INTERSTITIAL LUNG ABNORMALITIES (ILA)

M. ZOMPATORI

Alma Mater University of Bologna

Radiology Dept. MultiMedica IRCCS. Milano







<u>maurizio.zompatori@unibo.it</u> <u>maurizio.zompatori@multimedica.it</u>

Interstitial Lung Abnormality (ILA)



Non dependent, diffuse abnormality, involving at least 5% of any lung zone (upper, middle, lower)

Extensive when it involves 3/6 or more lung zones

Exclusion of cases with symptoms (ILD), familial fibrosis (pre clinical ILD), occupational exposures, post COVID residual disease or CTDs

Hatabu H et al Lancet Respir Med2020Podolanczuk AJ et alClin Chest Med 2021Hata A et alRadiologyHata A et alRadioGraphicsSpagnolo P et alLancet Resp MedHunninghake GM et al Chest2022Tomassetti S et al Eur Respir Rev2022

DIFFERENTIAL DIAGNOSIS

EXCLUSION OF: sub optimal inspiration; dependent opacities; centrilobular nodules; tree in bud; interstitial edema; focal or unilateral opacities; para-spinal fibrosis; PPFE



Osteophyte induced lung fibrosis (OIF)

Otake S et al AJR 2002 Salvatore M et al Clin Imaging 2017



PPFE and lower lobe fibrosis (more commonly UIP) coexist in >1/3 of PPFE cases This association correlates with more rapid functional decline and reduced survival

> Hiroshi I et al Chronic Respir Dis 2019 Kono M et al Respir Invest 2023

Interstitial lung abnormalities (ILAs) can be:

- 1) detected incidentally on CT, in individuals without a known or suspected diagnosis
- 2) detected by CT screening in relatives over age 50 of pts with pulmonary fibrosis (PrePF)

ILAs have been associated with many adverse clinical outcomes, including reductions in lung function and survival, and in some cases are a precursor for ILD and progressive fibrosis (PF)

ILAs are increasingly recognised in clinical practice, especially with the implementation of lung cancer screening (2-9%), which motivated the publication of a Fleischner Society Position Paper in 2020

Hatabu H et al Lancet Respir Med 2020 Ledda RE et al Insights into Imaging 2022 Rose JA et alAJRCCM 2023 Steele AM et al AJRCCM 2023





The lung cancer screening probably represents until today the best opportunity to detect ILA

A «preclinical» form of ILD?



Risk factors: old age, smoking history, genetic variants, 1° degree relatives of pts with pulmonary fibrosis

The prevalence of ILAs seems to increase linearly with age

Podolanczuk AJ et al Clin Chest Med 2021 Hata A et al Radiology 2021 Spagnolo P et al Lancet Resp Med 2021 Hunninghake GM et al Chest 2022 2022 Tomassetti S et al Eur Respir Rev Zhang Y et al AJRCCM 2022 Tseng S et al J Comp Assist Tomogr 2022 Choi B et al Chest 2023 Rose JA et al AJRCCM 2023 Moss BJ et al AJRCCM 2023 Steele AM et al AJRCCM 2023







The DX OF ILAs GENERALLY SHOULD BE CONFIRMED USING

A PRONE CT SCAN, BECAUSE...

HRCT in prone position is useful for distinguishing a real ILA from dependent opacities













ILA

- Prevalence: 2-7% in never smokers (mean age 70y); 4-10% in current or former smokers
- Up to 22% in patients with lung cancer and in 1° degree relatives of pts with pulmonary fibrosis (IPF or non IPF)
- In our experience (virtual colonoscopy in 625 asymptomatic patients, current, ex or never smokers; with prone and supine CT scan), ILAs prevalence was 2,6%





Poerio A et al Am J Roentgenol

Hatabu H et al Lancet Respir Med	2020
Lynch DA Chest	2020
Matsuo N Invest New drugs	2021
Ledda RE et al Insights into Imaging	2022
Cho SW et al Thorac Cancer	2022
Hewitt RJ et al Thorax	2022
Oh AS et al RCNA	2022
McGroder C et al AJRCCM	2023

2017

ILA OR EARLY ILD? MDD IS REQUIRED



>50% of ILAs have in fact the criteria of suspected ILD (1 or more):

- 1) definite fibrosis on CT
- 2) post-bronchodilator FVC, 80% predicted
- 3) DLCO,70% predicted after adjustment for emphysema

