LYMPHOPROLIFERATIVE LUNG DISORDERS. DIAGNOSIS,DIFFERENTIAL DIAGNOSIS AND TREATMENT

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Lymphoproliferative lung disorders: clinicopathological aspects

ERR 2013

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TABLE 1 Classification system for the pulmonary lymphoproliferative disorders

Spectrum of pulmonary lymphoproliferative disorders
Reactive pulmonary lymphoid diseases
Follicular bronchiolitis
Nodular lymphoid hyperplasia (pulmonary pseudo-lymphoma)
Lymphocytic interstitial pneumonia
Castleman's disease
Localised (hyaline-vascular, plasma cell type)
Multicentric
Primary pulmonary lymphoma
B-cell primary pulmonary non-Hodgkin lymphoma (MALT lymphoma)
Primary pulmonary diffuse large B-cell lymphoma
Lymphomatoid granulomatosis
Follicular lymphoma
Mantle cell lymphoma
Extra-osseous plasmacytoma
Intravascular large B-cell lymphoma
Large B-cell lymphoma
Plasmoblastic lymphoma
T-/NK-lymphoma
Anaplastic large cell lymphoma
Hodgkin lymphoma
Post-transplantation lymphoproliferative disorders

MALT: mucosa-associated lymphoid tissue; NK: natural killer cell.

Castleman Disease

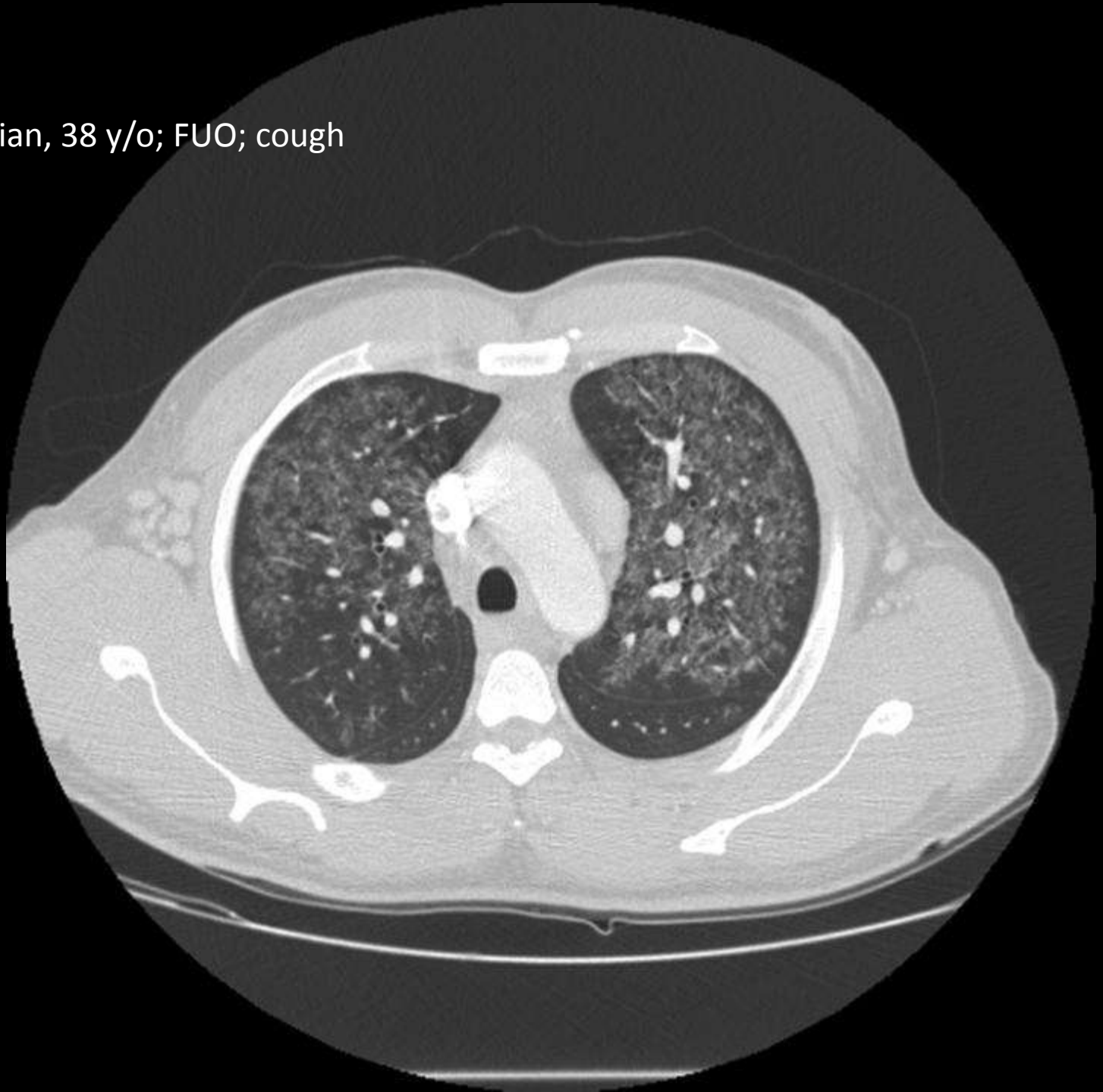
Castleman's disease is classified, according to the clinical profile, as **localised or multicentric**

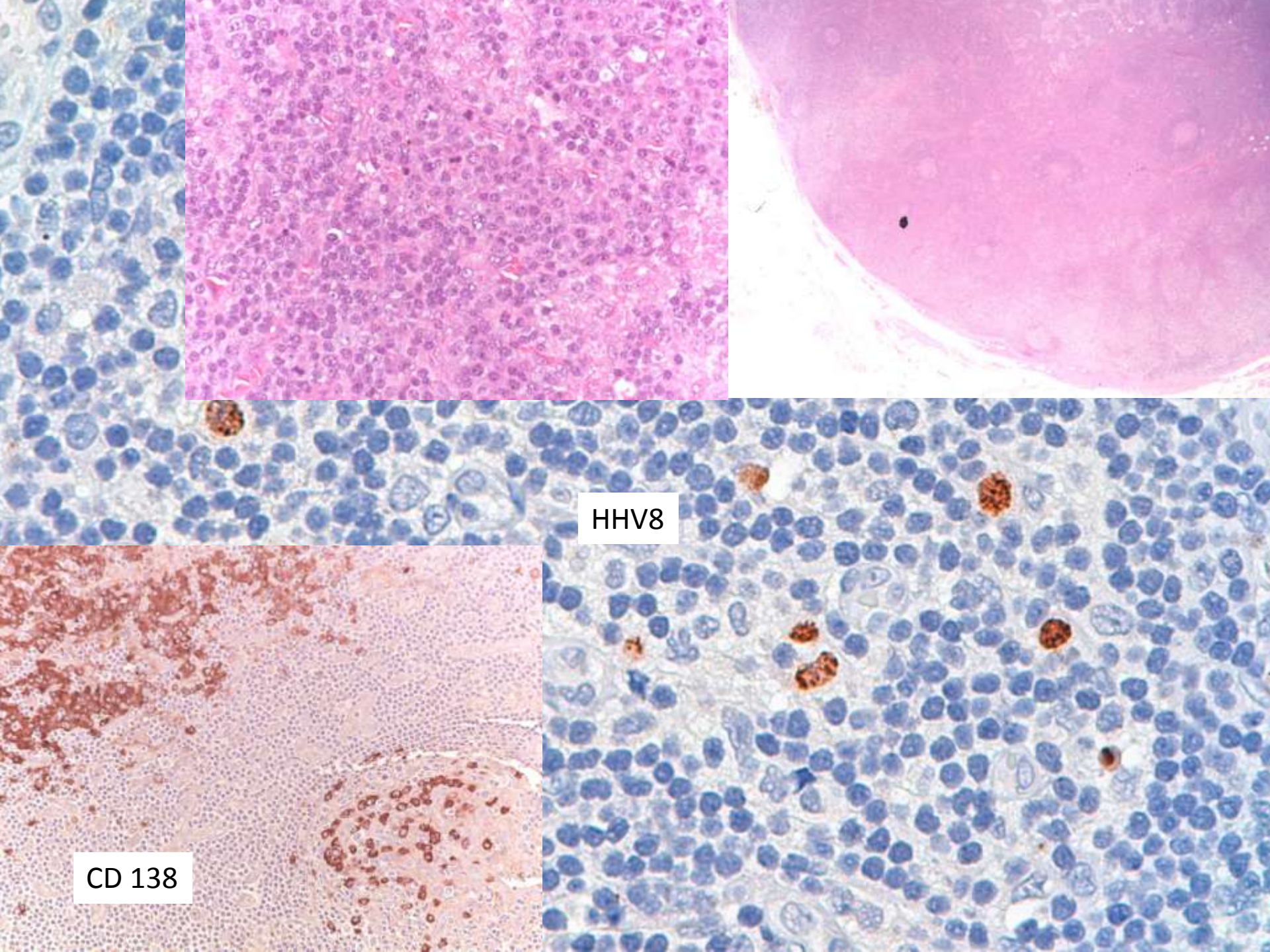
The histopathogenetic classification distinguishes a hyaline vascular type and a plasma cell type, with a mixed type of Castleman's disease characterised by the occurrence in the same patient of hyaline vascular and plasma cell features.

