PNEUMOLOGIA 2016

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LAM: quando sospettarla

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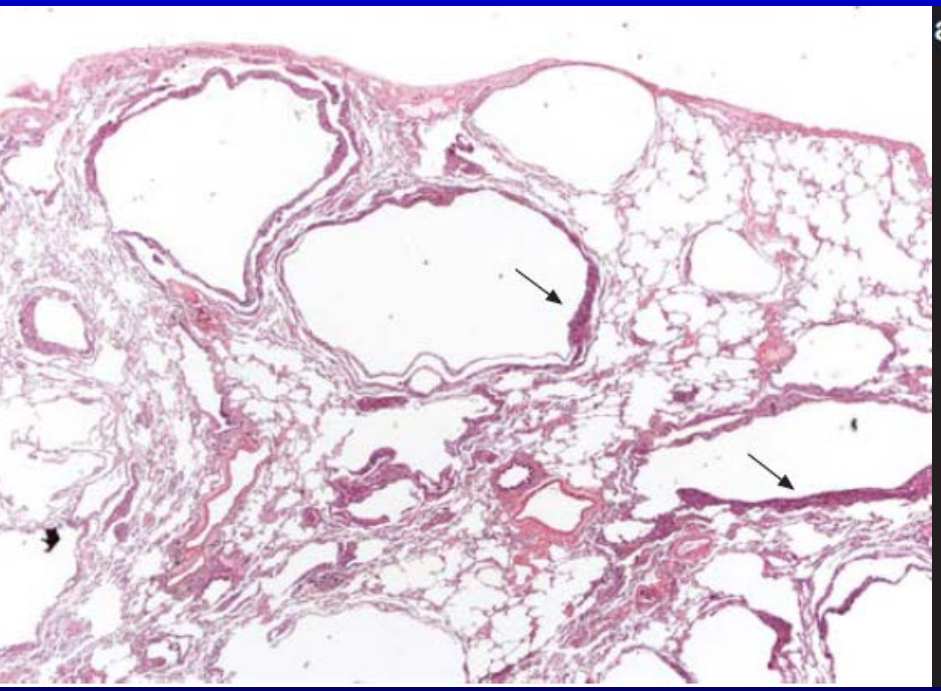
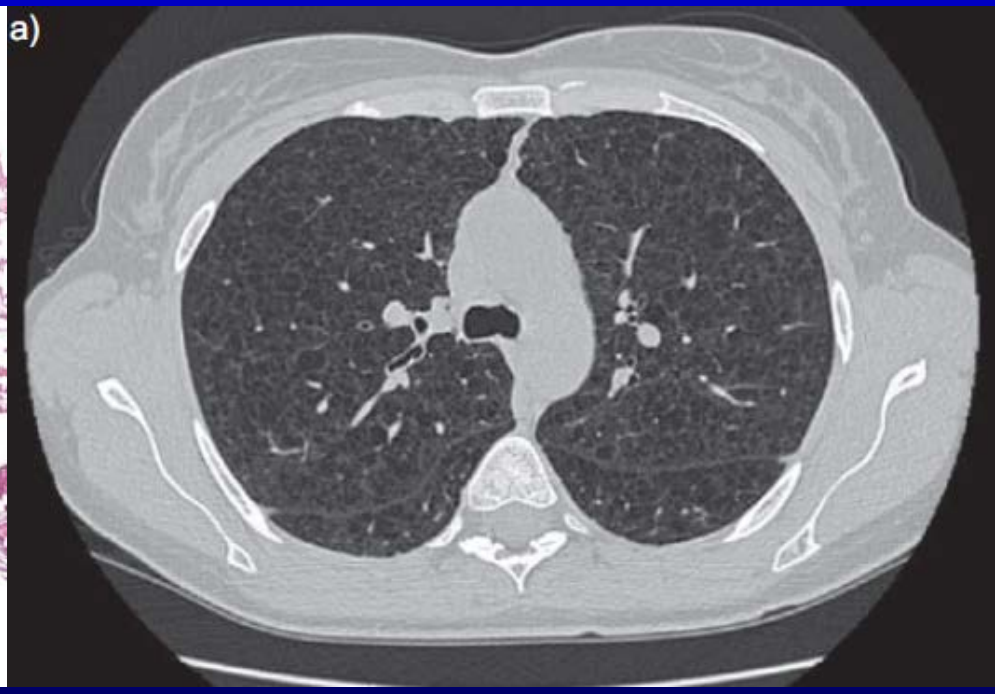
Lymphangioleiomyomatosis (LAM)



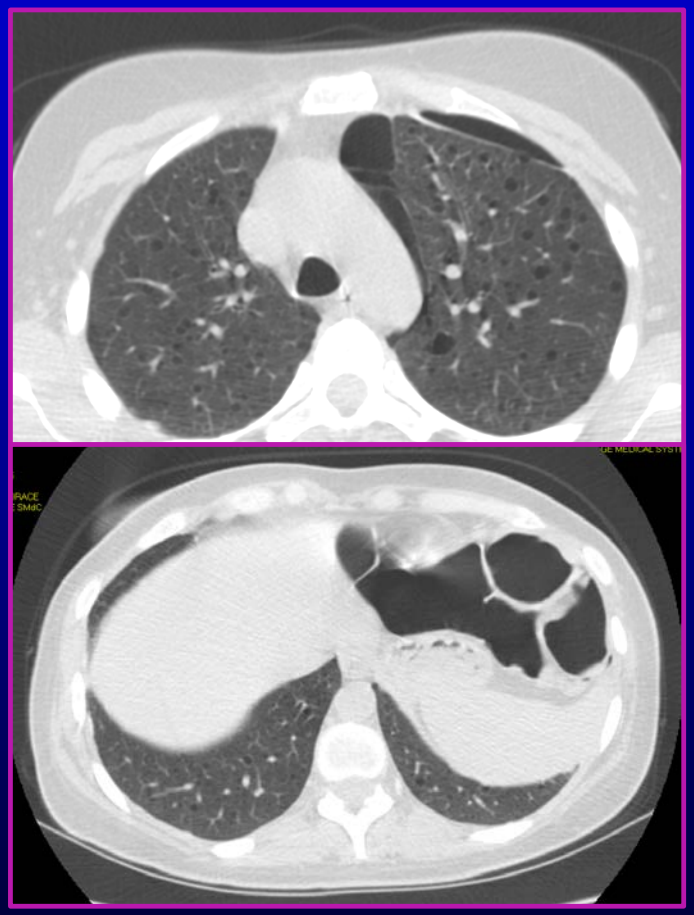


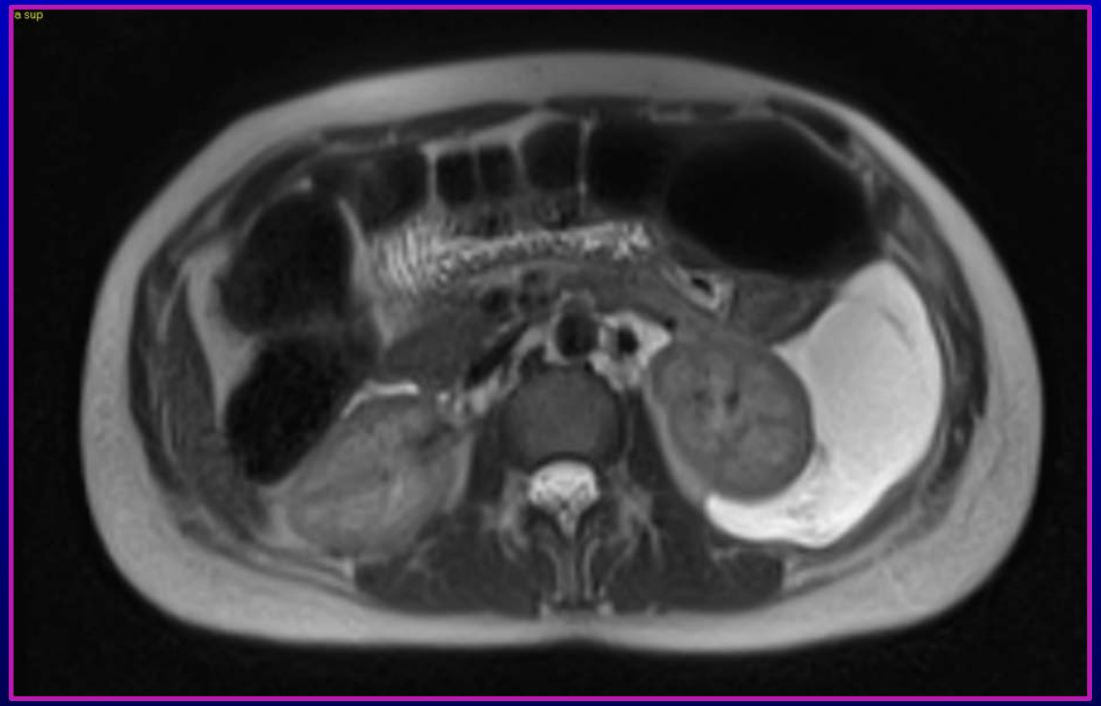
Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years.
It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours.