Suspected ILDs generally present with higher smoking history

and have worse prognosis and higher mortality

Hewitt RJ et al Thorax 2022 Rose JA et al AJRCCM 2023





The association of ILA and emphysema should not be defined as CPFE, however, ILAs associated with COPD are a significant risk factor for acute exacerbations

and represent an indipendent risk factor for the development of lung tumors (x6 vs non-ILA; prevalence 2,5%), with high cancer stage and worse prognosis

Cottin V et al AJRCCM 2022



In patients with emphysema and ILAs a short-term CT follow-up is advisable for early detection of cancer

Presence and extent of the associated emphysema should be reported by Radiologists

Chae KJ et al J Person Med 2022 Rose JA et al AJRCCM 2022 Hata A et al RadioGraphics 2022





In patients with lung cancer, the presence of an ILA pre therapy is also a significant risk factor for post treatment complications and development of a fibrotic ILD (after chemotherapy, RT, surgery, ICI)

Putman RK AJRCCM 2017 Nakanishi Y Respir Invest 2019 Cho SW et al Thorac Cancer 2022 Im Y et al Thorax 2022 Chae KJ et al J Pers Med 2022 Hata A et al RG 2022 Oh AS et al RCNA 2022 Rose J et al Thorax 2022 Im Y et al Thorax 2022



ICI TOXICITY IN A PATIENT WITH NSCLC AND PRE EXISTING ILA

ILAS CLASSIFICATION

- a) non dependent ground glass, centrilobular nodules, non emphysematous air cysts (NON FIBROTIC).
- b) reticular opacities, distorsion of lobular architecture, traction bronchiectasis/bronchiolectasis, subpleural irregularities, honeycombing (FIBROTIC, more common).
- c) mixed type

Jin GY et al Ra	2013	
Hatabu H et al	Lancet Respir Med	2020
Lynch DA	Chest	2020
Ledda RE et al	Insights into Imaging	2022
Lee TS et al	Chest	2022
Lee JE et al	Radiology	2023



ILAS CLASSIFICATION



MAX RISK OF PROGRESSION





MIN RISK

- 1) Subpleural fibrotic: 7-30% of the cases
- 2) Subpleural non fibrotic: 40%
- 3) Non subpleural:
- 22% (generally non fibrotic and non progressive)

Putman RK et al Am J Respir Crit Care Med2019Hatabu H et alLancet Respir Med2020Mori Y et alRespir Invest2021Hata A et alRadiology2021Buendia Roldan I et alEur Respir J 2021Zhang Y et al AJRCCM2022Chae KJ et al Eur Radiol 2022

PATHOLOGIC CORRELATIONS OF FIBROTIC ILA (obtained from cancer resection specimens)

- SRIF (smoking related interstitial fibrosis) or AEF (alveolar enlargement with fibrosis), probably the more common findings
- UIP
- NSIP
- Indeterminate findings



Paraseptal fibrosis and lymphocytic inflammation can be seen by Pathologist even in regions appearing normal at CT, along with vasculopathy, macrophage accumulation, bronchiolectasis

Fibroblastic foci are rare

Katzenstein A-L A Postgrad Med J 2014 Otani H et al Int J COPD 2016 Zaizen Y et al Surg Pathol Clin 2019 Chae KJ Europ Radiol 2022 Verleden SE et al RadioGraphics 2023

PATHOLOGIC CORRELATIONS



Subpleural fibrotic: in 70% pathology shows UIP typical or probable.

It is important to recognize subpleural fibrotic ILA on CT to predict disease progression (max risk, 6 fold) and mortality





Subpleural non fibrotic: in 10% pathology shows UIP typical or probable, in 90% indeterminate or

alternative pattern.

