous areas, as emphysema involves a distinct alveolar wall destruction process.[2]

If ILA is accompanied by clinical symptoms or impaired lung function, it may indicate the presence of ILD. In such cases, ILA is no longer considered incidental and requires further investigation to confirm or exclude ILD. Additionally, when ILA features are identified during targeted screening for ILD, they are not classified as

ILA, as these findings are expected and not incidental.[3,4]

Epidemiology

The term "ILA" first introduced by Washko et al, has gained recognition in recent years. Although global prevalence data are unavailable, studies report rates between 3% and 10%.[3,5] ILA is more common in individuals aged ≥70, predominantly men (43% vs 26%), and those with a history of smoking.[6]

A multicenter retrospective cohort study in South Korea analyzing thoracic CT scans found ILA in 3% (94 of 2,765) of cases. The prevalence was higher in males (4%; 81 of 2,068) compared to females (2%; 13 of 697) and more common among smokers (4%; 66 of 1,599) than non-smokers (2%; 28 of 1,166).[7]

A cohort study in Canada by Stuart et al found an ILA prevalence of 3.7% (30 of 806 subjects). Among these, 17% had nonsubpleural ILA, 17% had nonfibrotic subpleural ILA, and 67% had fibrotic subpleural ILA. Follow-up thoracic CT scans after two years revealed progressive ILA in 10% of cases, while 90% showed either stability or improvement.[8]

Risk factors

The ILA shares a similar pathological pathway with ILD. Histologically, the structural alterations are caused by a series of inflammations in the parenchyma. Numerous proteins and pro-fibrotic components reside in this compartment. Connective tissue builds up because of these proteins' recurrent activation cycles. Several studies have linked ILA risk to factors such as aging, smoking, inhaled substances, and genetics. The COPDGene study showed an ILA prevalence of 6% in the ≥70 years group, which increases compared to the younger group. Older individuals tend to have higher smoke exposure, though few are active smokers.[9] The risk for developing ILA increases 3.5 times for each 10-year increase in age ($P<0.001$; 95% CI=2.8-4.2), also by 3.6 times increase in mortality ($P<0.001$; 95% CI=3.0-4.5).[10]

Exposure to cigarette smoke is strongly linked to the development of interstitial lung disease (ILD) through fibrosis. In a group of 29,521 people, 9.7% of smokers had ILA, compared to 7.9% of those who never smoked.[11] A study by Sangani et al found that 52.8% of smokers had subclinical ILA or ILD. This group included many with a history of smoking (49%) and an average exposure of at least 30 pack-years.[12] Similarly, Washko et al reported that smokers were 1.82 times more likely to develop ILA. In people who smoked, ILA was associated with smaller lung volumes, reduced exercise ability, and higher death rates.[13,14]

The Multi-Ethnic Study of Atherosclerosis (MESA) found that air pollution is linked to ILA. For every 40 parts per billion (ppb) increase in nitric oxide (NOx), the risk of developing ILA rose by 1.77 times. NOx reacts with other particles in the airways, causing damage through inflammation.[15]