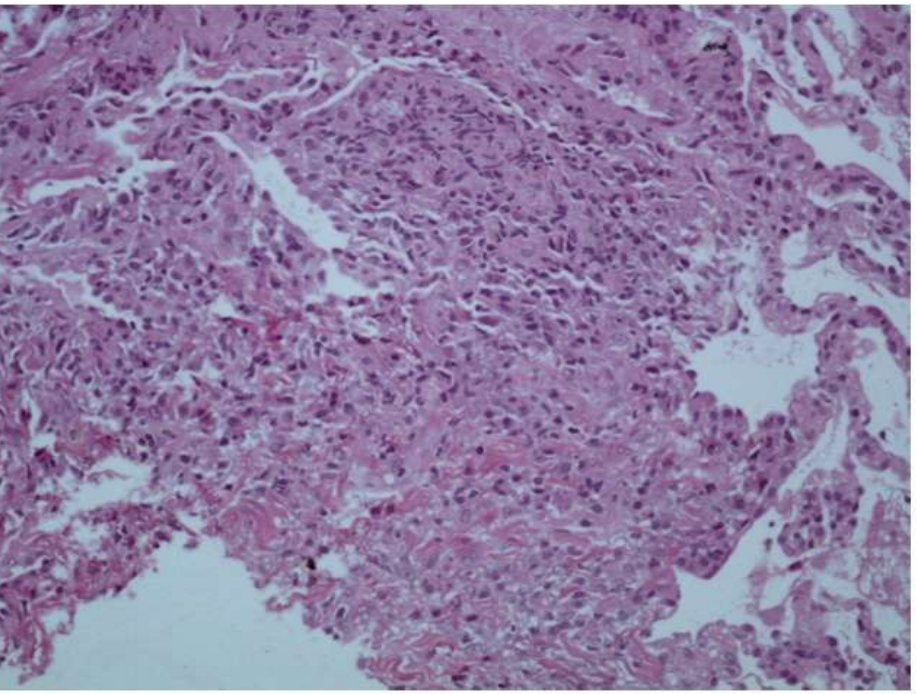
The **hyaline vascular** type shows numerous follicles with a concentric layering of small B-cells around an onion-skin appearance, depleted, abnormal germinal centres with penetrating hyalinised capillaries in a ''lollipop'' appearance, and large dysplastic cells with vesicular nuclei consistent with follicular dendritic cells. In fact, Castleman's disease has been recognised as a neoplasm of follicular dendritic cells as clonal cytogenetic abnormalities have been reported

The **plasma cell type** is characterised by diffuse polyclonal or monoclonal (more frequently IgM) plasma cell proliferation, often in sheets, in the inter-follicular stroma. Castleman's disease may be associated with HIV and **human herpes virus (HHV)-8 infection**, or Kaposi's sarcoma herpes virus and Epstein–Barr virus (EBV) infections.

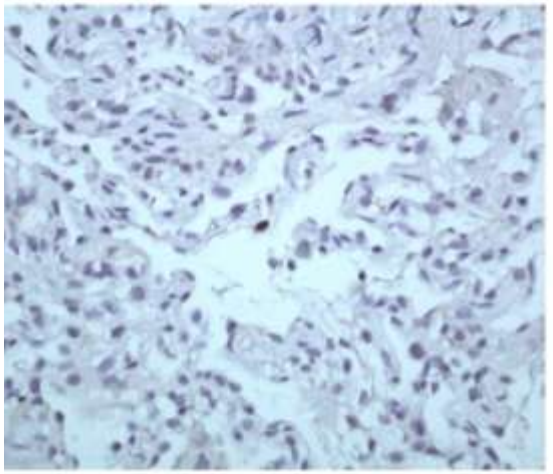
Nigerian, 38 y/o; FUO; cough




HHV8
CD 138



HHV8



Most of the patients with LIP have autoimmune diseases or immunodeficiency, most commonly

- Sjögren syndrome
- human immunodeficiency virus infection
- autoimmune thyroid disease

Table 1—*Diseases Associated With LIP*

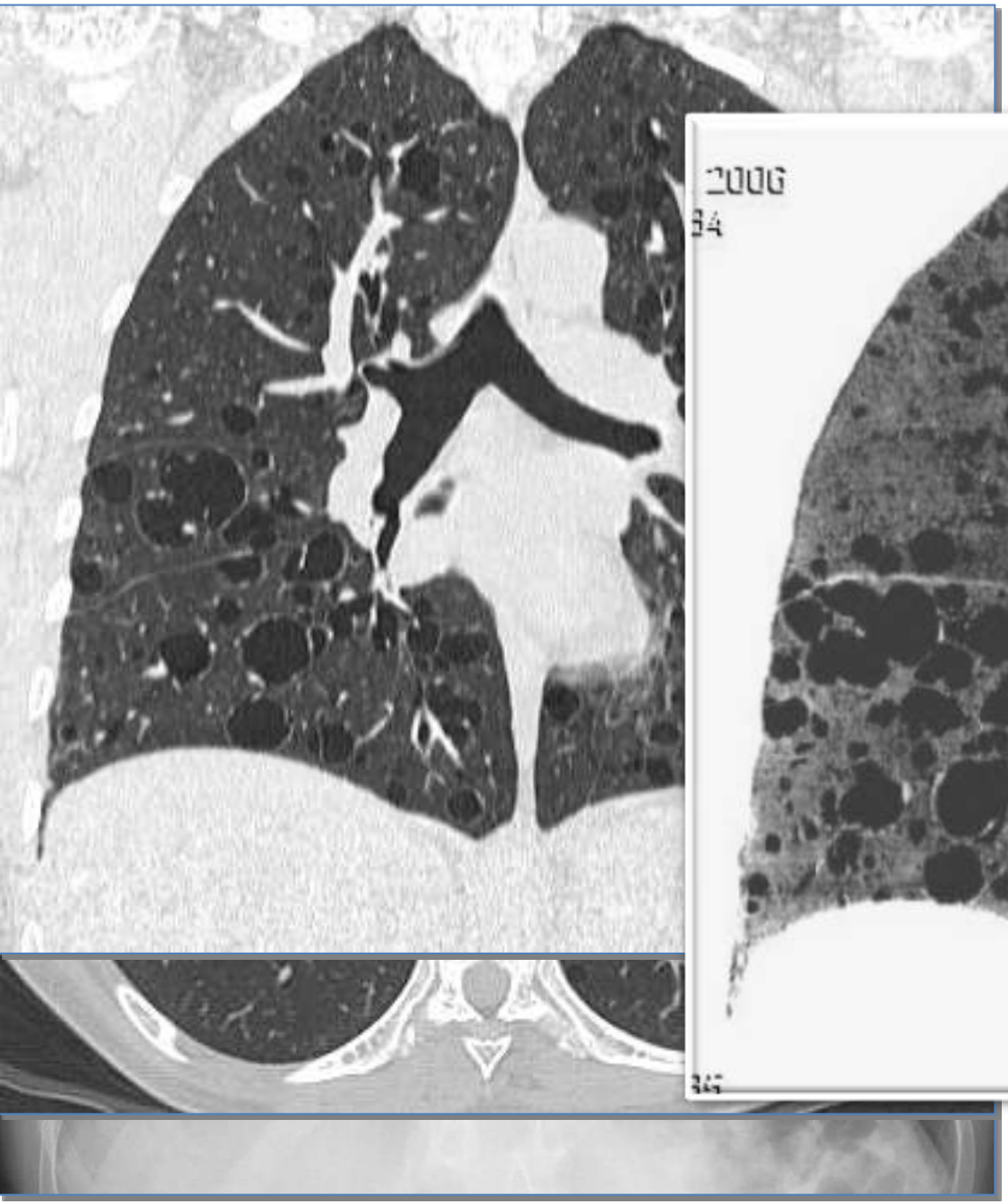
Diseases
Autoimmune (39%)*
Sjögren syndrome[45]
Systemic lupus erythematosus[55–57]
Rheumatoid arthritis[24]
Juvenile rheumatoid arthritis[58]
Hashimoto thyroiditis[24,26]
Myasthenia gravis[59]
Hemolytic anemia[26]
Pernicious anemia[60]
Autoerythrocyte sensitization syndrome[61]
Chronic active hepatitis[63]
Celiac sprue[64]
Primary biliary cirrhosis[62]
Systemic immunodeficiency states (14%)†
HIV/AIDS[103] with and without DILS
Common variable immunodeficiency†[46,47]
Agammaglobulinemia†[60]
Miscellaneous
Complication of allogeneic bone marrow transplantation[48,49]
Pulmonary alveolar microlithiasis[50]
Infections including Legionella pneumonia,[51] tuberculosis, Mycoplasma, Chlamydia
Diphenylhydantoin use[52]
Pulmonary alveolar proteinosis[53]
Idiopathic