Pz di 38 anni, non fumatrice

Dal 2009 al 2012 tentativi di procreazione assistita con esito negativo

Viene ricoverata per pneumotorace sx





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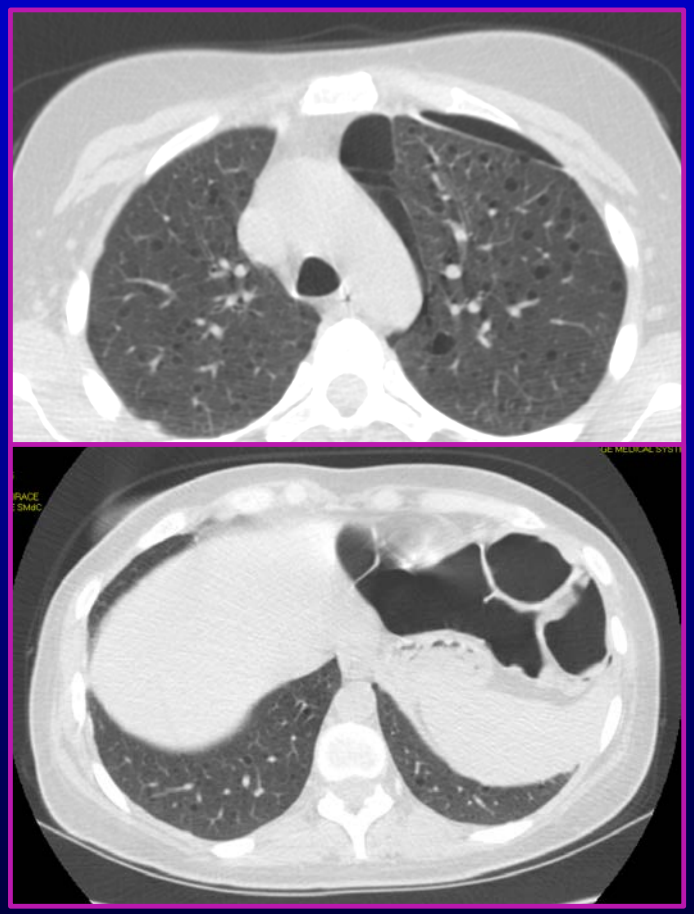
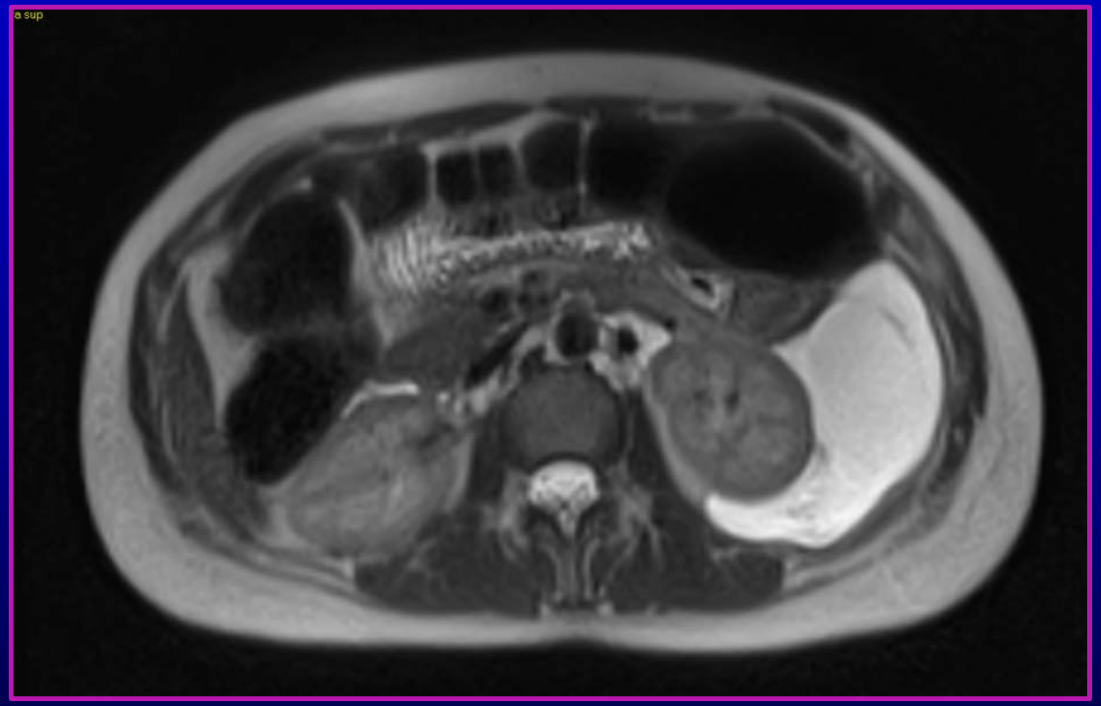
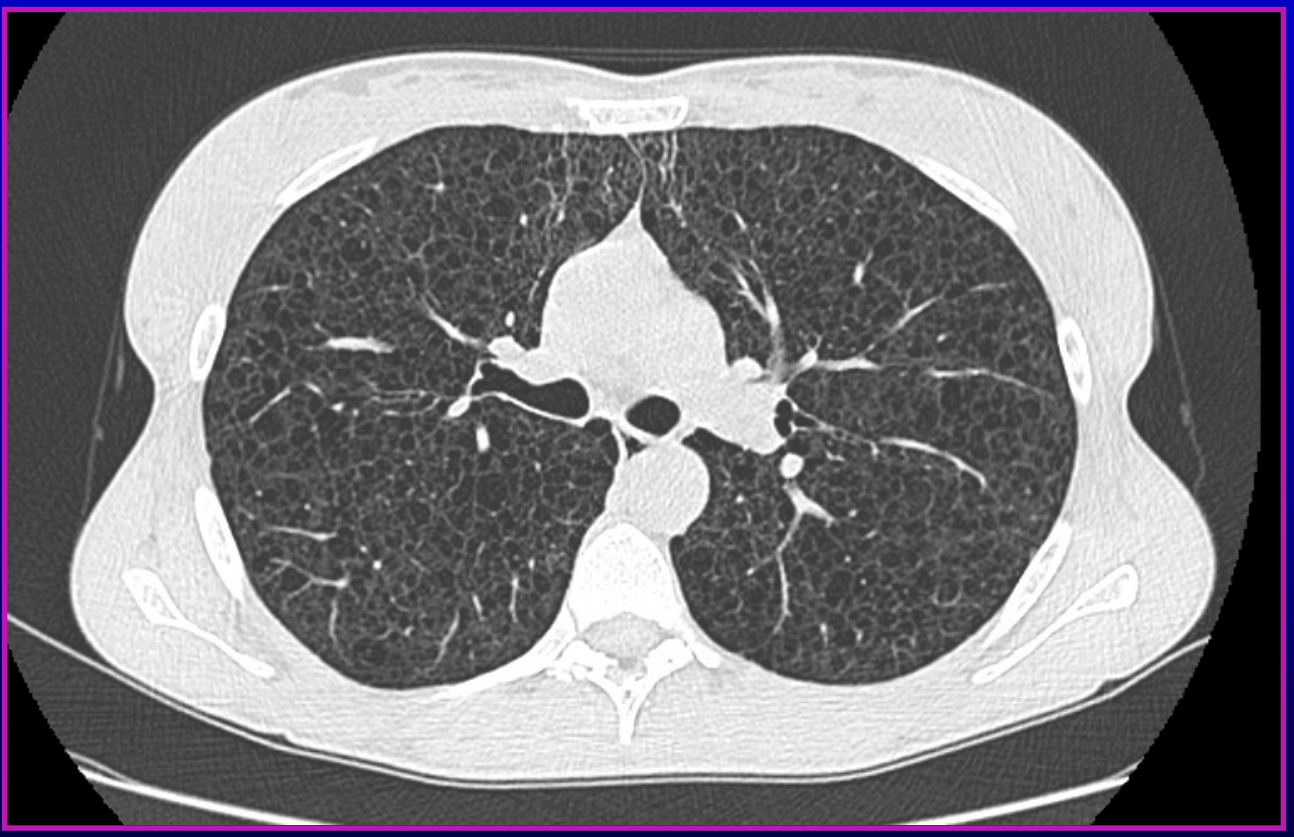