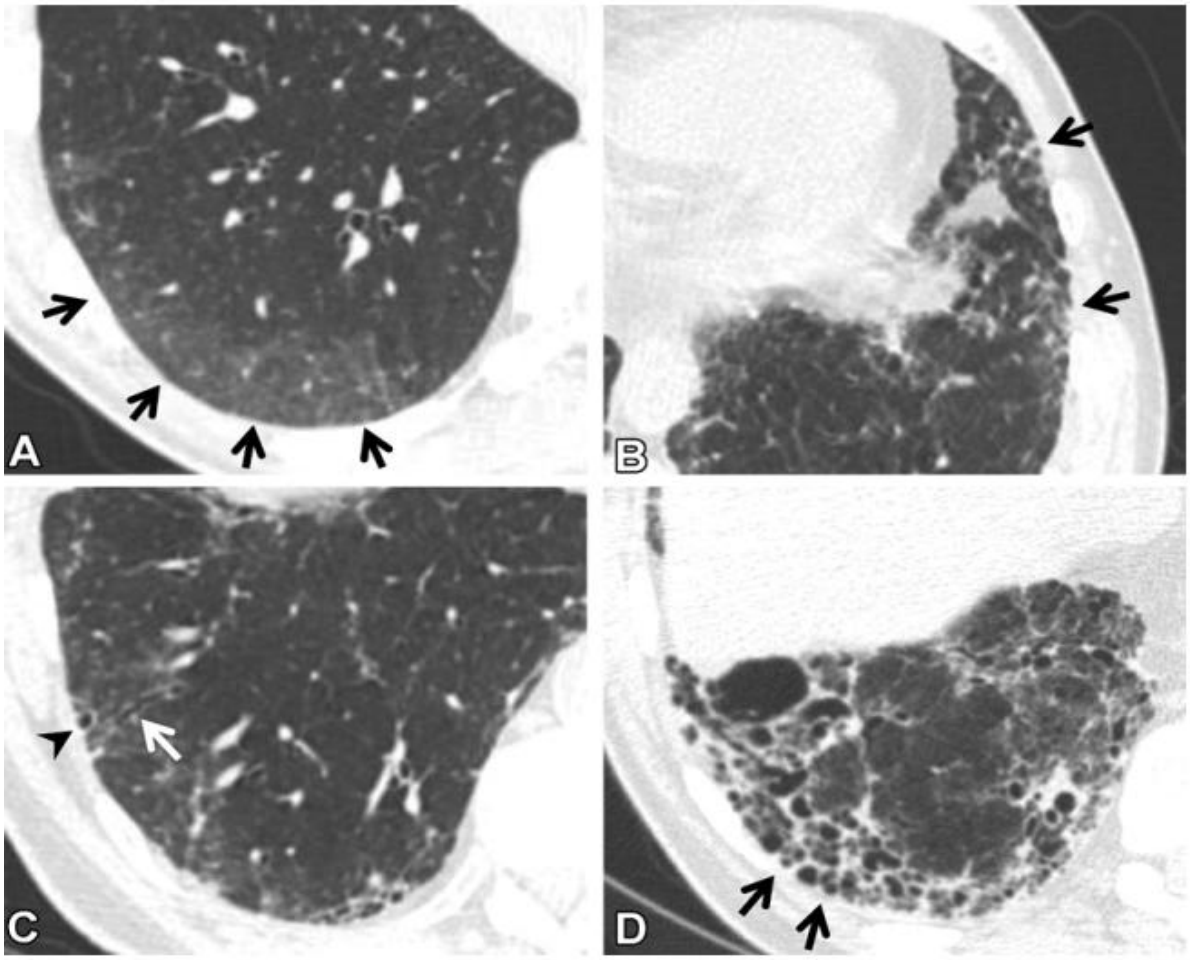

Figure 1. CT scan findings in ILA. Axial slices show ground-glass abnormalities (arrow in A), reticulation (arrow in B), traction bronchiectasis (arrow in C), non-emphysematous cysts (arrowhead in C), and honeycombing (arrow in D)[2]

This process triggers harmful molecules called reactive oxygen species (ROS), leading to ongoing inflammation and the release of chemicals that harm the lungs. Animal studies also showed that NOx exposure can cause lung cell damage, abnormal cell growth, and scarring (fibrosis).[15]

Hata et al discovered a strong link between a genetic variation in the MUC5B gene (rs35705950) and idiopathic pulmonary fibrosis (IPF) as well as familial interstitial pneumonia. This genetic variation was also associated with a higher risk of developing ILA and its progression. People with this variation had a 2.8 times greater risk of ILA compared to those without it.[16] The minor version of this gene occurs in about 10.5% of the population, and having more copies further increases the risk.[9,17] Ivette et al confirmed a strong connection between genetic variations in the MUC5B promoter and ILA. They reported that individuals with these variations were 3.5 times more likely to develop ILA, further supporting the genetic link to the condition.[6]

High levels of certain proteins in the body, like Matrix Metalloproteinase (MMP) 1,7,13, surfactant protein D (SP-D), and resistin, are linked to a higher risk of ILA. However, after considering factors like

age, sex, and lung function, only resistin and MMP-13 were strongly associated with ILA. Some of these proteins, such as MMP-7 and MMP-1, are also thought to be indicators of IPF.[6]