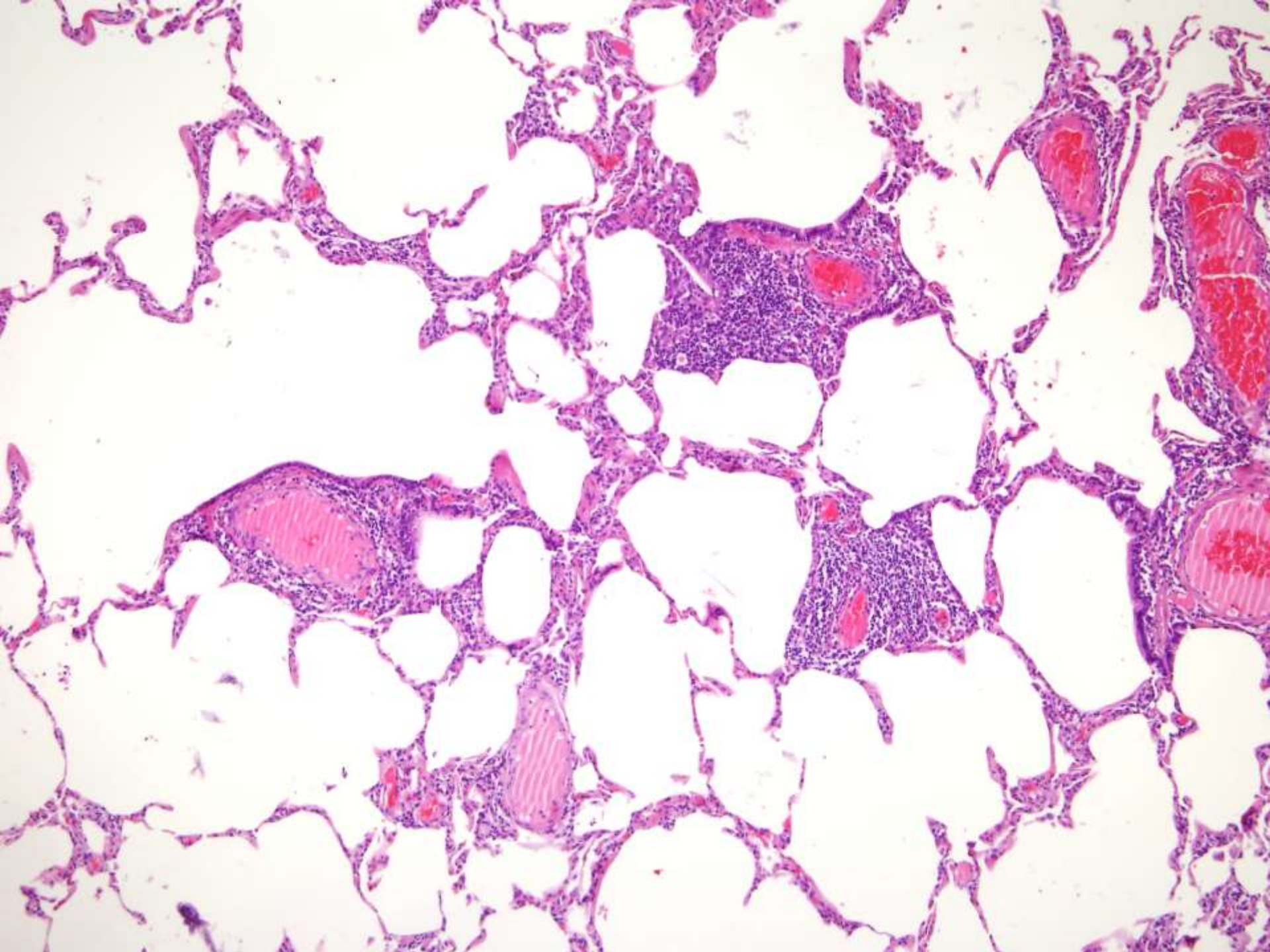
JOURNAL OF THORACIC IMAGING

2006

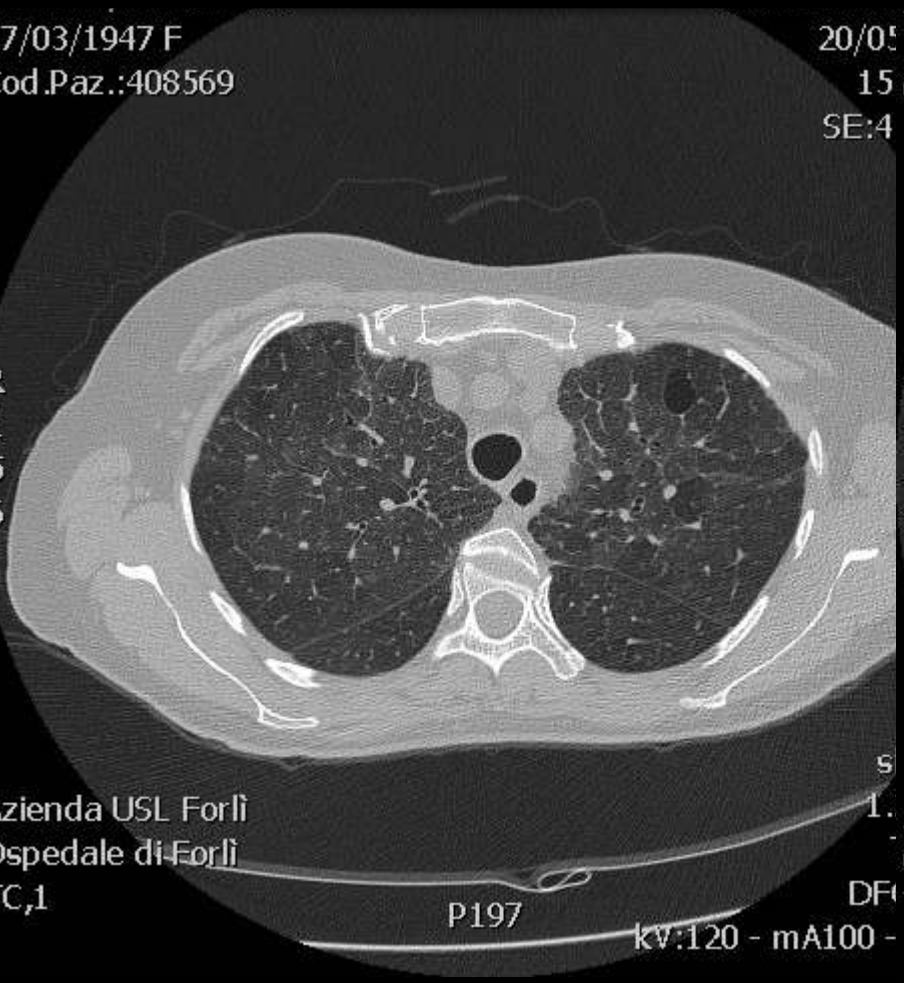
CHEST The Cardiopulmonary and Critical Care Journal

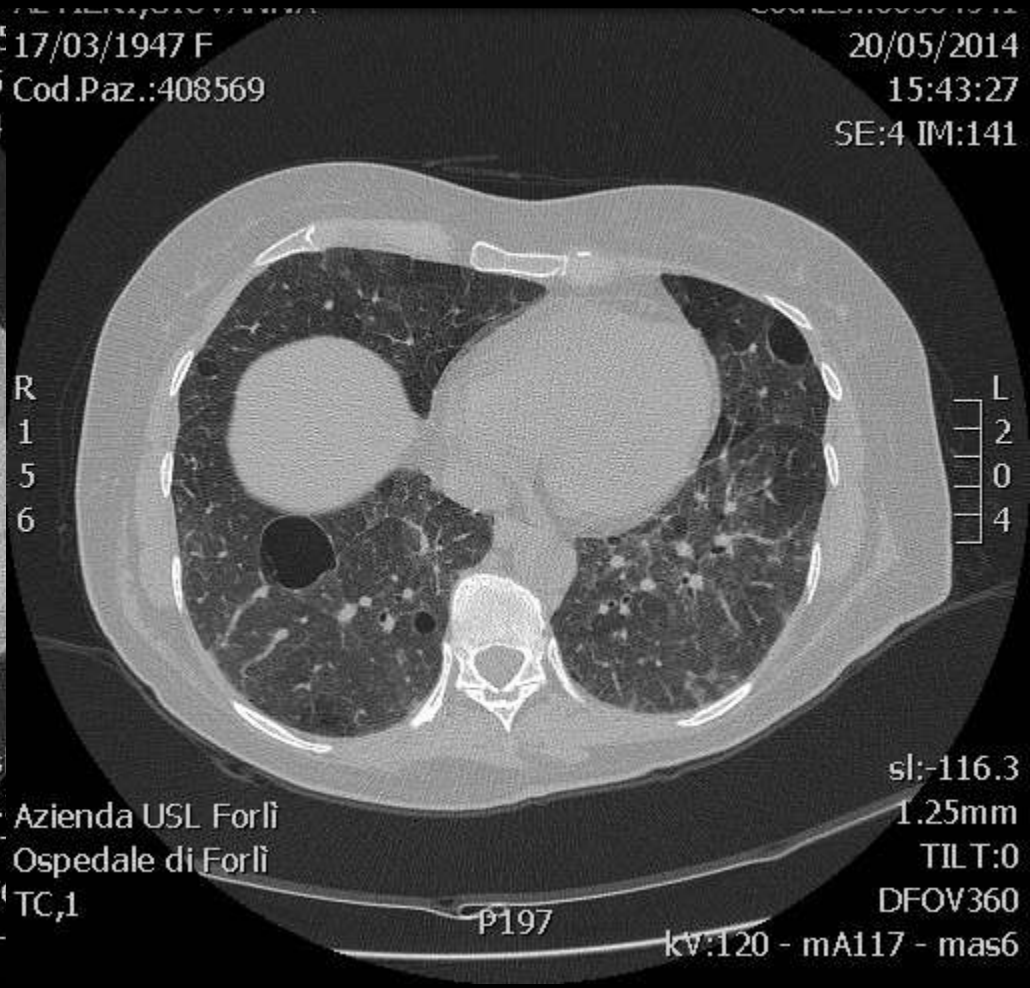
Lymphoid Interstitial Pneumonia. A Narrative Review. 2002


2006



LGL proliferation





SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

BAL

Data Nascita: 17/03/1947 Età: 67 Anni Sesso: F
Id. Paz.: 15093269

Doc. n. 25058932 prodotto il: 23/05/2014 Ore: 14:09 Routine
Richiesta: **16377812** **21/05/2014** Ore: 13:00

Esame	*Esito*	*U.M.*	*Intervalli Riferimento*
[51] BAL (l.bronchiolo-alveolare)-Tipizzazione II livello			
Cellule totali	**540**	*10^6/L*	
Neutrofili	**8.0**	%	
Eosinofili	**0.0**	%	
Linfociti	**70.0**	%	
Macrofagi	**22.0**	%	
[51] Analisi Citofluorimetrica			
Linfociti T CD3+	**65.0**	%	
Linfociti T CD3+ CD4+	**46.0**	%	
Linfociti T CD3+ CD8+	**18**	%	
Linfociti B CD19+	**1**	%	
Linfociti NK CD3-CD16+/CD56+	**34**	%	
LINFOCITI T attivati CD3+ HLA-DR+	**38**	%	

Firma digitale Dr. ROMOLO DORIZZI

SEDE DI ESECUZIONE ESAMI E DIRETTORI RESPONSABILI

[51] Pievesestina	Laboratorio di riferimento tel. 0547394811 dr. R.Dorizzi, prof. V.Sambri	
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[21] Cesena	Lab.R.R. tel. 0547394811 dr. R.Dorizzi	S.Trasfusionale tel. 0547352920 dr.ssa R.Santarelli
[11] Forlì	Lab.R.R. tel. 0543731663 dr.ssa R.Nunziatini	S.Trasfusionale tel. 0543735070 dr. G.Migliori
[31] Rimini, [32] Riccione	Lab.R.R. tel. 0541705364 dr. A.Argento	S.Trasfusionale tel. 0541705371 dr.ssa S.Nucci
[41] Ravenna, [42] Faenza, [43] Lugo	Lab.R.R. tel. 0544285313 dr.ssa S.Valenti	S.Trasfusionale tel. 0544285632 dr.ssa I.Tomasini