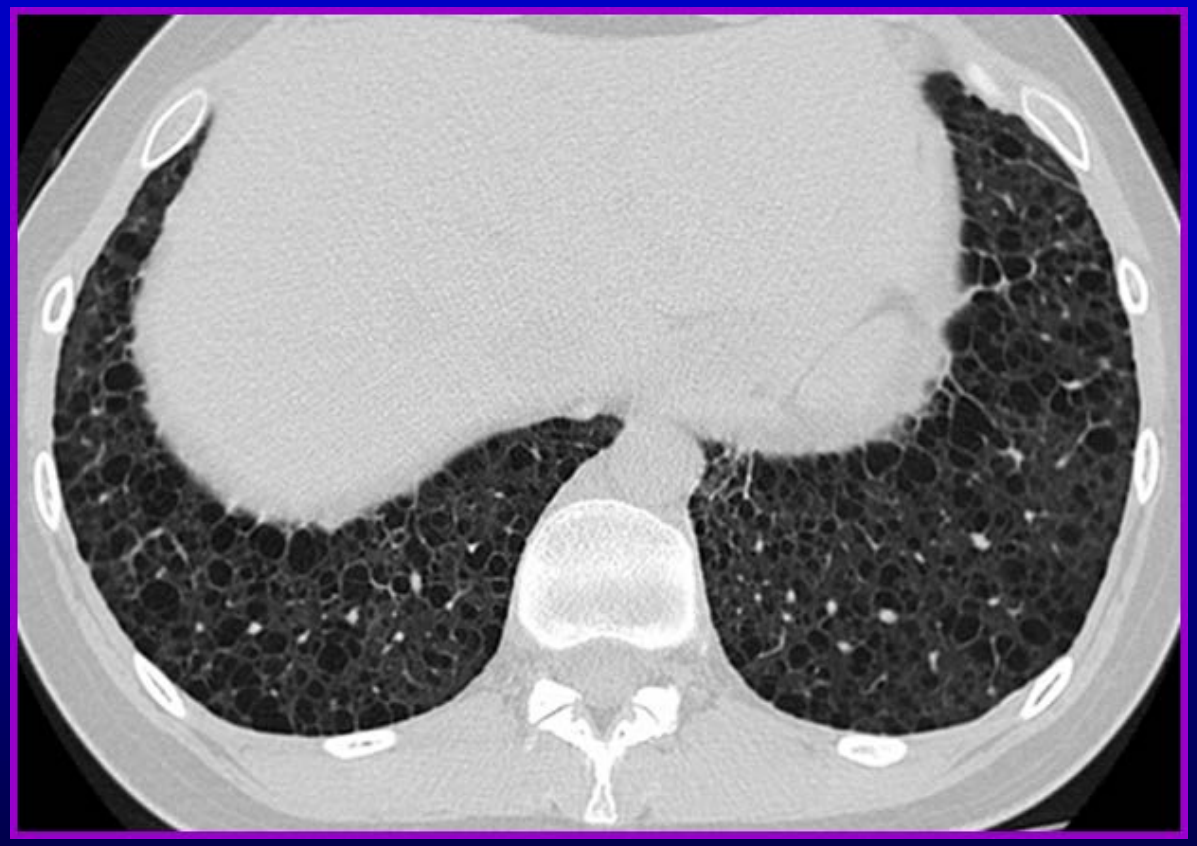
La diagnosi di LAM è DEFINITIVA

The essential tool: HRTC



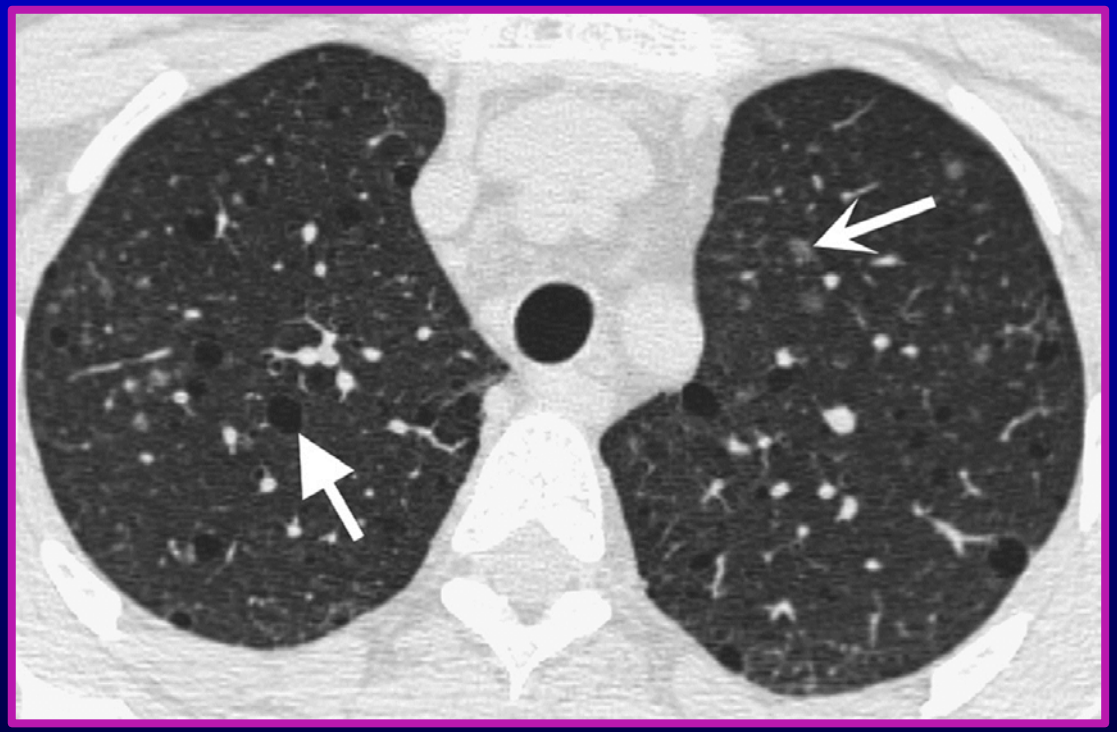
Characteristic HRCT findings are multiple (more than 10) thin-walled round well-defined air-filled cysts

The essential tool: HRTC



No sparing of lung bases…

The essential tool: HRTC



No other significant pulmonary involvement with the exception of possible features of multifocal micronodular pneumocyte hyperplasia (MMPH)

Lymphangioleiomyoma

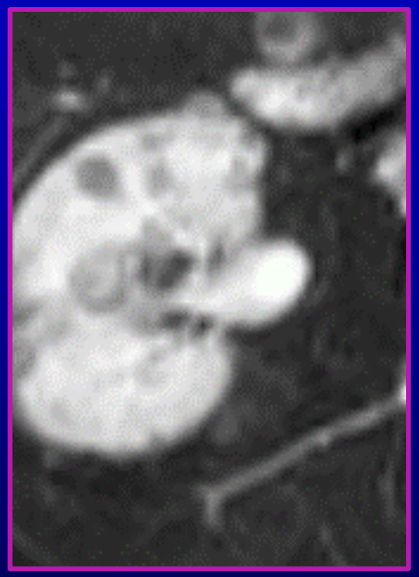
- Lymphangioleiomyomas are large cystic tumours primarily occuring in the abdomen, retroperitoneum and pelvis (less frequently in the mediastinum)
- They can been found in up to 10% of patients
- Associated symptoms are nausea, abdominal distension, peripheral oedema and urinary symptoms
- They can appear larger in the evening due to accumulation of chyle in the cystic structures
- They are PET negative or weakly positive

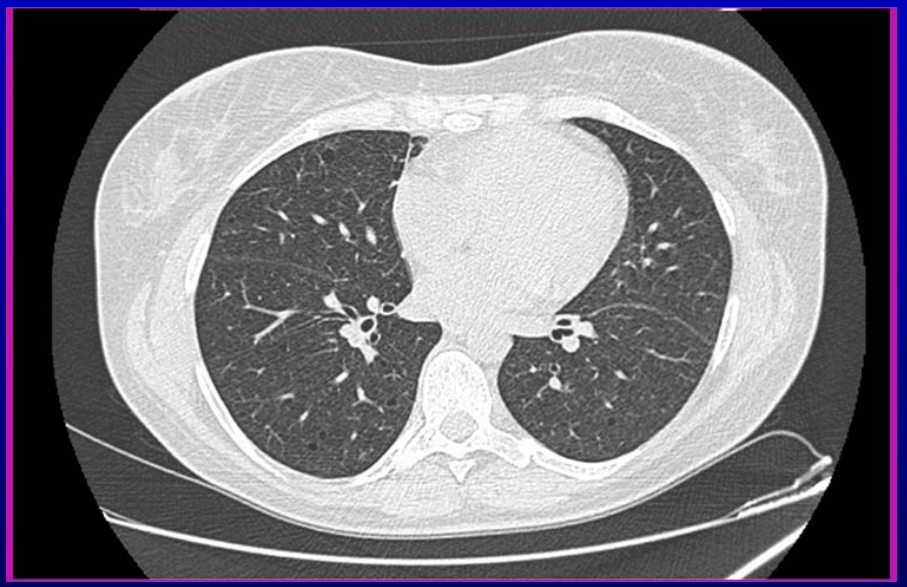
Harari S et al, ERJ 2015

Pz di 47 anni, non fumatrice

Recente riscontro di ipertensione arteriosa sistemica

Esegue ecografia addome con evidenza di lesione renale sospetta per angiomiolipoma