ILA AND IPF RELATION

The ILA and IPF share similarities, particularly their higher prevalence in the elderly, with each decade of age associated with a 2.2-fold increase in ILA risk. Distinguishing between normal aging and progressive ILA is essential to prevent unnecessary monitoring and delays in IPF treatment. Additionally, the male gender is a common risk factor, with male smokers experiencing a 1.7-fold increased incidence of ILA.[1]

Smoking is a well-established independent risk factor for both ILA and IPF. The MESA study linked the severity of parenchymal abnormalities to annual pack consumption.[15] Sack et al found significant associations between air pollution exposure and these conditions, with occupational exposure to pollutants also increasing incidence rates. Specifically, a 40-ppb rise in NOx was correlated with a 1.62-fold increased risk (P=0.06; 95% CI=0.97-2.71) for IPF progression.[1]

The ILA and the IPF differ in definition and characteristics. IPF is marked by a usual interstitial pneumonia (UIP) pattern without a known cause, while ILA is an incidental finding on CT scans. ILA is more common (7% vs. 0.063%) and varies in presentation, unlike the consistently fibrotic and progressive IPF. The histopathology of ILA remains largely unknown.[18]

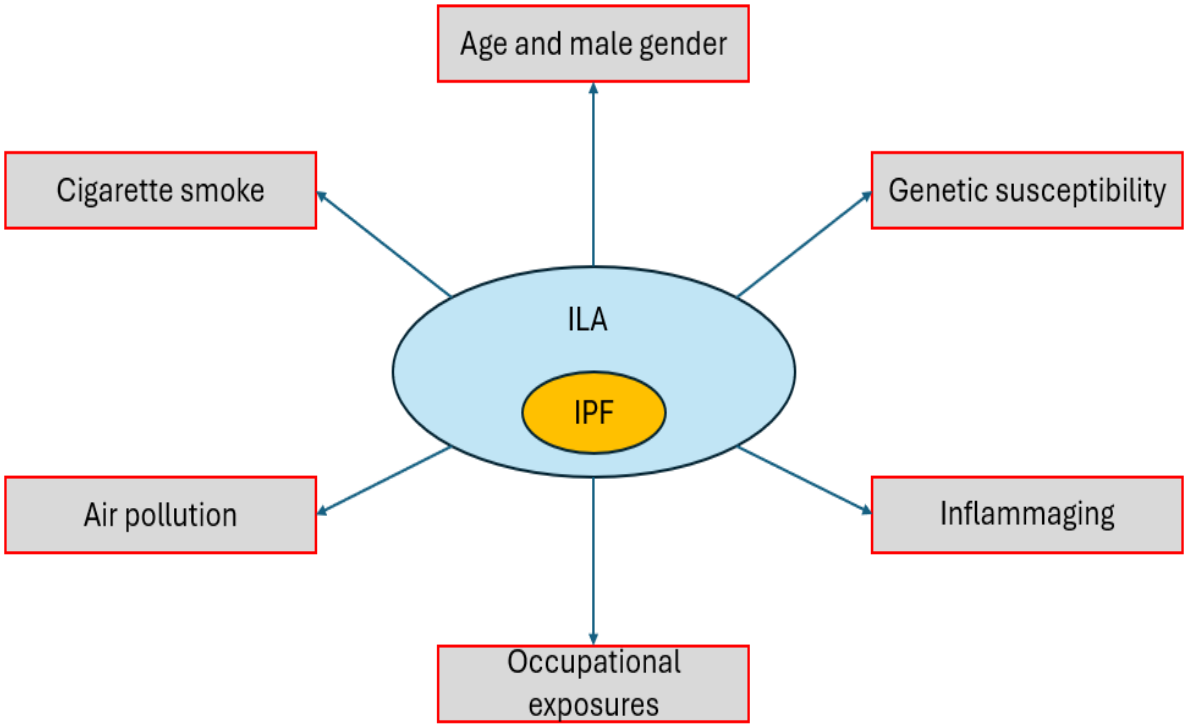

Figure 2. ILA and IPF relation[1]