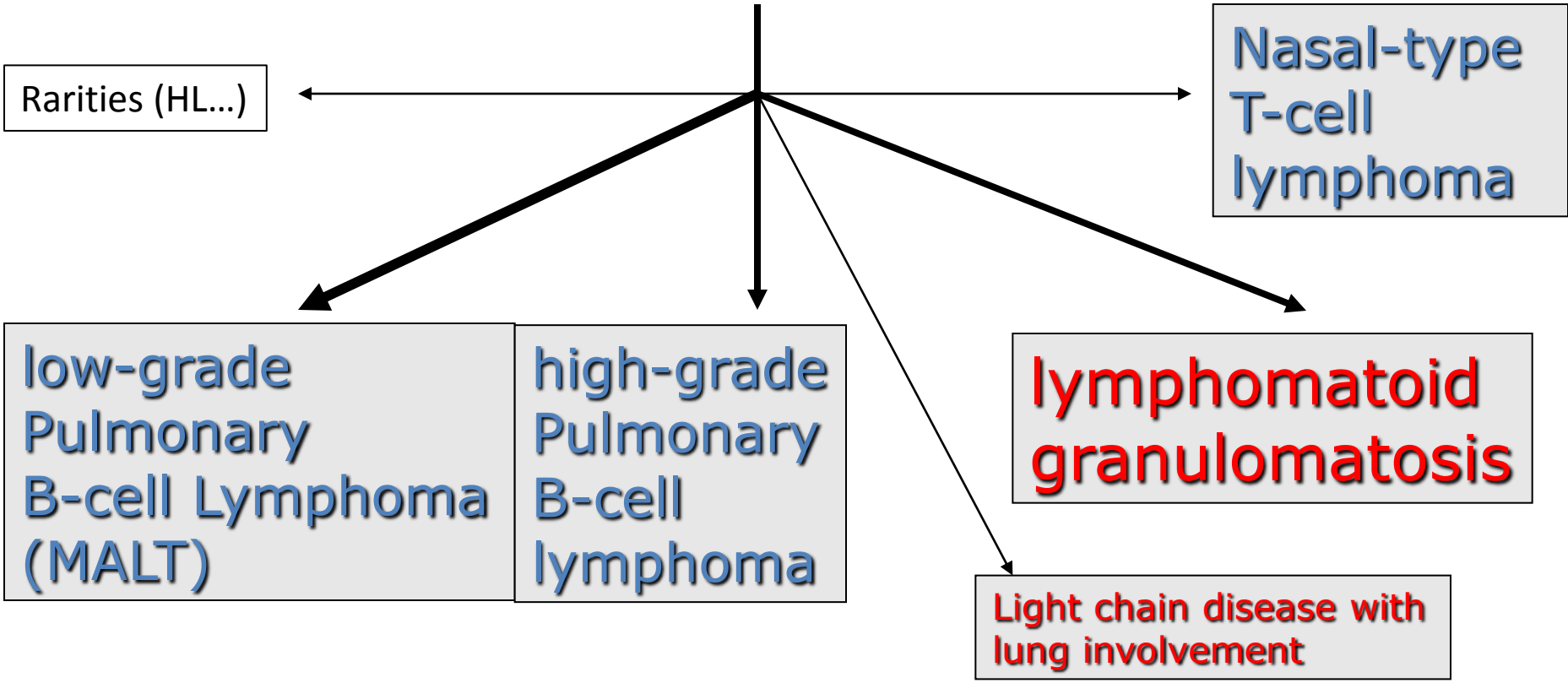
LIP: practical key points

- When nodules/halo sign are detected by CT scan malignant lymphoma is the highest probable diagnosis inspite of histology
- The clinical background is fundamental (autoimmunity, CVID, GVHD, ….)
- Cystic lesions may be due to other (monoclonal) lymphoproliferative disorders

Primary pulmonary lymphomas

These are defined as a clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in patients with no detectable extrapulmonary involvement at the time of diagnosis or during the subsequent 3 months (table 1). However, this definition is not precise because indolent extra-nodal lymphoma may present clinically and radiologically as primary pulmonary lesions [14–16], and aggressive lymphoid tumours may initially manifest as disorders mainly involving the respiratory tract. Therefore, primary pulmonary lymphomas should be defined as lymphoid neoplasms that become manifest as respiratory diseases.

Primary Pulmonary Lymphoma



Eur Respir J 2009; 34: 1408–1416
DOI: 10.1183/09031936.00039309

Clinical characteristics and prognostic factors of pulmonary MALT lymphoma

R. Borie, M. Wislez, G. Thabut, M. Antoine, A. Rabbat, L-J. Couderc, I. Monnet, H. Nunes, F-X. Blanc, H. Mal, A. Bergeron, D. Dusser, D. Israël-Biet, B. Crestani and J. Cadranel

TABLE 1 Main clinical and biological characteristics of the 63 patients

Characteristics	Value
Age yrs	60 (24–83)
Females	29 (47)
Active or former tobacco use	24 (37)
Respiratory tract infection	6 (9)
Including tuberculosis	4 (6)
Autoimmune background	10 (16)
Respiratory symptoms	37 (58)
B symptoms	14 (22)
Cytopenia	12 (19)
LDH level more than twice the upper limit	2 (3)

Data are presented as or median (range) or n (%). B symptoms include weight loss, fever and night sweats. LDH: lactate dehydrogenase.

1: Leuk Lymphoma. 2006 Feb;47(2):343-6.

Lymphoma of mucosa-associated lymphoid tissue in common variable immunodeficiency.

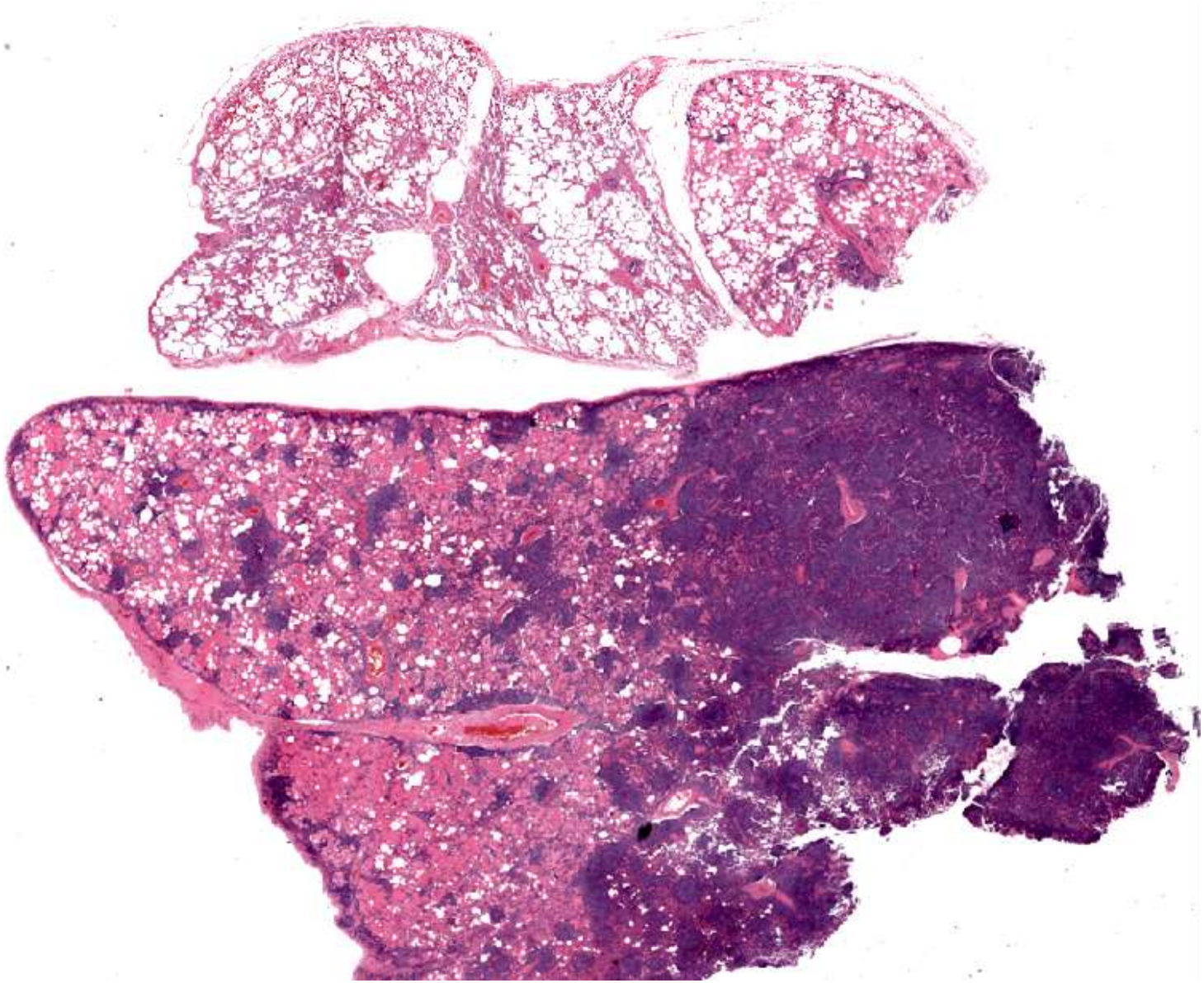
Aghamohammadi A, Parvaneh N, Tirgari F, Mahjoob F, Movahedi M, Gharagozlou M, Mansouri M, Kouhi A, Rezaei N, Webster D.

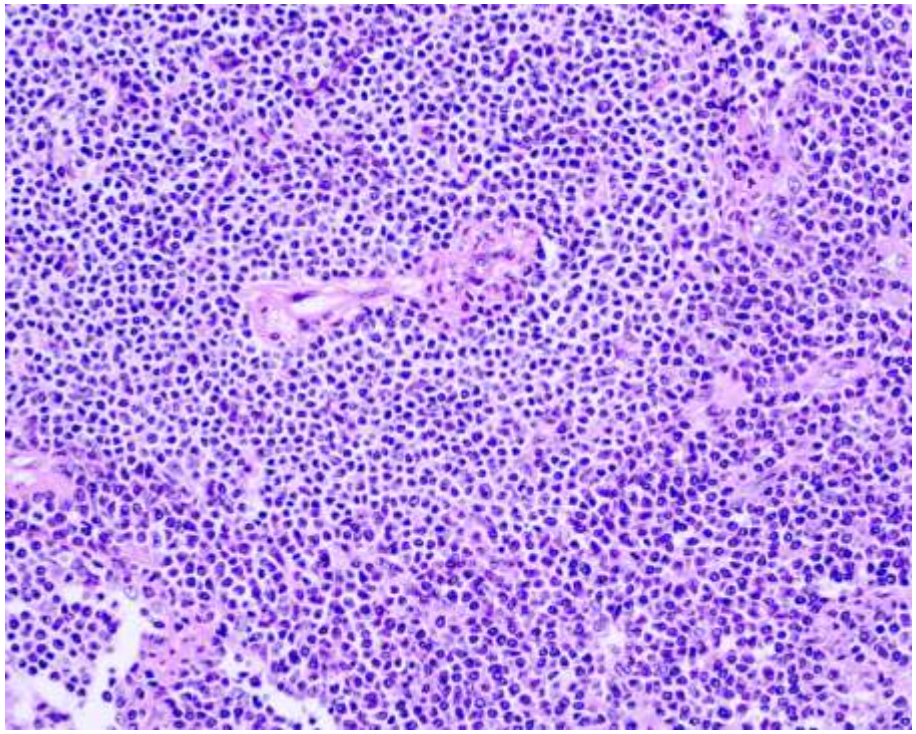
Department of Clinical Pediatric Immunology, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran. aghamohammadi@iranianpia.org