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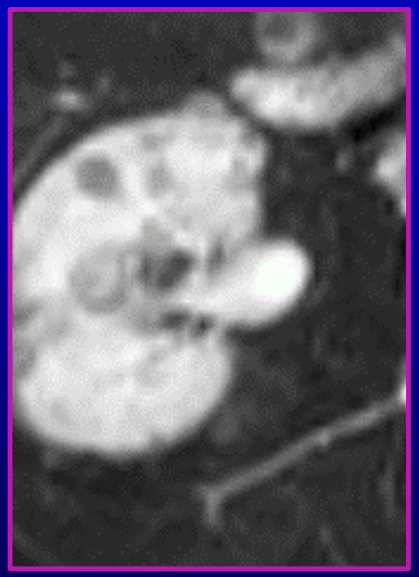
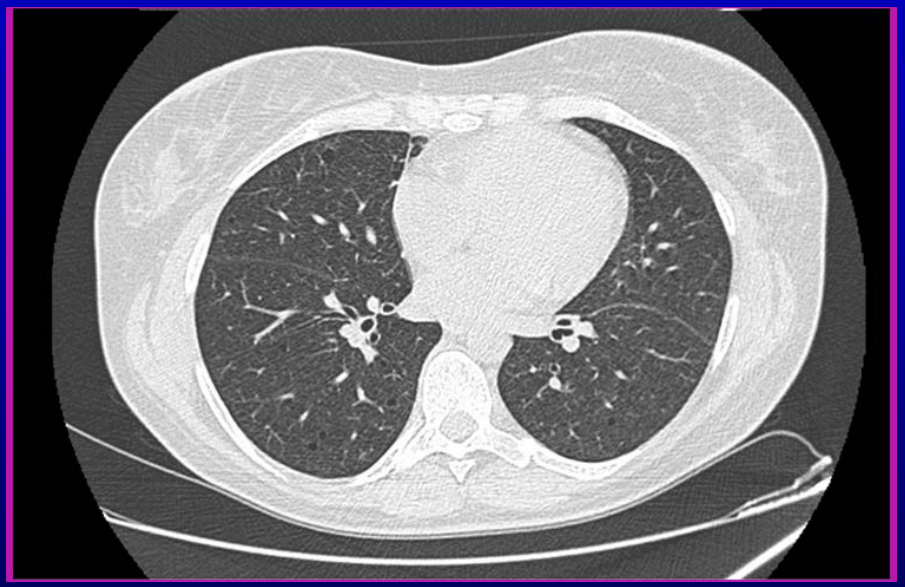
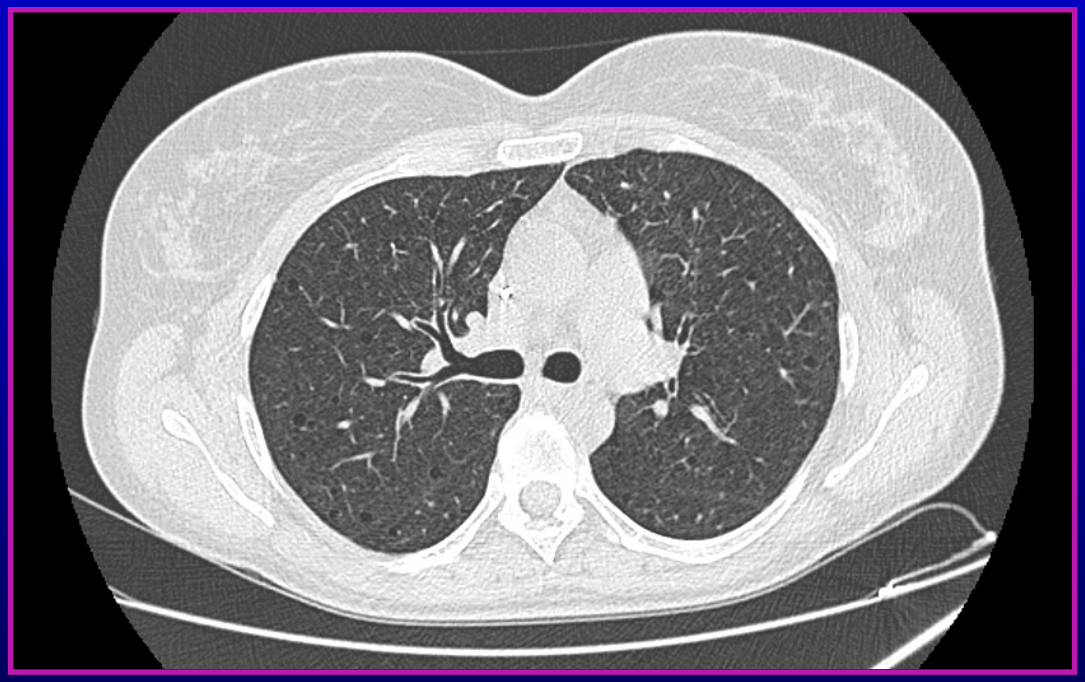




La diagnosi di LAM è PROBABILE

The essential tool: HRTC



Possible HRCT:
Less than 10 but more than two cysts

Angiomyolipomas

- Angiomyolipomas are benign tumours that occur mainly in the kidneys. They may vary in size from 1 mm to more than 20 cm in diameter
- Data from recent studies indicate that angiomyolipomas occur in up to 100% of patients with TSC-LAM and in up to 50% of those with sporadic LAM .
- Angiomyolipomas are often asymptomatic, but larger tumours can cause bleeding
- Patients with TSC commonly have multiple and large angiomyolipomas.

Harari S et al, ERJ 2015

Take home message 1

- In presenza di un quadro TC compatibile con LAM studiare sempre l'addome
- Se possibile RM o in alternativa TC con mdc
- Lesioni addomino-pelviche sono evidenziabili con l'imaging fino al 70% dei casi di LAM

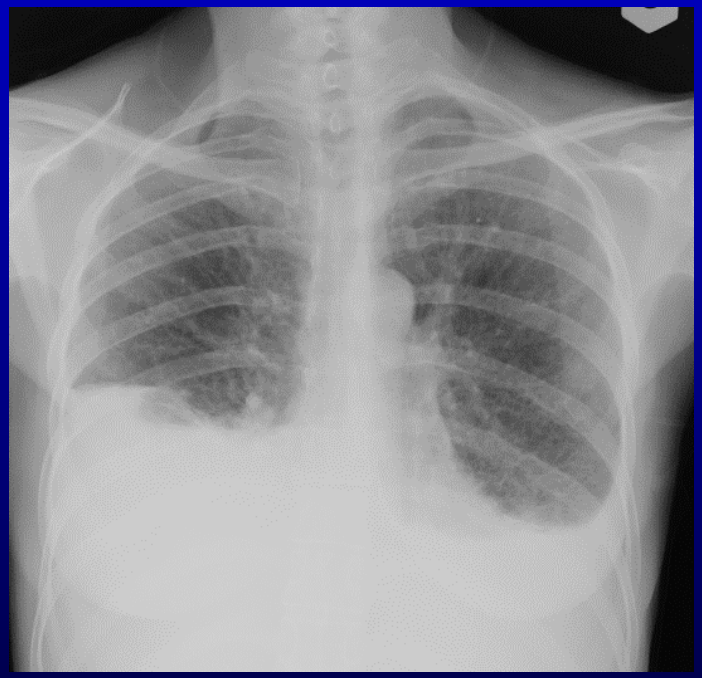
Take home message 2

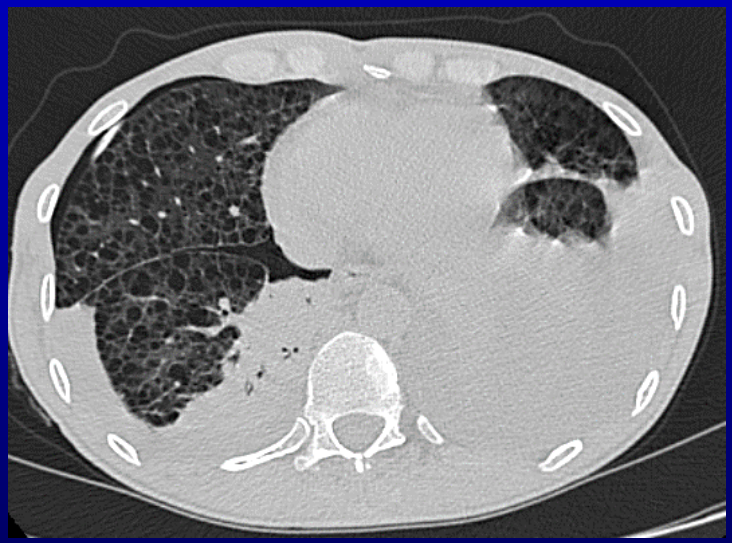
In caso di riscontro di lesione addomino-pelvica compatibile con linfangioleiomioma o di angiomiolipoma richiedere l'HRTC del torace al fine di escludere/confermare la possibilità di LAM

Pz di 35 anni, modica fumatrice

Appendicectomia, pregressa polmonite

Tosse secca e dispnea





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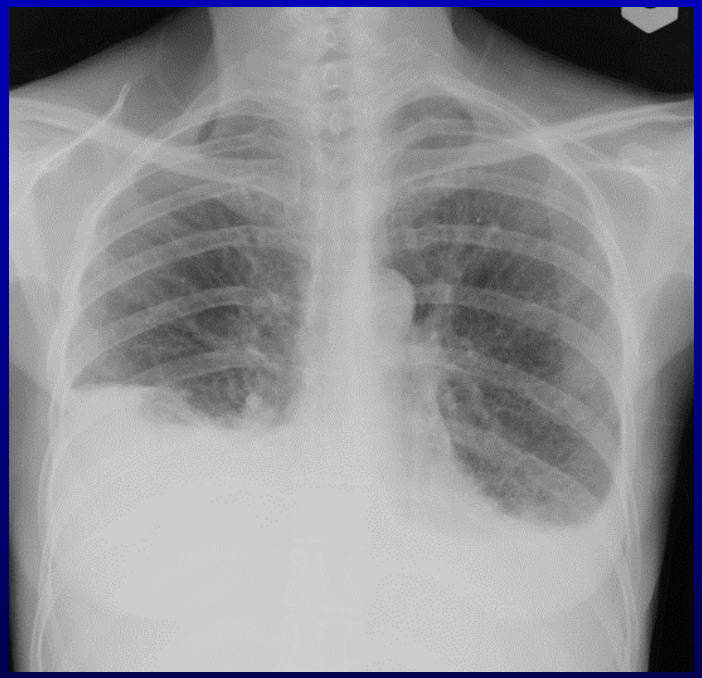
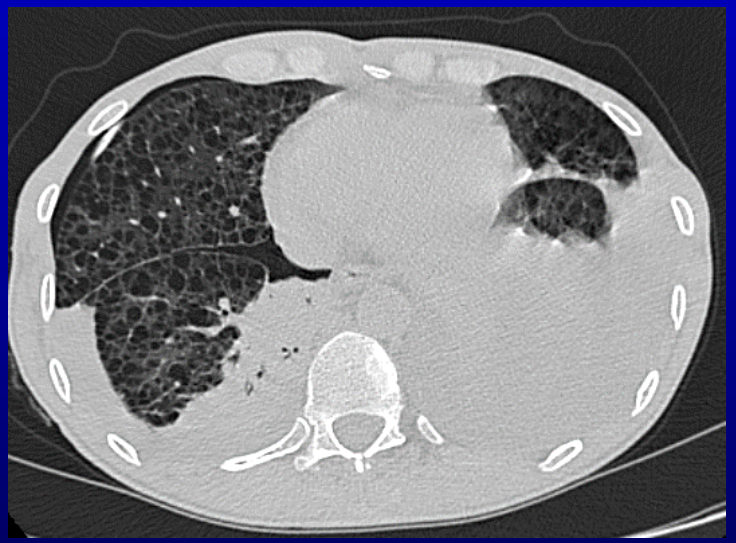