RADIOLOGICAL FEATURES

The Fleischner Society categorizes ILA into nonsubpleural, nonfibrotic subpleural, and fibrotic subpleural types. The subtypes of ILA are shown in Figure 3. Fibrotic ILA, often with traction or honeycomb bronchiectasis, shows greater progression (P=0.004; OR=6.6) and is associated with higher mortality (P<0.001; HR=1.5). Other studies confirm fibrotic ILA's link to increased mortality risk (P<0.001; HR=1.7).[19]

The prevalence of ILA subcategories differs notably. In a study of 80 subjects, subpleural nonfibrotic ILA was found in 48% of cases, subpleural fibrotic ILA in 30%, and nonsubpleural ILA in 22%. Nonsubpleural ILA was nonprogressive and not linked to increased mortality. In contrast, centrilobular subpleural ILA was associated with greater progression (P=0.004; OR=6.7; 95% CI=1.8-25) and higher mortality risk (aOR=1.6; 95% CI=1.0-2.7; P=0.05). However, centrilobular nodules significantly reduced the likelihood of progression (OR=0.2; 95% CI=0.1-0.5; P=0.002).[1]

Various radiologic features can complicate the diagnosis of ILA by obscuring clinically significant abnormalities. Distinguishing meaningful findings from minor and insignificant ones is essential for identifying cases requiring further evaluation. Although these features are typically not classified as ILA, they can be difficult to differentiate. Comparison with previous images and the use of a pronated CT scan may be necessary for accurate diagnosis.[2]

Centrilobular nodules

Centrilobular nodules, often linked to smoking-related bronchiolitis, are typically non-progressive. Differential diagnoses include infection or aspiration bronchiolitis, hypersensitivity pneumonitis, pneumoconiosis, diffuse alveolar hemorrhage, and lipoid pneumonia.[2]

Apical cap lession

An apical cap is an age-related lesion at the lung apex caused by chronic ischemia, leading to pleural plaque formation or fibrosis. It appears as soft tissue attenuation at one or both apices and is often found incidentally. However, it is not classified as an ILA as it is a distinct radiologic entity.[2]

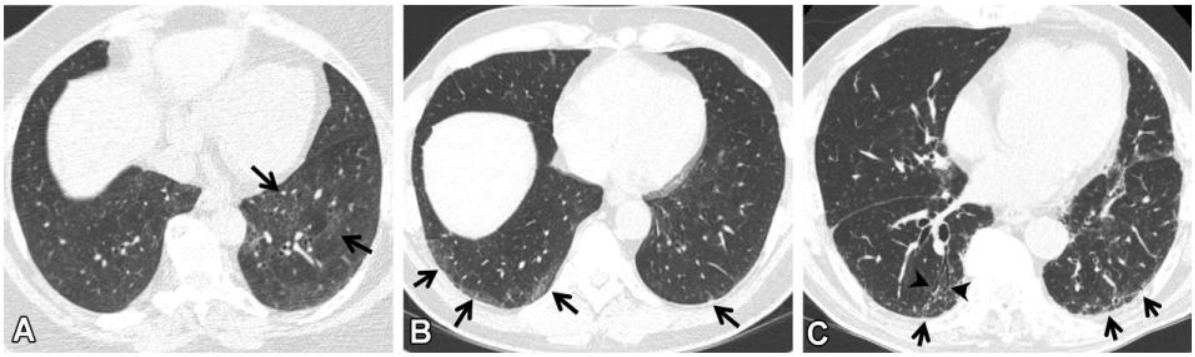

Figure 3. Subcategories of ILA on axial CT images
(A) Nonsubpleural ILA; (B) Nonfibrotic subpleural ILA; (C) Fibrotic subpleural ILA[2]