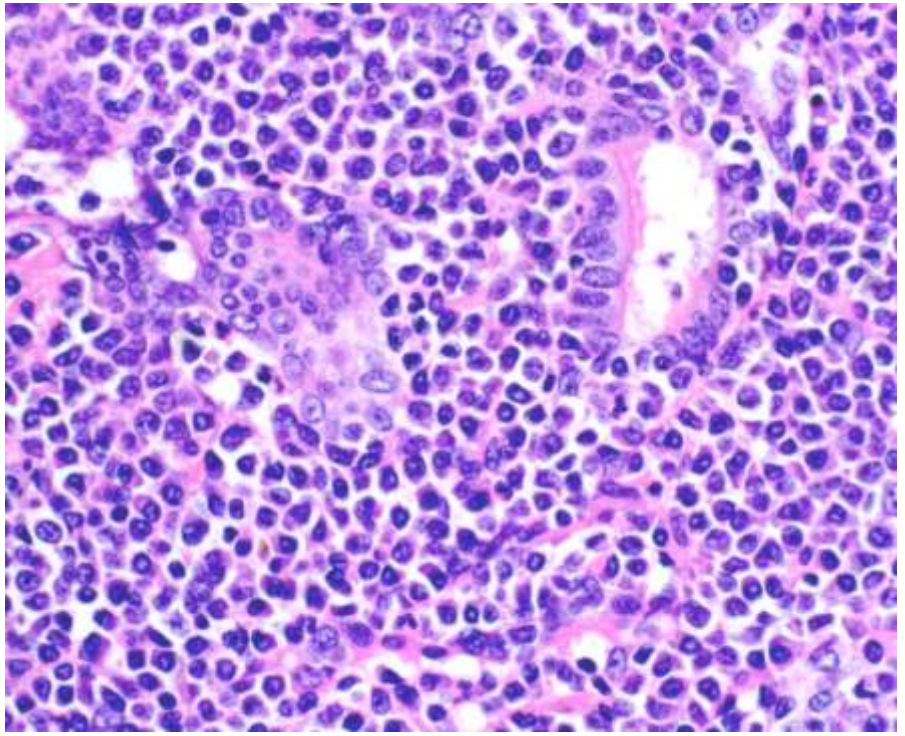
Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency characterized by reduced levels of all major immunoglobuline classes and recurrent c infections. The risk of non-Hodgkin's lymphoma (NHL) among patients with CVID was found to be increased in different studies. Mucosa-associated lymphoid tissue (MALT) lymphomas are a recently recognized sub-set of low-grade B-cell NHL composed of marginal zone-related cells. MALT lymphomas appear in the lymphoid tissues as a result of chronic inflammatory or autoimmune stimulation. This study briefly reviews previously published cases and reports a patient suffering from CVID with a history of chronic diarrhea and recurrent sinopulmonary infections. Despite treatment with intravenous immunoglobulin, chronic cough and wheezing progressed. Open lung biopsy showed a MALT lymphoma. Although a rare complication, pulmonary low grade B-cell lymphoma is a diagnosis that must be kept in mind in CVID patients with chronic pulmonary symptoms unresponsive to conventional therapies.

PMID: 16321869 [PubMed - indexed for MEDLINE]

06-1353 S. B CELL LYMPHOMA- MALT TYPE



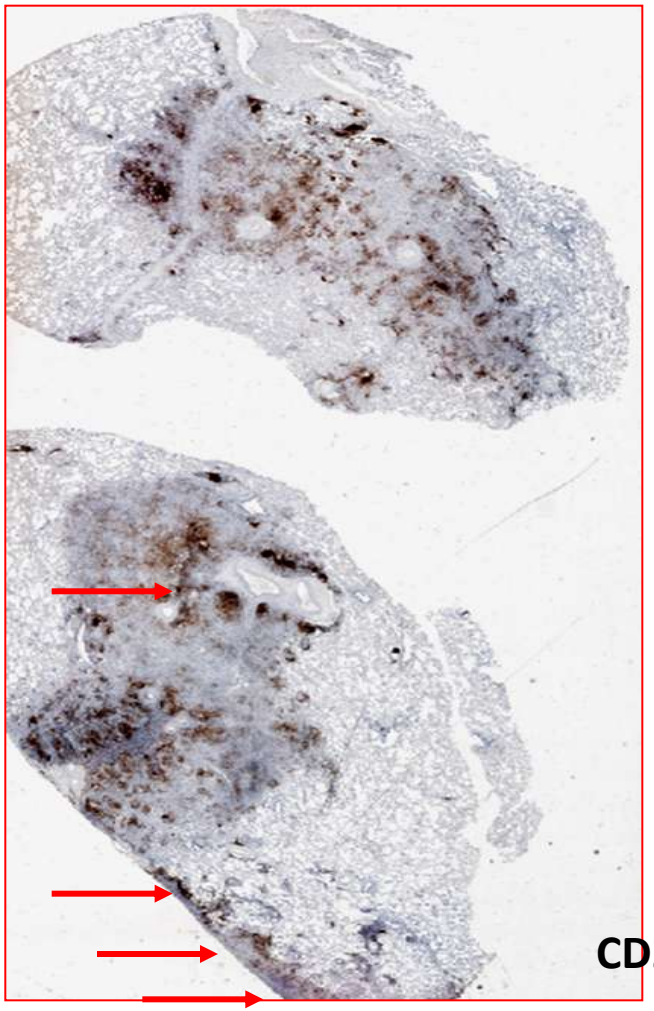




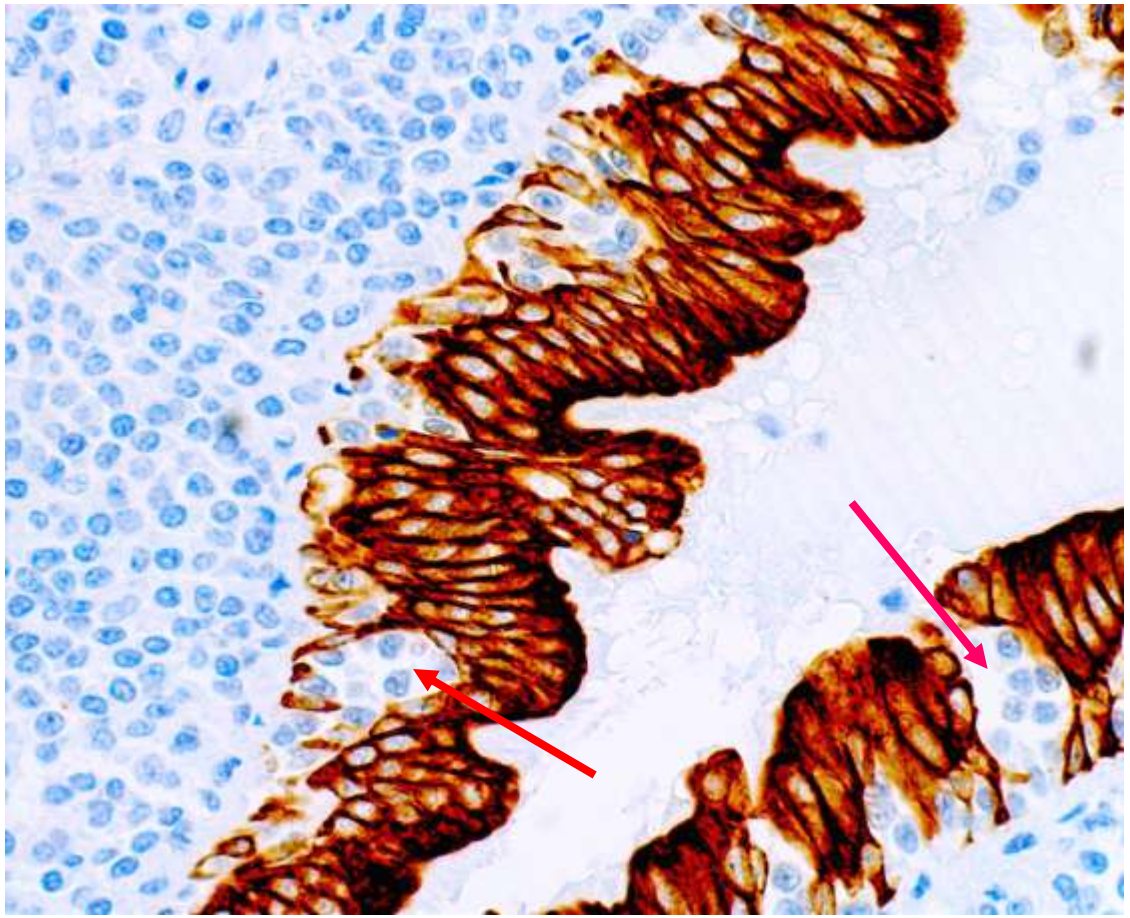
Cytological heterogeneity

Histological Features

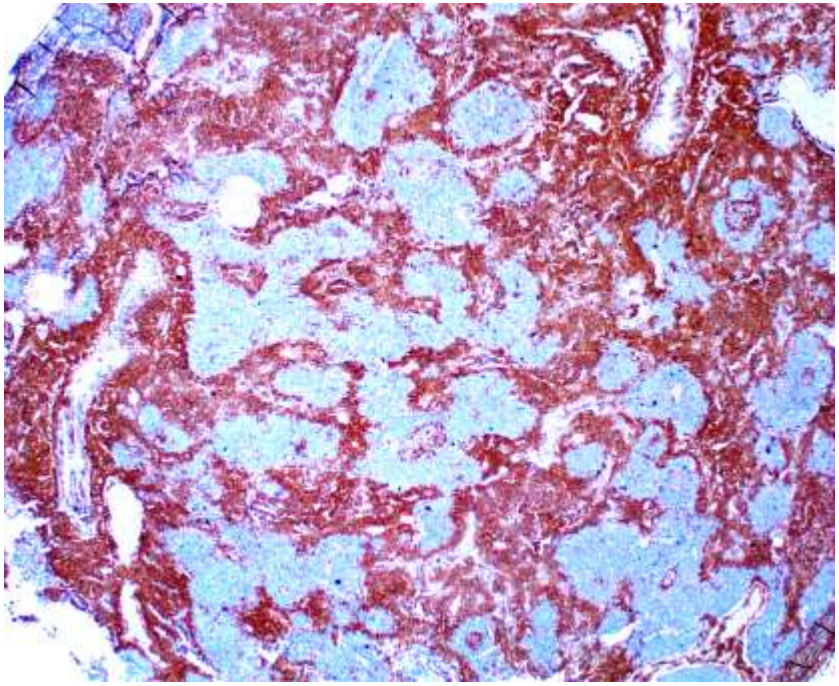
At histological analysis the pulmonary structure is effaced by abnormal lymphocyte infiltration, predominantly localised along bronchovascular bundles, interlobular septa and visceral pleura, in a lymphangitic pattern.