La diagnosi di LAM è DEFINITIVA

Take home message 3

- L’associazione di quadro TC caratteristico di LAM e angiomiolipoma, linfangioleiomioma o versamenti chilosi rende la diagnosi di LAM DEFINITIVA

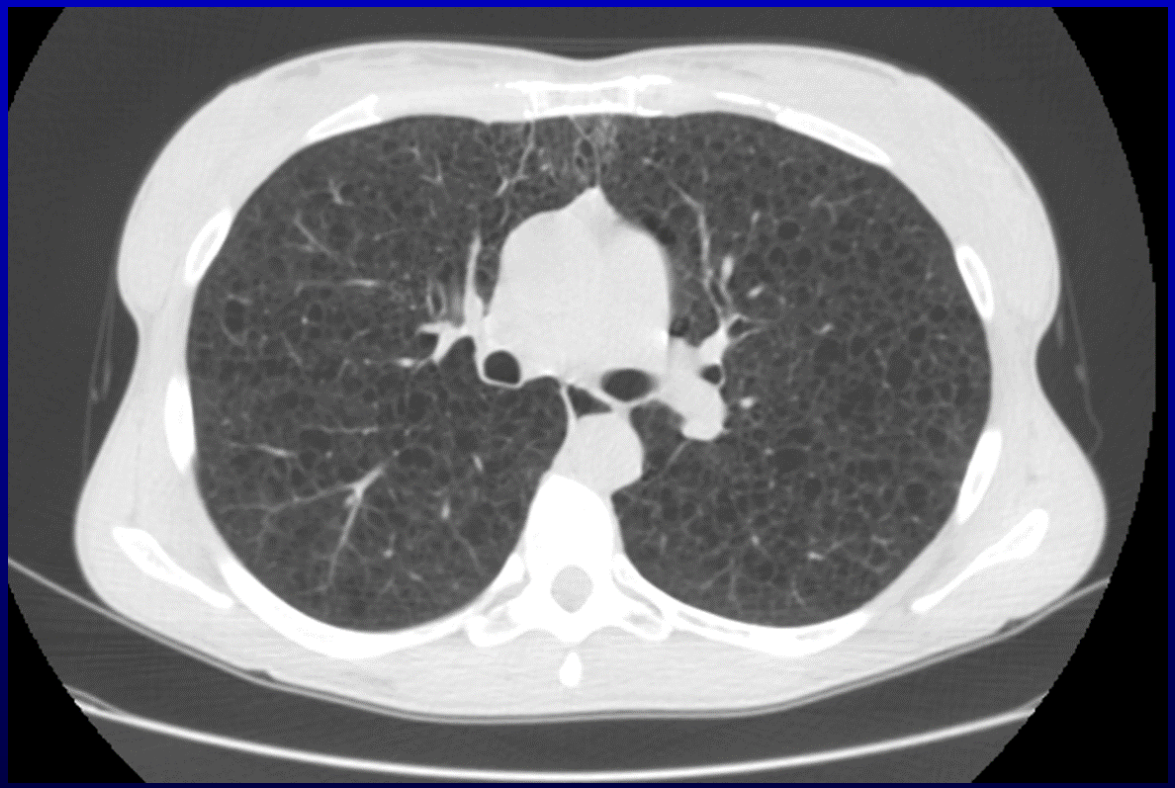
- L’associazione di quadro Tc compatibile con LAM e angiomiolipoma o versamenti chilosi rende la diagnosi di LAM PROBABILE

Johnson SR et al, ERJ 2010

Pz di 29 anni, non fumatrice

Affetta da Sclerosi Tuberosa

Lamenta dispnea da sforzo



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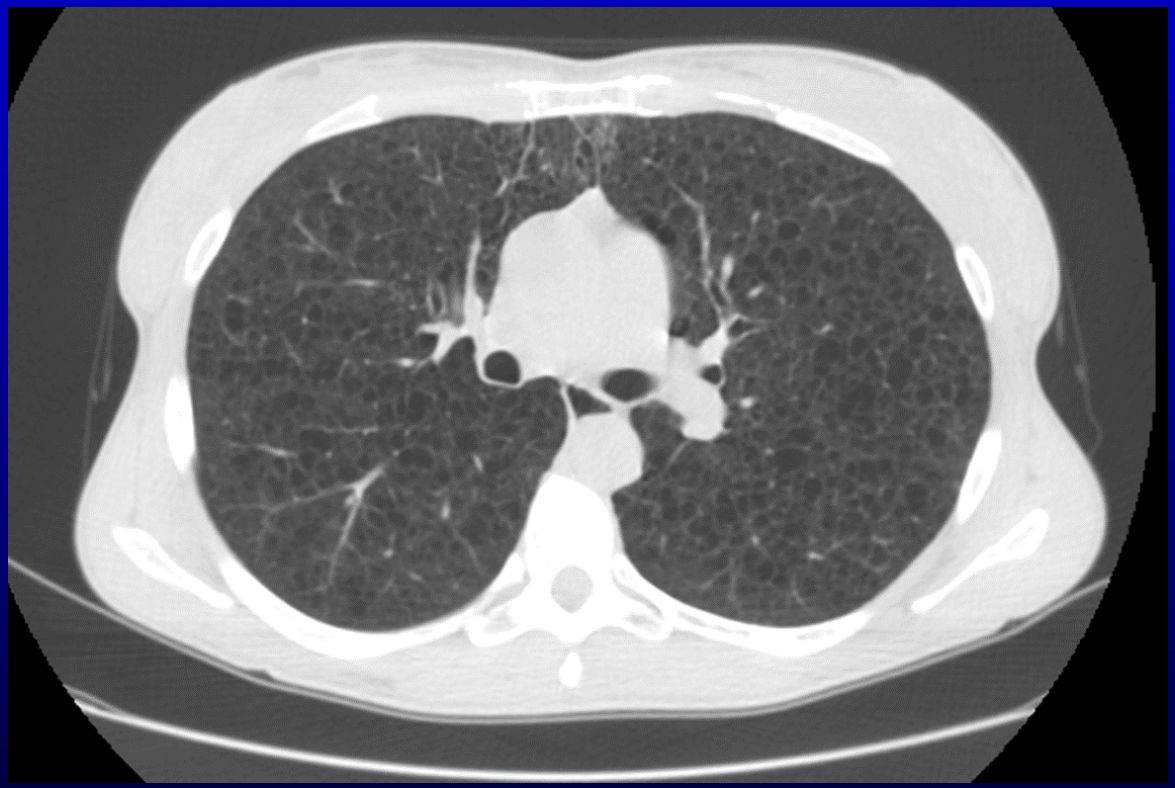
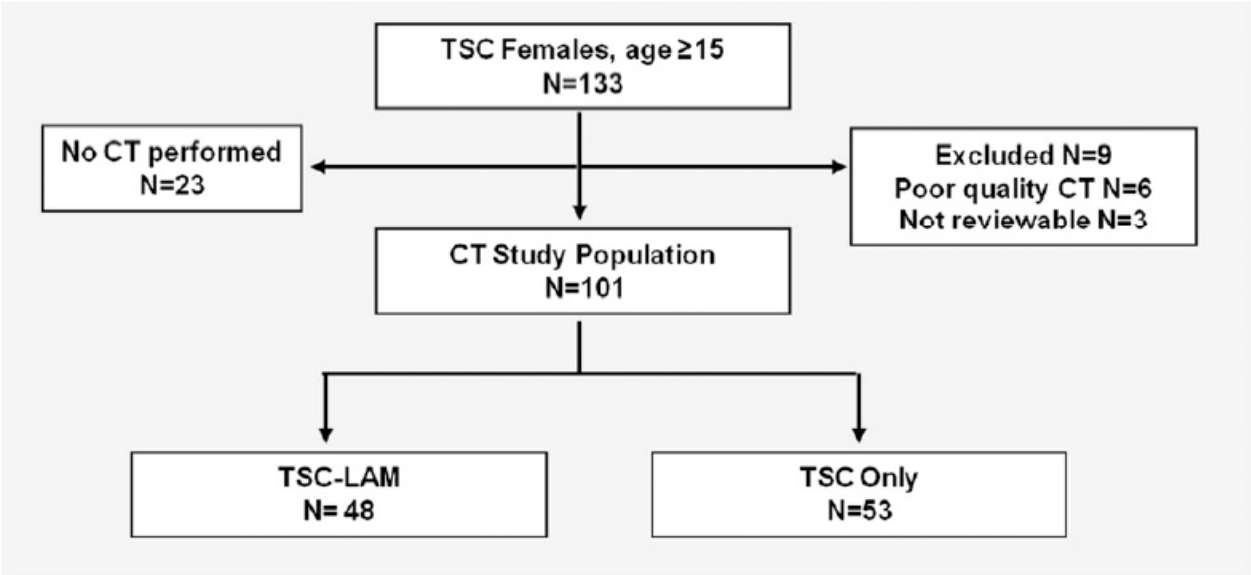
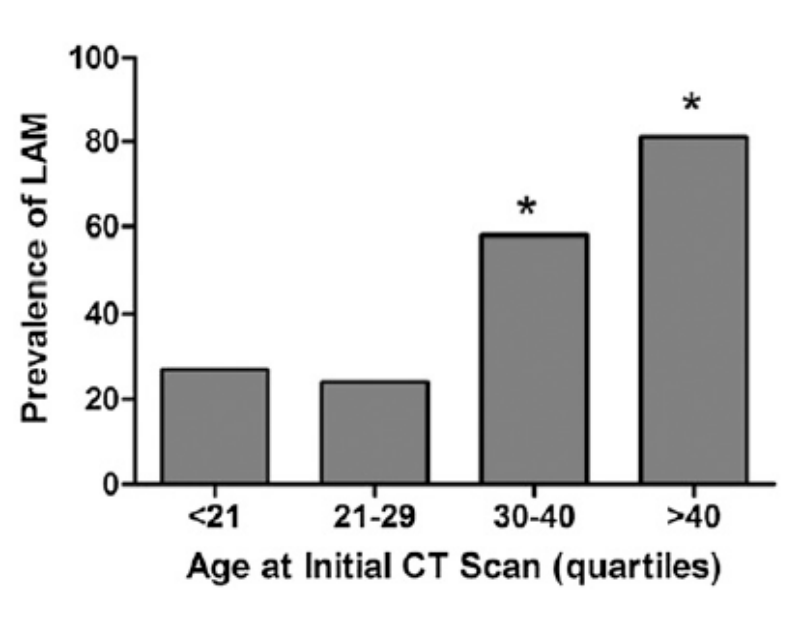