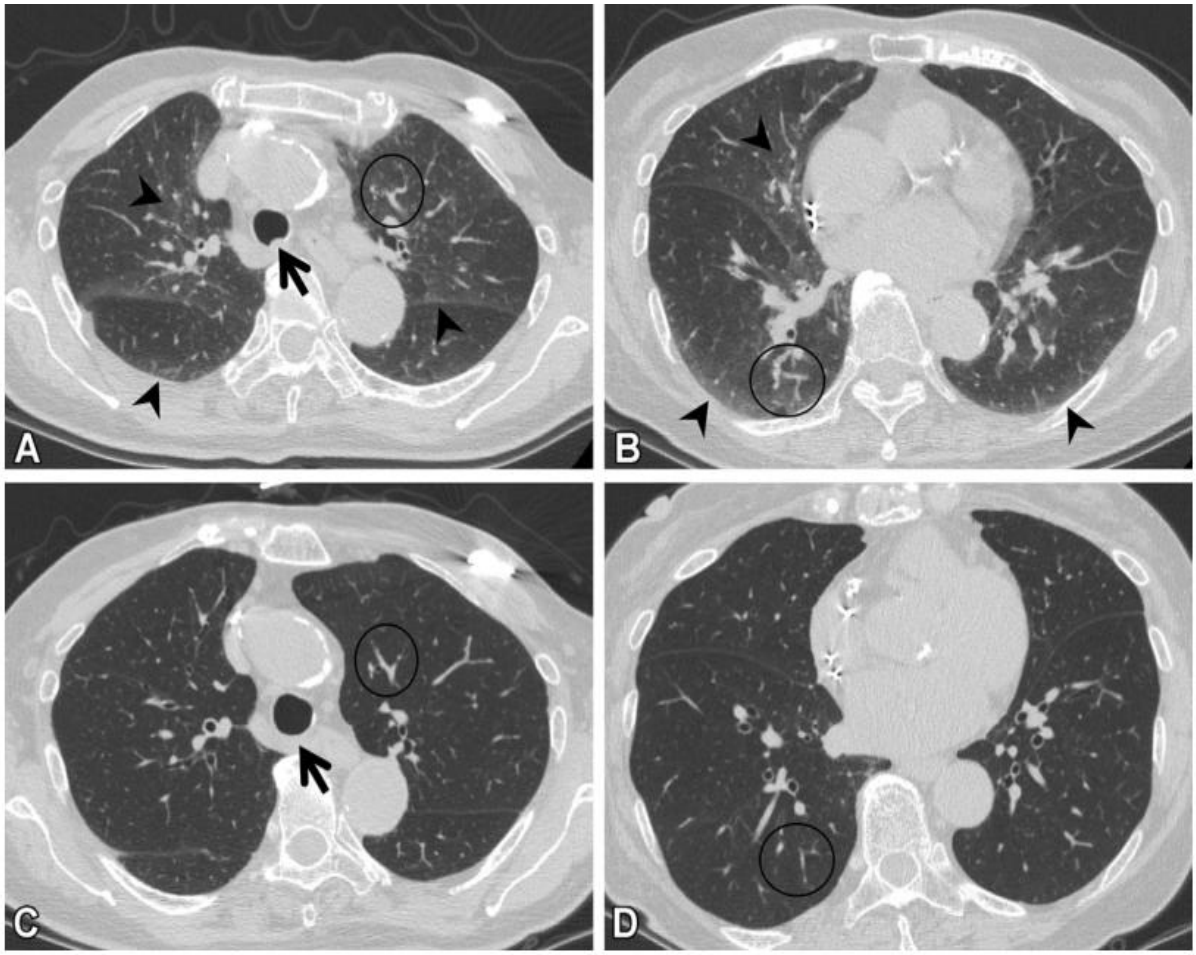

Figure 4. (A, B) CT images show ground-glass abnormalities (arrowheads) in subpleural and central areas of the lung zone. Anterior bulging of the posterior membranous portion of the trachea (arrow in A) and tortuosity of the vessels (circle) suggest a suboptimal inspiration; (C, D) Follow-up axial CT images show that the ground-glass abnormality has disappeared, and the normal round shape of the trachea is seen (arrow in C). The tortuosity of the vessels (circle) is no longer seen[2]