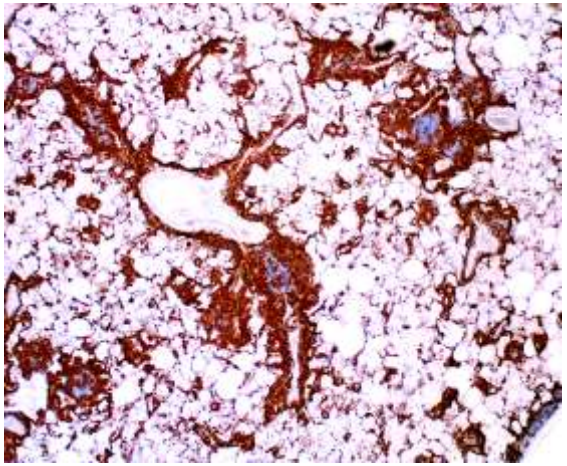
The presence of lympho-epithelial lesions (neoplastic lymphoid cells infiltrating bronchiolar epithelium) is frequent and involve bronchiolar and bronchial epithelial structures.

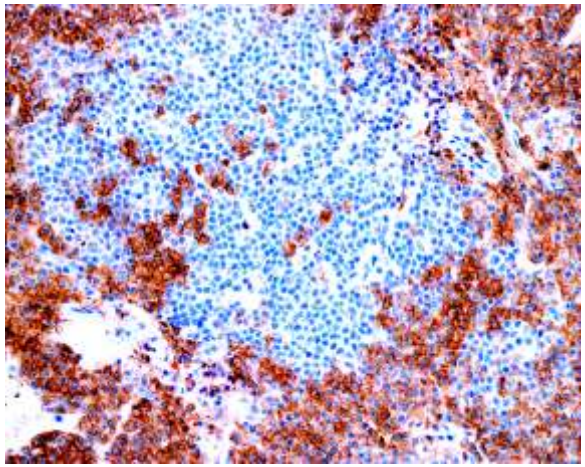


Plasma-cell differentiation



CD38

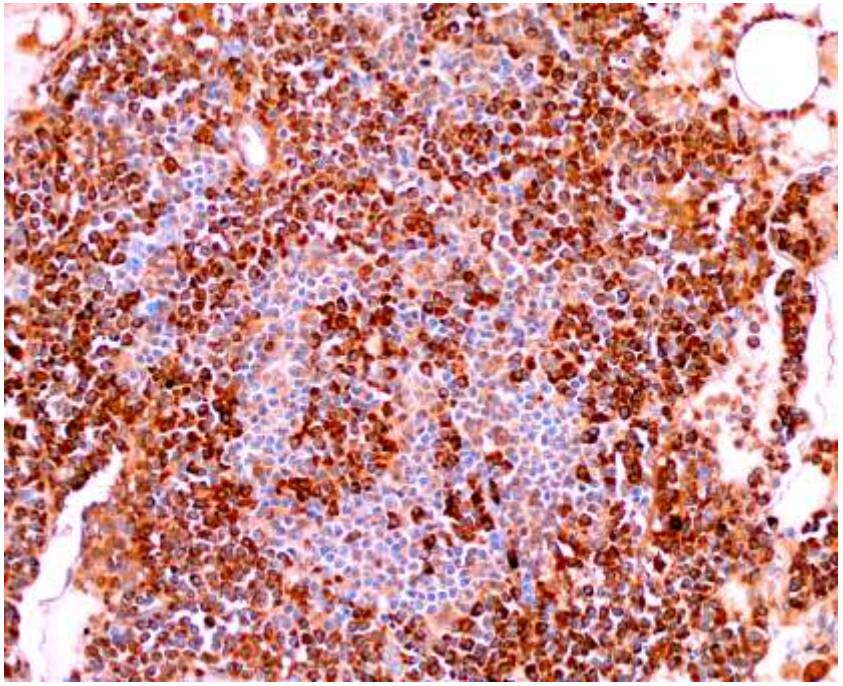




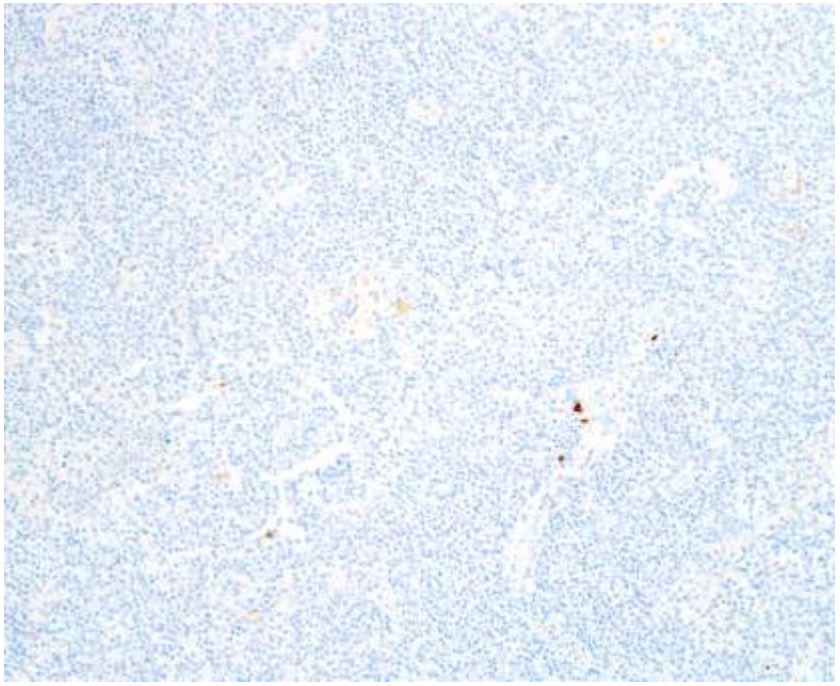
CD138

- In a consistent proportion of cases it is possible to demonstrate **lymphoplasmacytic differentiation**, with a significant plasma cell component exhibiting immunoglobulin light chain restriction.
- It is possible that at least some cases of primary plasmacytoma of the lung (a rare low-grade tumor of unclear etio-pathogenesis presenting as isolated nodules or diffuse) can in fact be included in the clinico-pathologic spectrum of MALT lymphomas, together with localised pulmonary amyloidosis (another lesion that has been described in association with pulmonary marginal lymphoma).