La diagnosi di LAM è DEFINITIVA

Prevalence of LAM in TSC





Cudzilo CJ et al, *Chest* 2013

Epidemiologia

LAM in maschi con ST

Table 2 Eleven men with TSC and cystic lung disease.

Age (yr)	Smoking	Renal AML	CT type	Indication for CT	Lung cysts, No.	Pulmonary function	Follow-up data
25	Never	NA	Chest	Cardiac mass	6	NA	NA
30	Never	Numerous, bilateral	Abdomen	AML	>10	NA	NA
30	Never	Numerous, bilateral	Chest	Dyspnea	>10	NA	NA
31	Current	Numerous, bilateral	Chest	Focal infiltrate	>10	Moderate obstruction, mildly reduced D_{LCO}	Mild progression 115 months later
33	Never	Numerous, bilateral	Chest	LAM?	9	NA	NA
41	Current	Numerous, bilateral	Abdomen	Pain, AML	>10	NA	NA
45	Current	Numerous, bilateral	Chest	LAM?	7	NA	NA
55	Never	NA	Chest	Interstitial infiltrates	>10	Moderate obstruction, mildly reduced D_{LCO}	No radiologic change 13 months later
70	Previous	No	Abdomen	Aortic aneurysm	10	NA	NA
73	Previous	NA	Chest	Chronic cough	>10	Moderate obstruction, normal D_{LCO}	NA
76	Previous	No	Chest	Chronic cough	9	Mild obstruction, mildly reduced D_{LCO}	NA

Ryu JH, Respiratory Medicine 2012

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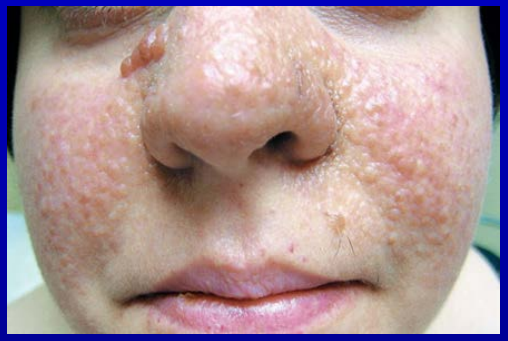
- Studio retrospettivo con piccolo n di pz
- Bias di selezione
- Non diagnosi istologica

La prevalenza di LAM nei maschi con ST e la sua rilevanza clinica restano da definire

Ryu JH, Respiratory Medicine 2012

Take home message 4

- La presenza di quadro TC caratteristico in pz con TSC rende la diagnosi di LAM DEFINITIVA



- La prevalenza della LAM nei pazienti con TSC probabilmente è maggiore rispetto a quello che si riteneva e aumenta con l'età

- Screening iniziale con HRTC a 18-21 anni

  Ulteriore screening a 30 anni

Diagnosis – ERS guidelines

Definite LAM	characteristic lung HRCT + any of the following - angiomyolipoma - thoracic or abdominal chylous effusion, - lymphangioleiomyoma - biopsy-proven lymph node involved by LAM, -TSC
Probable LAM	characteristic lung HRTC + compatible clinical history compatible lung HRTC + angiomyolipoma or chylous effusion
Possible LAM	characteristic or compatible lung HRTC alone

Characteristic HRCT: multiple (more than 10) thin-walled round well-defined air-filled cysts with no other significant pulmonary involvement (with the exception of MMPH in TSC)

Compatible HRTC: few (more than two and fewer than 10) typical cysts

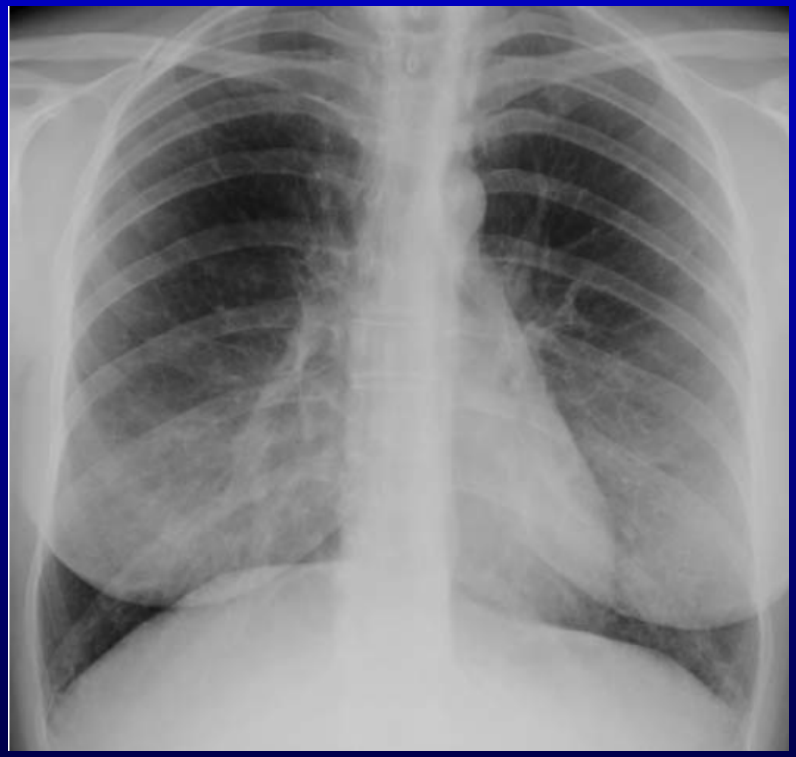
Johnson SR et al, ERJ 2010

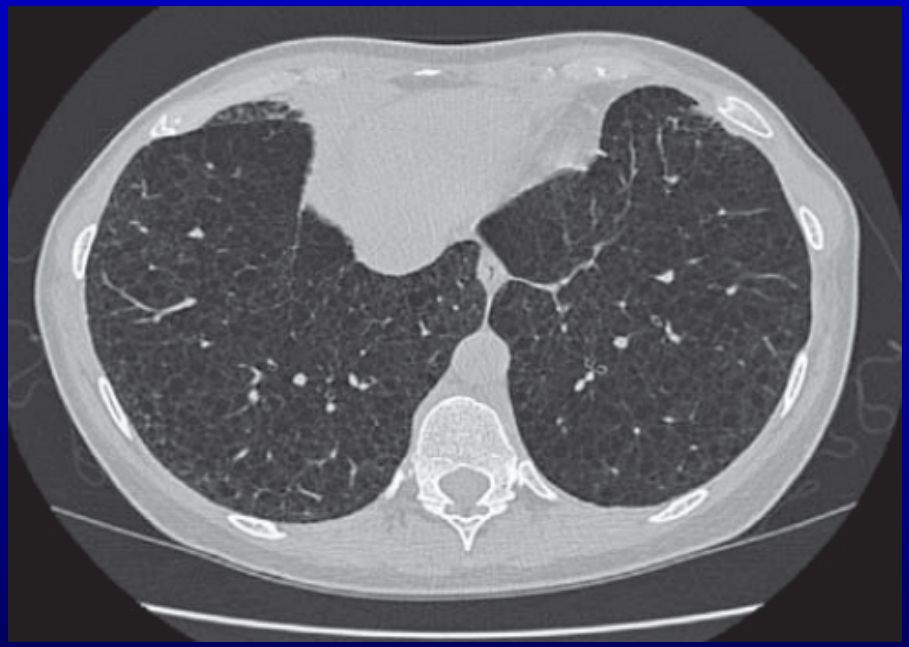
Pz di 39 anni, non fumatrice

Nulla di rilevante in APR

Lamenta dispnea da sforzo da 7-8 mesi

PFR: deficit ostruttivo moderato reversibile





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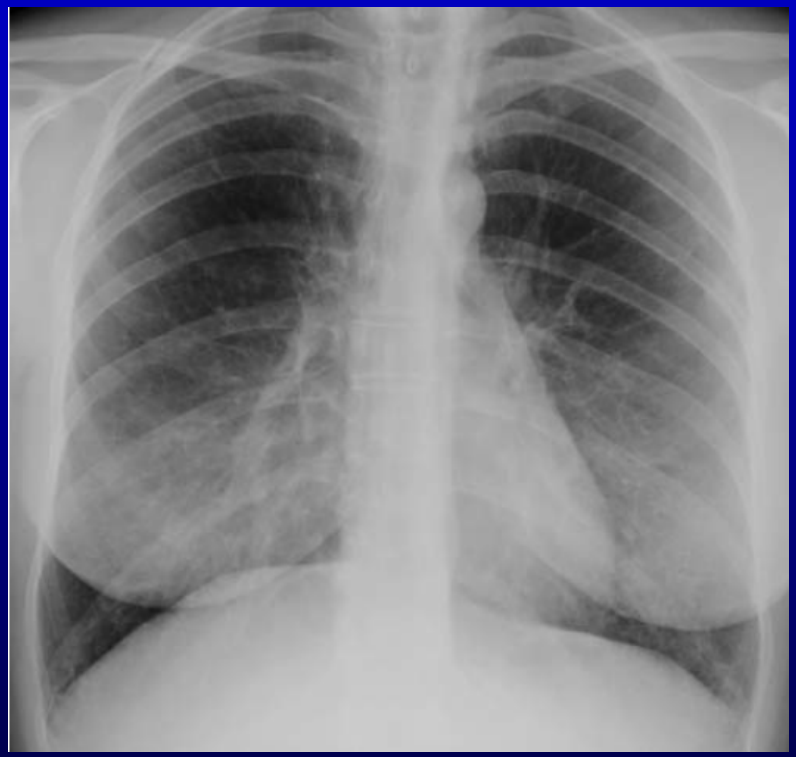