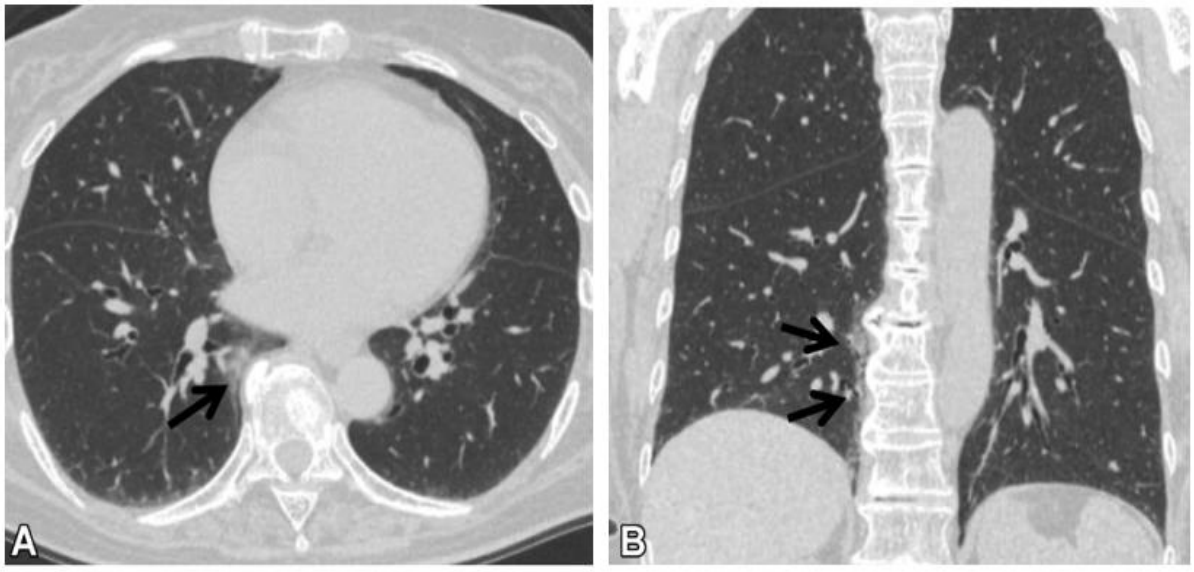

Figure 5. The osteophyte-related lesion in a 72-year-old woman with no respiratory symptoms.
(A) Axial CT image shows ground-glass abnormality adjacent to an osteophyte (arrow)
(B) Coronal CT image shows the craniocaudal alignment (arrows) of the abnormality[2]

Ostheophyte-related lession

Osteophyte-related lesions, including focal reticulation and GGO, are often seen near thoracic vertebral osteophytes on CT scans, particularly in the elderly. These lesions typically appear in the medial right lower lung lobe, as osteophytes are more prominent on the right. These minor abnormalities rarely progress and are not classified as ILA.[2]

Suboptimum inspiration

As we see in Figure 4, GGO abnormalities can result from suboptimal inspiration, where insufficient deep breathing leads to signs like tortuous blood vessels, anterior protrusion of the posterior tracheal membrane, and reduced lung volume compared to prior scans. Distinguishing true ILA often requires both supine and prone CT scans for confirmation.[2]

MANAGEMENT

Currently, insufficient evidence exists to establish a definitive management plan for ILA. The Fleischner Society recommends categorizing individuals as high or low risk based on clinical and radiological factors, following the exclusion of ILD. High-risk individuals present with one or more risk factors. Both groups should aim to reduce risk factors such as smoking and inhalation exposures, and all patients should be educated about the potential long-term effects of ILA.[9]

Low-risk individuals should be re-evaluated if respiratory symptoms or signs of ILD progression, such as reduced lung function, develop. High-risk groups require systematic follow-up. Clinical assessments, including physical exams and pulmonary function tests, are recommended every 3-12 months to monitor ILA progression. Follow-up CT scans should occur every 12-24 months, with earlier scans if symptoms arise. The optimal follow-up interval remains unclear due to limited evidence.[9]