CLONALITY



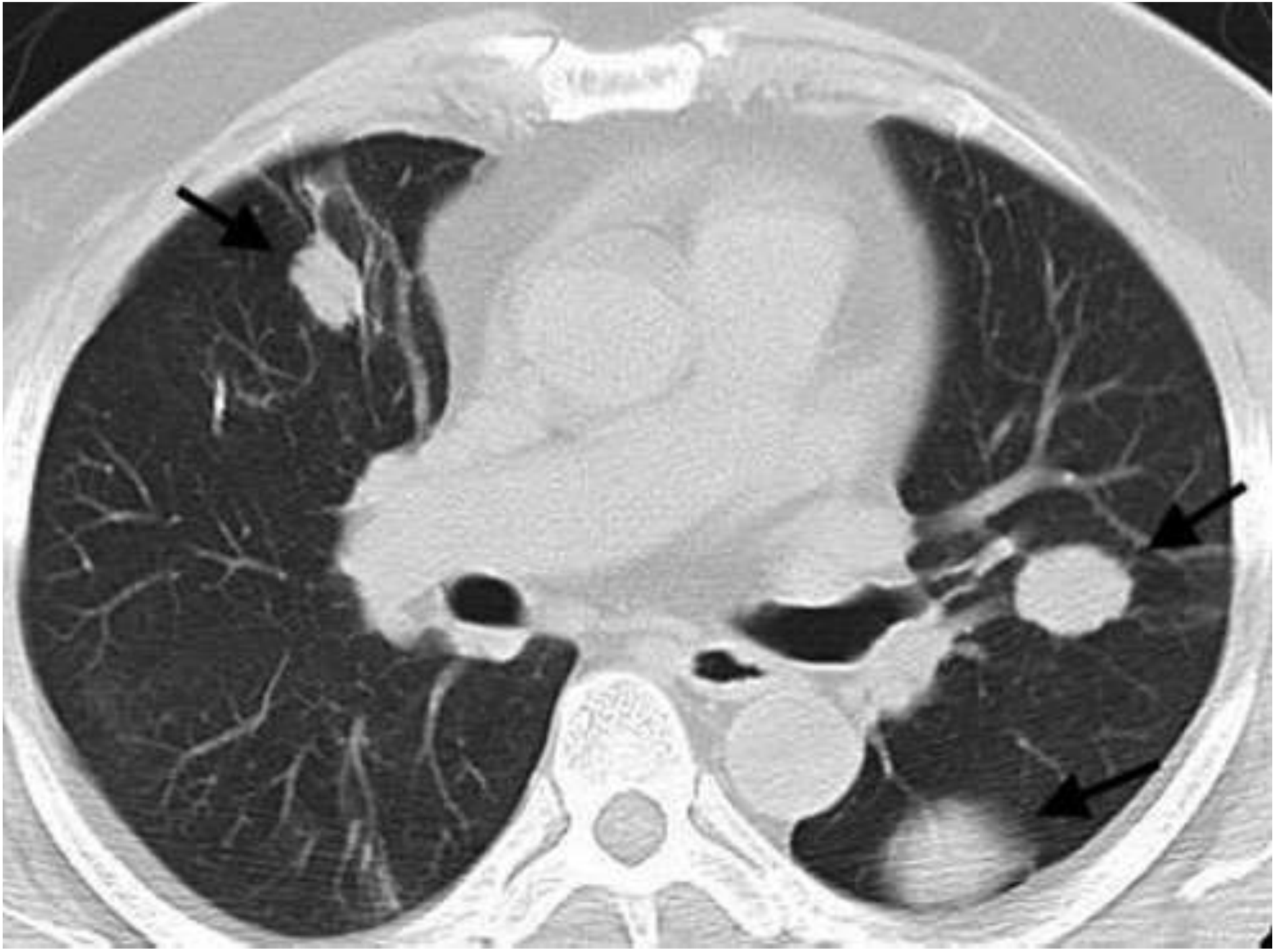
LAMBDA

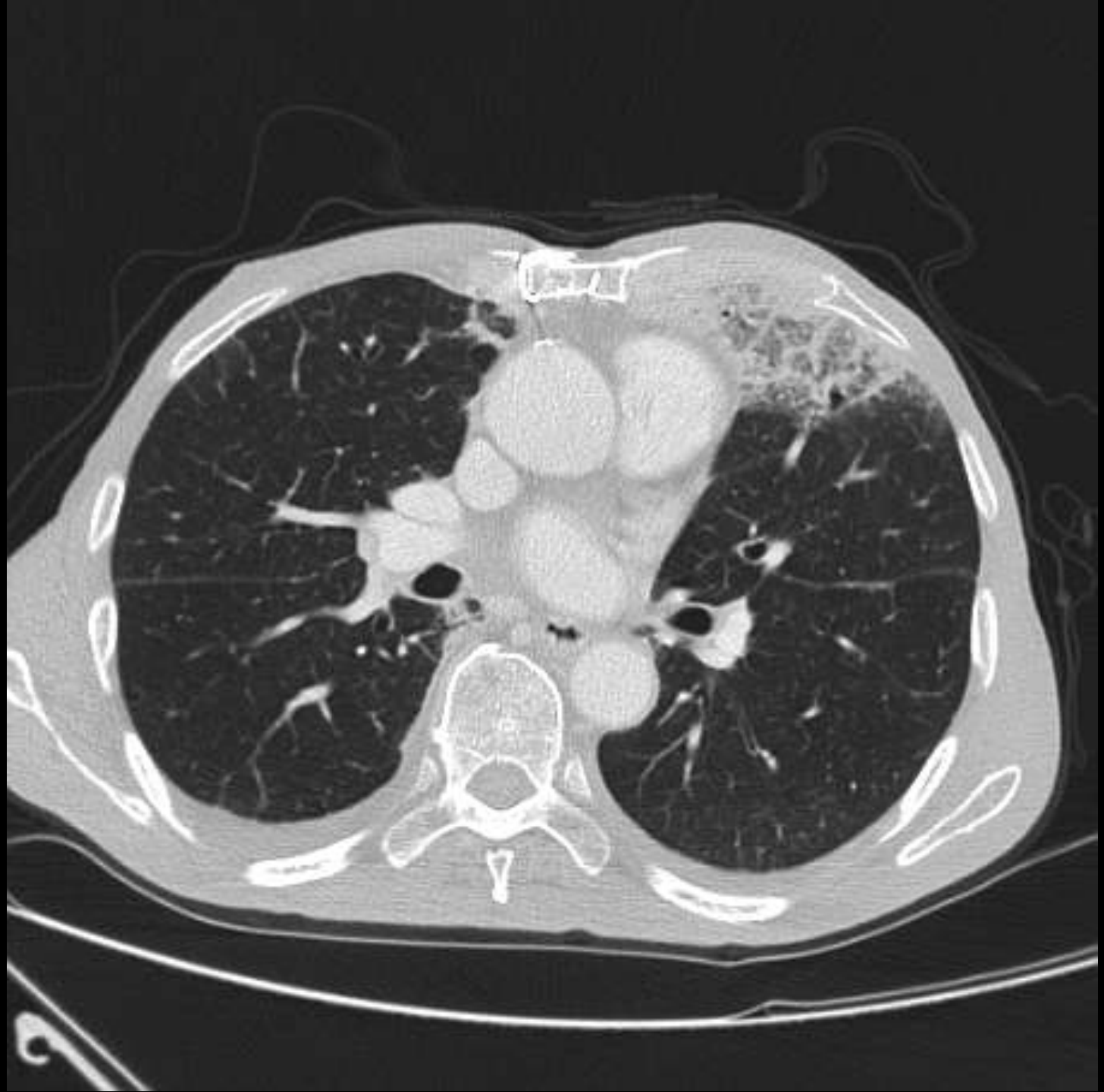


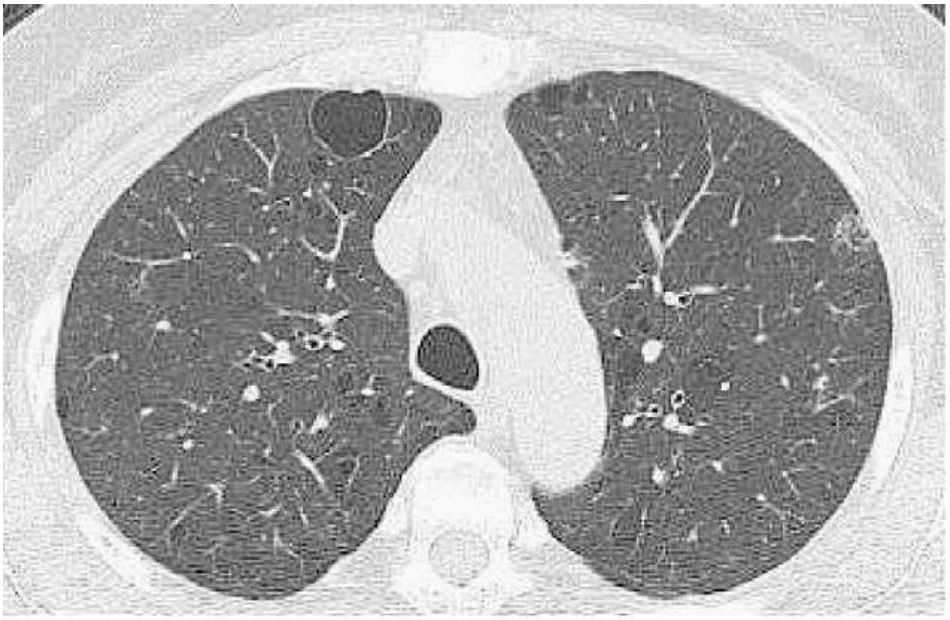
KAPPA

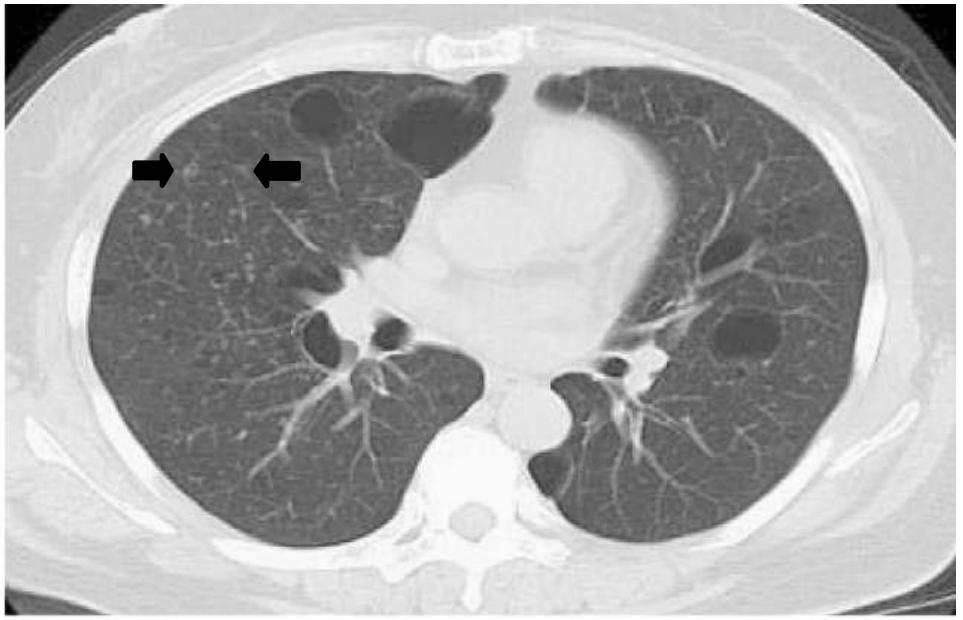
CT scan findings in MALT Lymphomas , primary in the lungs

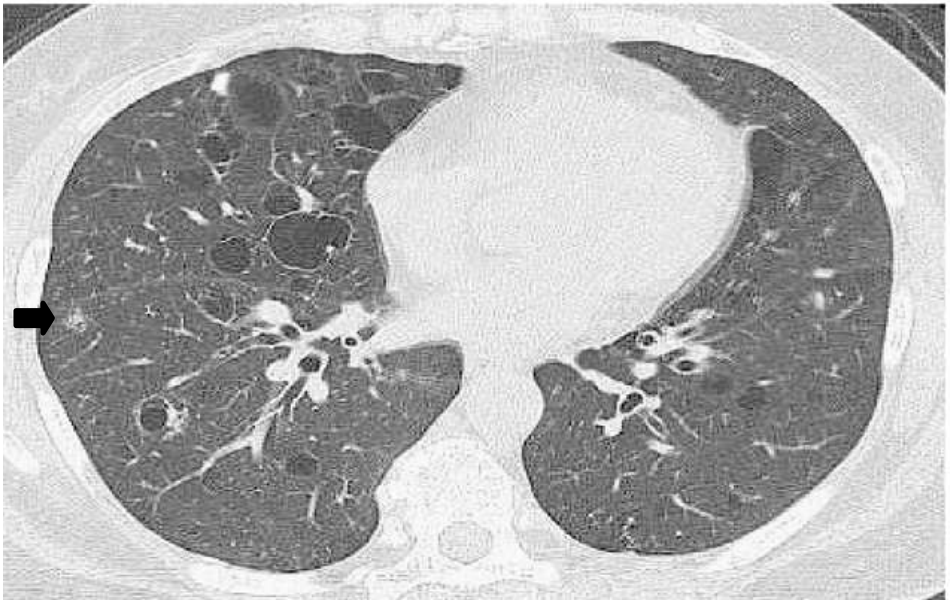
(1) single nodule or single consolidative opacity (33%)
(2) multiple nodules or multiple areas of consolidation (43%)
(3) bronchiectasis and bronchiolitis (14%)
(4) diffuse interstitial lung disease (10%).