The presence of reticulations is anyway considered a risk factor for radiological progression

Chae KJ et al Europ Radiol 2022 Zhang Y et al AJRCCM 2022



MICROSCOPIC HONEYCOMBING

- Imaging techniques cannot demonstrate fibroblastic foci or microscopic honeycombing
- Ground Glass associated with reticular opacities, bronchiectasis or bronchiolectasis is generally fibrotic and irreversible (often corresponding to microscopic honeycombing)
- Radiologic-histologic correlations in this setting are not perfect

PROGRESSION





Extensive disease and radiological progression are findings of prognostic value

Progression seems also to be associated with gastro esophageal reflux

Araki T et al Am J Respir Crit Care Med 2016 Raghu G et al Am J Respir Crit Care Med 2022 Lee JE et al Radiology 2023 ILAs have a tendency to progress with time, not always with corresponding symptoms and loss of function (20% over 2y, up to 80% over 8 y in fibrotic ILAs)

ILAs, EARLY ILD or MILD ILD may reflect different stages of the same disease process

Increased respiratory symptoms, reduced lung function and increased mortality (specific and all-cause) are seen in individuals with progressive ILAs

However, not always ILAs represent a preclinical phase of UIP/IPF and they can also be not progressive

Jin GY Radiology 2013 Hata A et al Radiology 2021 Tomassetti S et al Eur Respir Rev 2022 Lee TS et al Chest 2022 Hata A et al RG 2022 Rose JA et al AJRCCM 2023











Some cases progress by changing from a probable pattern to a definite UIP, others only increasing extent or changing both extent and pattern

Not all patients who progress with the development of a UIP pattern increase also the extent of disease

Abu Qubo AA et al Front Med 2022

THE AGING LUNG CONUNDRUM (EARLY DISEASE OR SIMPLE LUNG WRINKLES?)

Mild interstitial abnormalities were found in up to 60% of normal subjects over the age of 75y, never in subjects with less than 55y of age In the subsequent Lit., 2-10% of asymptomatic elderly people: same prevalence of ILA

There is a significative overlap between the so called aging lung and ILAs, with risk of under-overdiagnosis and overtreatment

Lung wrinkles are common, ILAs are common, UIP/IPF is rare (prevalence 0,06%)





Copley SJ et al Radiology 2009 Winter DH et al Lung 2015 Zhang Y et al AMRCCM 2022

OVERLAPPING AND UNCERTAIN BOUNDARIES



THE BORDERLANDS OF THE NORMAL AGING FOR THE ILA

AND BETWEEN

ILA AND EARLY ILD ARE STILL POORLY DEFINED

Dalal PU et al Eur Radiol 2006 Hansell DM Radiology 2010 Ledda RE et al Insights into Imaging 2022

RESEARCH NEEDS



- Better definition of the ILAs, their longitudinal outcome (particularly the transition from simple abnormality to pathology) and risk stratification
- Identification of subjects to be screened and screening modalities
- ILAs can be a post COVID 19 abnormality?
- How to assess progression? (HRCT, functional tests, specific biomarkers and endotypes such as a short telomere endotype?)
- Indications for biopsy or cryobiopsy
- Indications for anti fibrotic therapy
- HRCT systematic F/U

Hatabu H et al Lancet Respir Med 2020 Han X et al Radiology 2021 Ledda RE et al Insights into Imaging 2022 Tomassetti S et al Eur Respir Rev 2022 Im Y et al Thorax 2022 Amati F et al Lancet Respir Med 2023 Steele AM et al AJRCCM 2023

Active monitoring for the high risk group



Hatabu H et al Lancet Respir Med2020Ledda RE et al Insights into Imaging2022Fleischner Soc. Position Paper2022

RESEARCH NEEDS

- Introduce a standard radiological reporting with accurate and common terminology
- Define intra and inter observer variations (still unknown)
- 5% is a purely conventional threshold. Is it really acceptable?
- Extent evaluation with CT visual score or quantitative analysis (ex: CALIPER)?
- Role of the new scanner technology, AI and deep learning

Hatabu H et al Lancet Respir Med 2020 Ledda RE et al Insights into Imaging 2022 Tomassetti S et al Eur Respir Rev 2022 Jeudy J Radiographics 2023

Radiological classification is only relatively sensitive to progression, so the question is:

«How useful is a strict separation between fibrotic and non fibrotic ILAs...?"

Tomassetti S et al AJRCCM 2022

There is still a significant delay between the development of symptoms and the diagnosis of lung fibrosis, with a median time of 2 y

and the pre clinical phase begins only now to be detected

TAKE HOME MESSAGE FOR RADIOLOGISTS

ILAs always must be reported, along with a descriptive category, because early identification might improve the clinical outcomes

Furthermore, seize the opportunity to make this diagnosis

Cristoforo Armeno 1548 Voltaire 1747 Walpole 1754

THE DIAGNOSIS OF ILAS IS A PERFECT EXAMPLE OF SERENDIPITY

IN MEDICINE

Thanks for your attention