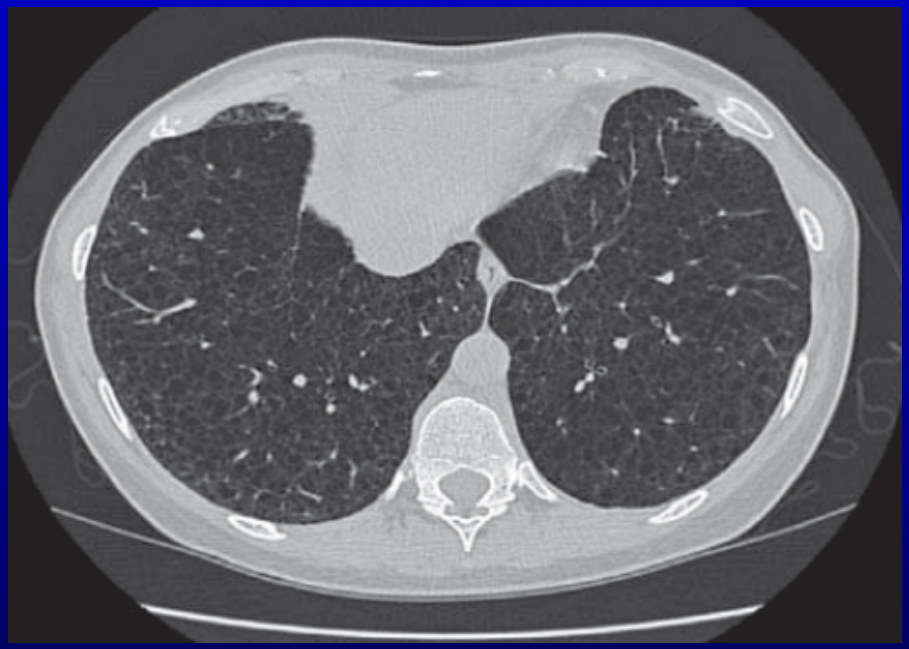

RMN addome nella norma

VEGFD sierico: 1550 pg/mL

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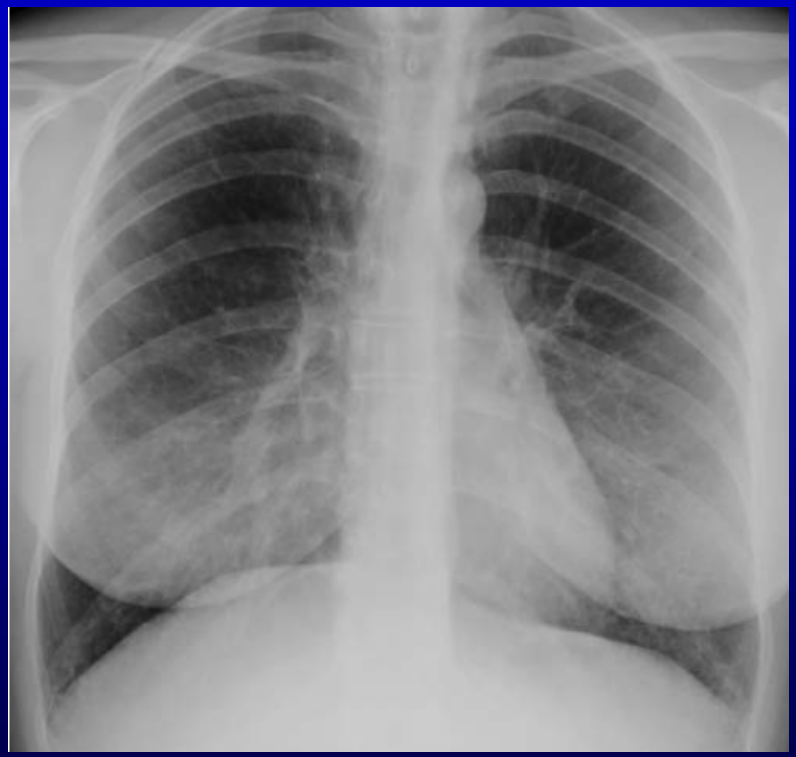

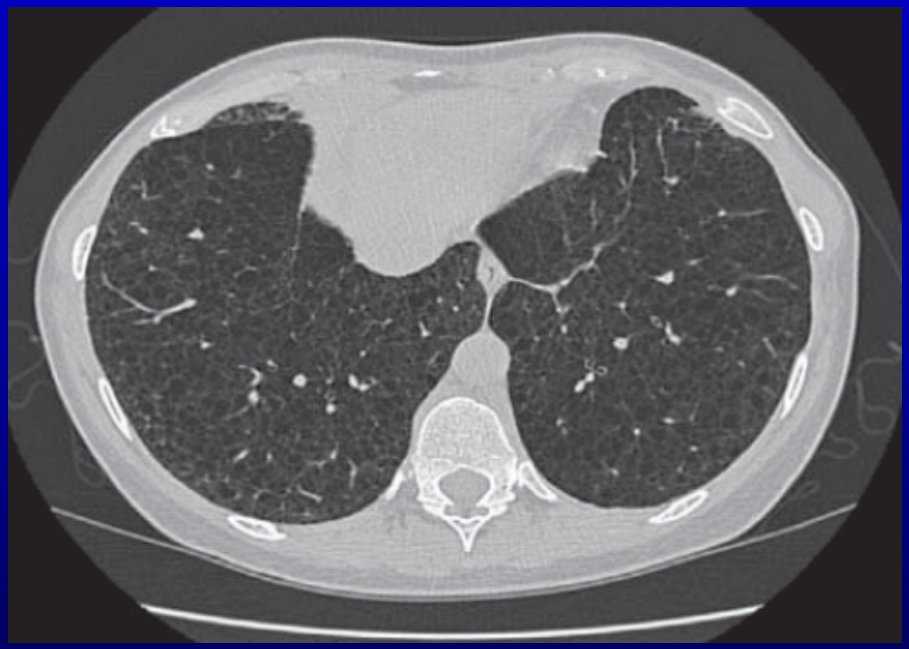

RMN addome nella norma

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La diagnosi di LAM è DEFINITIVA

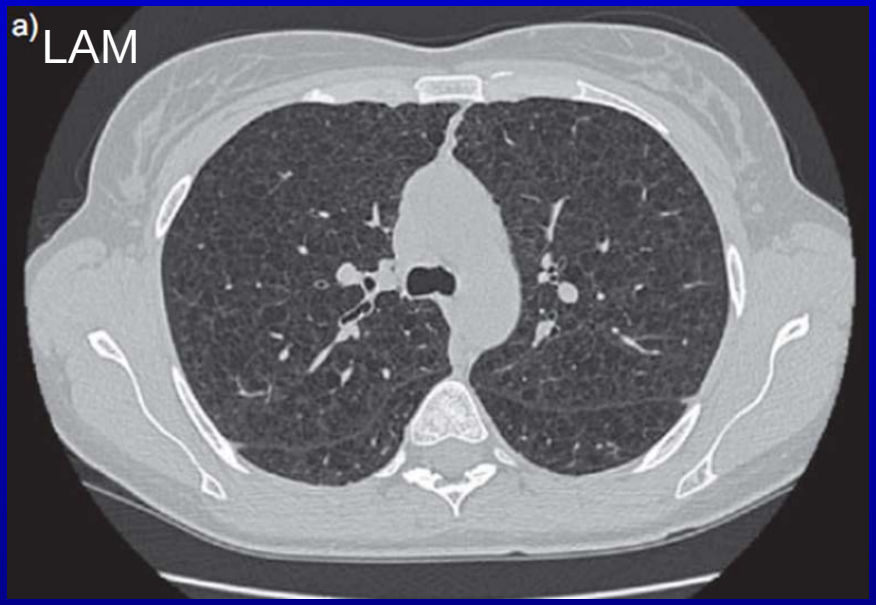
Take home message 5

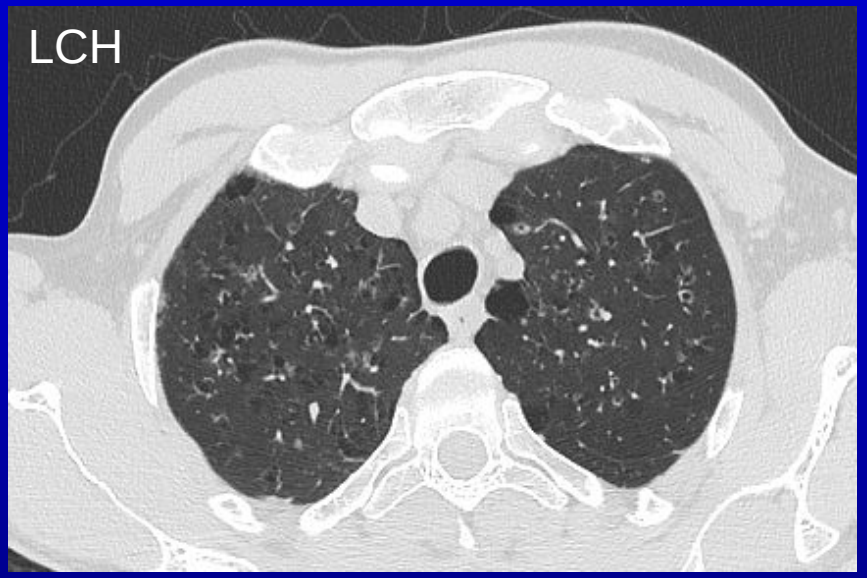
- Vascular endothelial growth factor-D (VEGF-D) is a lymphangiogenic growth factor that induces formation of lymphatics and promotes the spread of tumour cells to lymph nodes.