Currently, no specific therapy exists for ILA progression. Antifibrotic agents may reduce progression in fibrotic interstitial lung disease (ILD), with early intervention possibly benefiting high-risk ILA patients. However, the costs and side effects of these treatments necessitate further research to identify higher-risk groups for progression and to understand the natural course of ILA toward clinically significant pulmonary fibrosis.[9]

PROGNOSIS

A 12-year prospective study in Denmark demonstrated increased morbidity in ILA patients, marked by higher rehospitalization rates for respiratory diseases, including chronic obstructive pulmonary disease (COPD), pneumonia, asthma, empyema, and lung cancer. Furthermore, the ILA group had more frequent emergency department visits than the control group. The precise mechanisms underlying this increased morbidity are unclear, but the nonspecific radiologic findings may indicate inflammatory, premalignant, or structural alterations in the pulmonary vasculature.[18]

About 80% of ILA patients showed progressivity on follow-up thoracic CT scans, with fibrotic ILA being a significant risk factor for both ILA progression (HR=10.3; 95% CI=6.4-16.4; P<0.001) and lung cancer (HR=4.4; 95% CI=2.1-9.1; P<0.001). The 10-year mortality rate for patients with fibrotic ILA was 36%, corresponding to a 6.7-fold increased risk of death (HR=6.7; 95% CI=3.7-12.2; P<0.001). Additionally, ILA was associated with a mean decline in forced vital capacity (FVC) of 64 ml per year, 30-35 ml more than normal aging, yet less than the decline seen in IPF patients (±200 ml per year).[1]

Mortality rates among ILA patients vary by study. The Framingham Heart Society (FHS) reported a 7% mortality rate (12 patients) in the ILA group over 4 years, compared to 1% in controls. The Age Gene/Environment Susceptibility (AGES) Reykjavik study found a 56% mortality rate (210 patients) in ILA patients versus 33% (1,065 patients) in non-ILA individuals over 8.9 years. In the COPDGene study, 16% of ILA patients (25 deaths) died compared to 11% (133 deaths) in controls over 6.5 years. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study showed an 11% mortality rate (18 deaths) in the ILA group versus 5% (27 deaths) in non-ILA individuals within 2.9 years.[5]

All the studies, FHS (HR=2.7; 95% CI=1.1-6.5), AGES Reykjavik (HR=1.3; 95% CI=1.2-1.4), COPDGene (HR=1.8; 95% CI=1.1-2.8), and ECLIPSE (HR=1.4; 95% CI=1.1-2.0) showed a substantial increase in mortality risk after controlling for variables. Cardiovascular illness (42%), lung cancer (25%), and respiratory disorders (13%), of which almost half were associated with pulmonary fibrosis, were the main reasons for mortality for ILA patients at AGES Reykjavik.[1,5]

CONCLUSION

In summary, ILA are incidental radiologic findings identified on thoracic CT scans, characterized by more than 5% of lung area involvement. Common imaging features include ground-glass opacities, reticular patterns, diffuse centrilobular nodules, non-emphysematous cysts, honeycombing, and traction bronchiectasis. Risk factors for ILA encompass age, gender, smoking, inhalation exposures, genetic polymorphisms, and elevated inflammatory biomarkers. Assessing ILA can be complicated by overlapping radiologic features, necessitating comparisons with prior imaging and, when appropriate, prone-position scans.

Current management approaches are primarily conservative, focusing on risk stratification, exposure reduction, and follow-up evaluations within 6-12 months. Patients with ILA face increased morbidity from respiratory conditions and heightened mortality risk, highlighting the need for continued research and careful clinical monitoring in this demographic.

Future ILA research faces several difficulties. The Fleischner Society's

recently suggested definition of interstitial lung abnormalities must be widely accepted to compare various ILA studies, not just ILA in general, but also ILA subtypes and imaging patterns. In addition to a recent expert review, clinical studies on the most effective ways to evaluate and monitor individuals with ILA are required. These investigations should focus on biomarkers that may reveal which individuals are at risk, particularly blood-based biomarkers because of their widespread usage in clinical practice and ease of access. It is feasible that the value of ILA biomarker research might not only forecast ILA development and ILD-related mortality but extend to predicting more severe clinical outcomes linked to ILA, such as cancer and death from all causes.

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