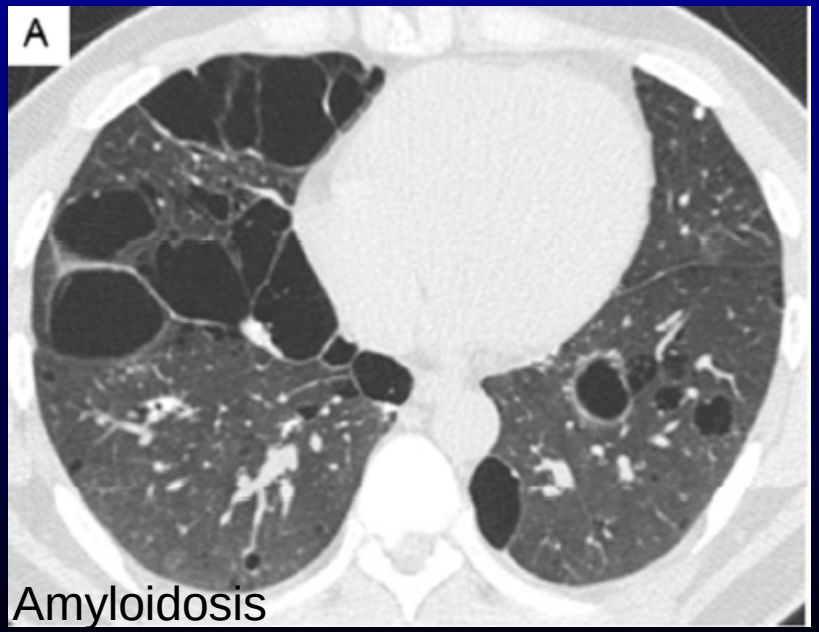
- A serum VEGF-D level higher than 800 pg/mL in a woman with typical changes on high-resolution CT is diagnostically specific for LAM, reducing the need for lung biopsy

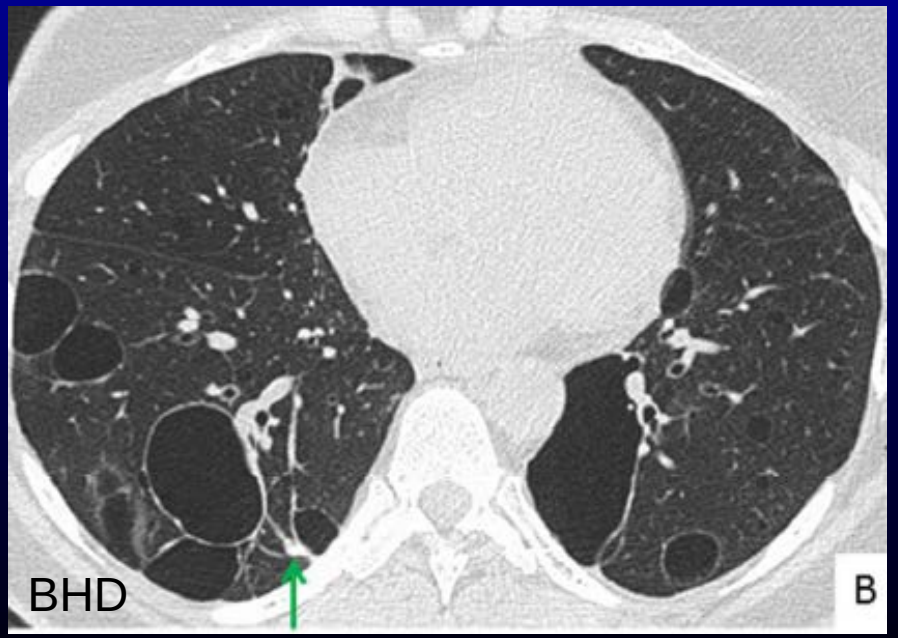
Young LR et al, Chest 2010

The essential tool: HRTC









	LAM	PLCH	BHD	LIP/FB	Amyloid/LCDD
Distribution	Diffuse, random	Upper & middle lung zones; sparing costophrenic angles	Basilar/peripheral/ subpleural and near vessels	Diffuse, random, often near vessels	Diffuse, random
Size	2 mm – 2 cm	Variable, 2mm - >2cm	75% <1cm	Average size 3mm – 1cm	4 – 45 mm, majority larger than 1cm
Shape	Round-uniform	Bizarre, irregular	Elliptical, lentiform	Round - variable	Round - variable
Pathological examination diagnostic	Yes	Yes	No	Yes	Yes
Pathologic findings	Infiltration by HMB-45 positive LAM cells with smooth muscle phenotype	S100, CD1a positive Langerhans cells with intracellular Birbeck granules by electron microscopy; stellate fibrotic scars in late stages	Intraparenchymal and subpleural cysts abutting interlobular septae and lacking abnormal cell proliferations or significant fibroinflammatory component	LIP: Diffuse interstitial polyclonal lymphocytic infiltrate FB: Peribronchiolar polyclonal follicular lymphoid hyperplasia with germinal centers	Amyloid: Amorphous protein deposits with fibrillar ultrastructure and apple-green birefringence by Congo red stain viewed under polarized light. LCDD: Typically monotypic kappa light chain deposition with finely granular ultrastructure lacking apple-green birefringence by Congo red stain and polarized light.
Other associated findings on HRCT	Pleural effusions	Micro and macro nodules with or without cavitation, thick walled cysts, cavities and reticulation	Cysts frequently abut pleura and proximal vessels	Ground glass attenuation, poorly defined centrilobular nodules, interlobular septal thickening, cysts may contain internal structure	Multiple nodules of varying attenuation and random distribution; nodules abut cyst walls

Gupta N et al, AJRCCM 2015

Linfangioleiomiomatosi non è Linfagiomatosi

- Lymphangiomatosis or Generalized Lymphatic Anomaly (GLA), is a rare disease caused by congenital abnormalities of lymphatic development
- It usually presents in childhood, but can also be diagnosed in adults
- It is characterized by the presence of lymphangiomas in different organs

Linfangioleiomiomatosi non è Linfagiomatosi

- Within the thorax, single or multiple lymphangiomas may be discovered in the mediastinum, pleura, heart, lung and chest wall.
- Proliferation of lymphangiomas only within the lung lead to the rare syndrome of diffuse pulmonary lymphangiomatosis (DPL)
- Usually no lung cysts are evident

Luisi F et al, ERR 2016

Take home messages

- Di fronte a un quadro TC caratteristico o compatibile con LAM studiare sempre l'addome (RM o TC)
- In caso di riscontro di lesione addomino-pelvica compatibile con linfangioleiomioma o angiomiolipoma richiedere l'HRTC del torace
- L'associazione di quadro TC caratteristico di LAM e TSC, angiomiolipoma, linfangioleiomioma, versamenti chilosi rende la diagnosi di LAM DEFINITIVA
- Il VEGFD sierico > 800 pg/mL in presenza di TC caratteristica è diagnostico per LAM

Centro LAM e TSC dell'adulto

Ospedale San Giuseppe

Team multidisciplinare

- Pneumologia
  - Dott.Harari Sergio
  - Dott.ssa Torre Olga
  - Dott. Cassandro Roberto
- Nefrologia
  - Dott. Bertoli Silvio Volmer
  - Dott.ssa Villa Margarita Nora
- Neurologia
  - Dott. Bassi Pietro
  - Dott.ssa Vanotti Alessandra
- Medicina Interna
  - Dott.ssa Lonati Chiara
- Cardiologia
  - Dott. Lombardo Michele
  - Dott. Sonaglioni Andrea
- Ginecologia
  - Prof. Stefano Bianchi
  - Dott.ssa Margherita Bradascio
- Radiologia
  - Dott. Fabio Motta
  - Dott.ssa Elisabetta Uslenghi
  - Dott.ssa Roberta Trevisan
- Dermatologia
  - Dott.ssa Rossini Patrizia

Centro LAM e TSC dell'adulto

Ospedale San Giuseppe

Collaborazioni

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  Prof. Abrignani Sergio
  Prof. Pagani Matteo
  Dott.ssa Bulgheroni Elisabetta

- Genetica, Istituto Auxologico
  Dott.ssa Diblasio Anna

- NIH
  Prof. Moss Joel

Grazie