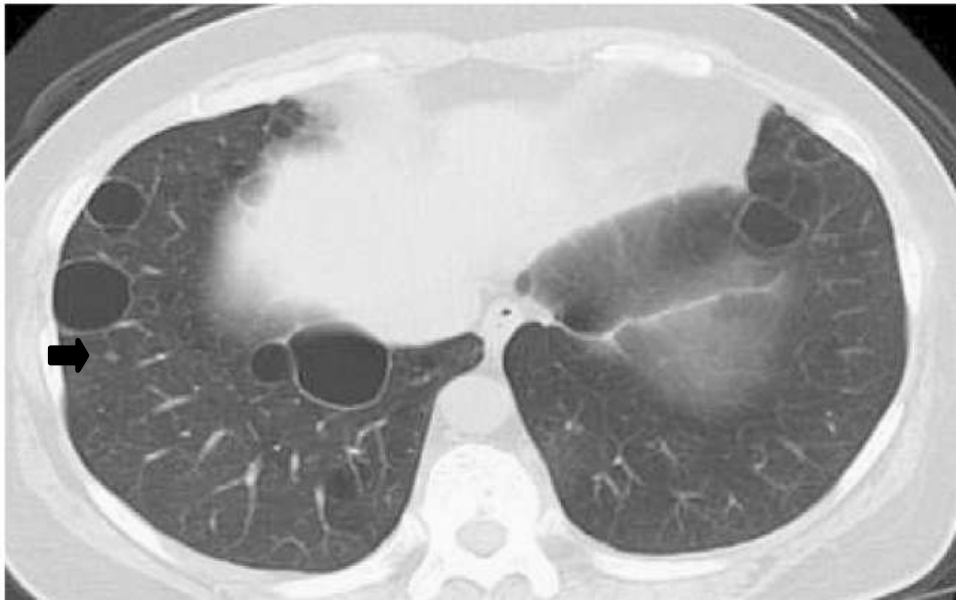




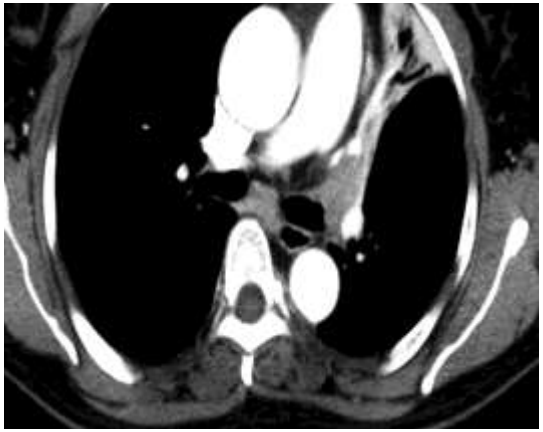








ENDOBRONCHIAL MALT LYMPHOMA



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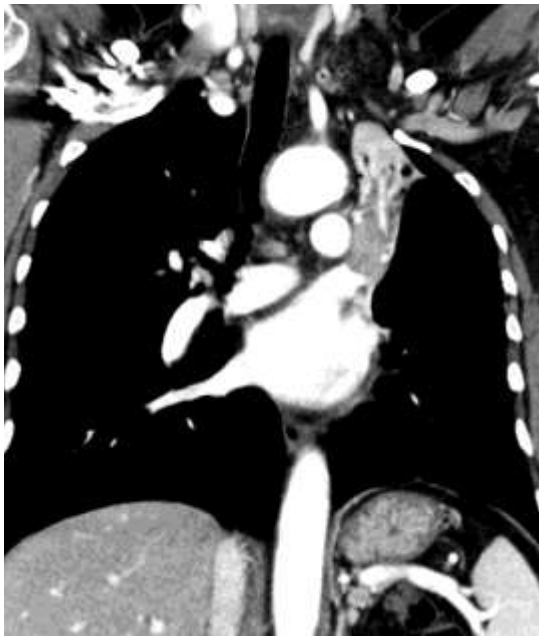

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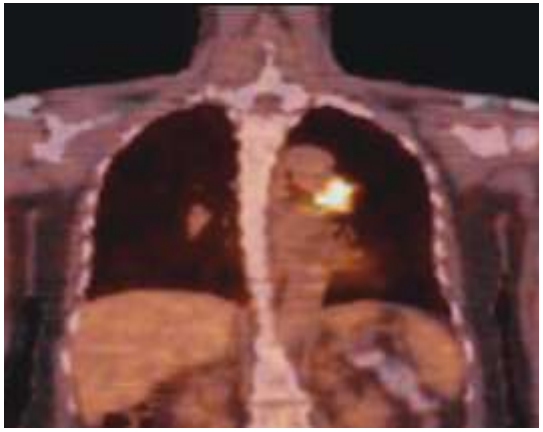

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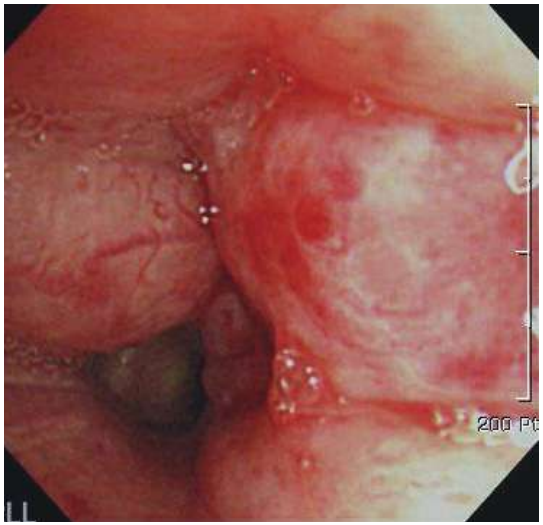

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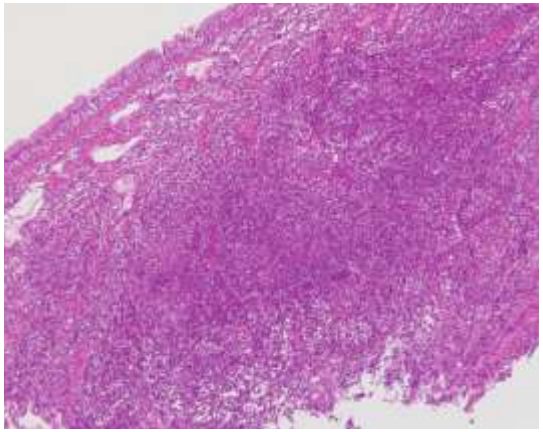

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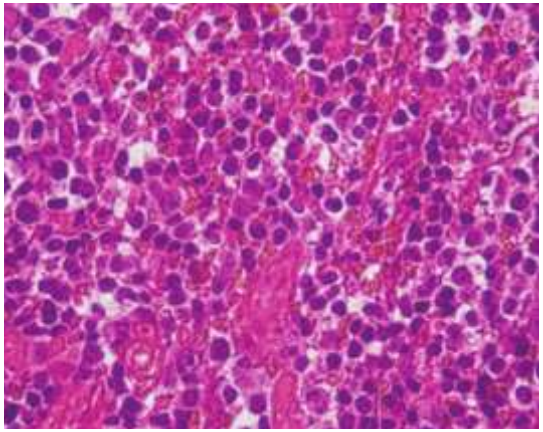


F

CYTOGENETIC FEATURES

- As in other extranodal-MALT lymphomas, an heterogeneous pattern of cytogenetic abnormalities has been demonstrated in pulmonary lymphomas, including aneuploidy (observed in nearly 40% of cases, with trisomy 3 and 18 being the most common), and specific chromosomal translocations.
- Translocation t(11;18)(q21;q21) which characterizes about one third of extranodal marginal MALT lymphomas is the most frequent chromosome translocation occurring in pulmonary MALT lymphomas (38,3-41% in different series).
- This translocation involves the API2 and MALT1 genes, and can be then directly correlated to the pathogenesis of this lymphoma. Accordingly, API2 is a member of the IAP (inhibitor of apoptosis) gene family, whereas MALT1, a paracaspase of unknown functions, is able to interact with bcl-10 inducing NF-kB activation. The abnormal fusion of MALT1 with API2 produces chimeric transcripts involved in inhibition of apoptosis, thus contributing to lymphoma development.

t(11;18)(q21;q21)

Frequente nei MALT-L del polmone

55-75%

Nelle serie più ampie

40-45%

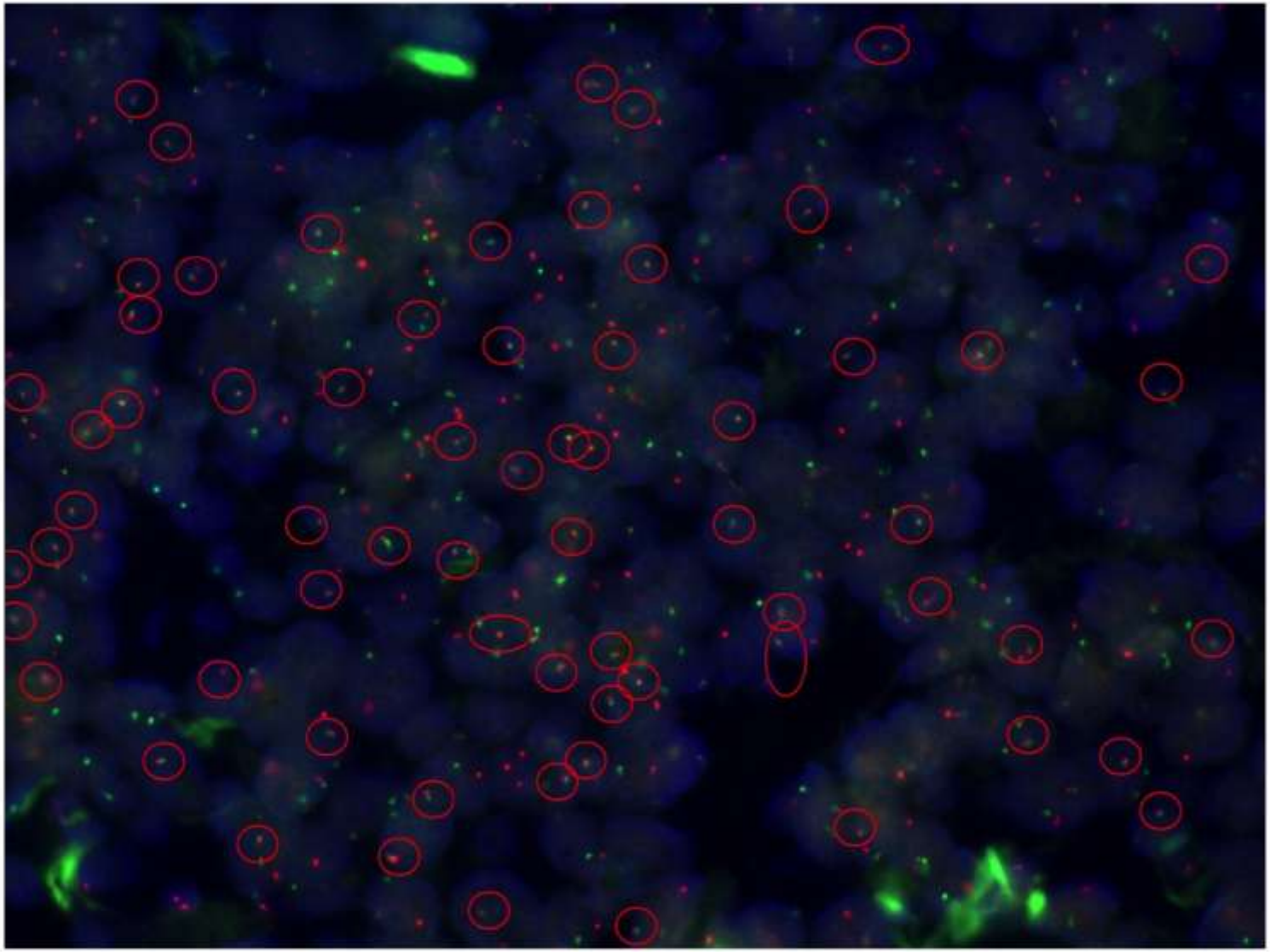
t(11;18)(q21;q21)

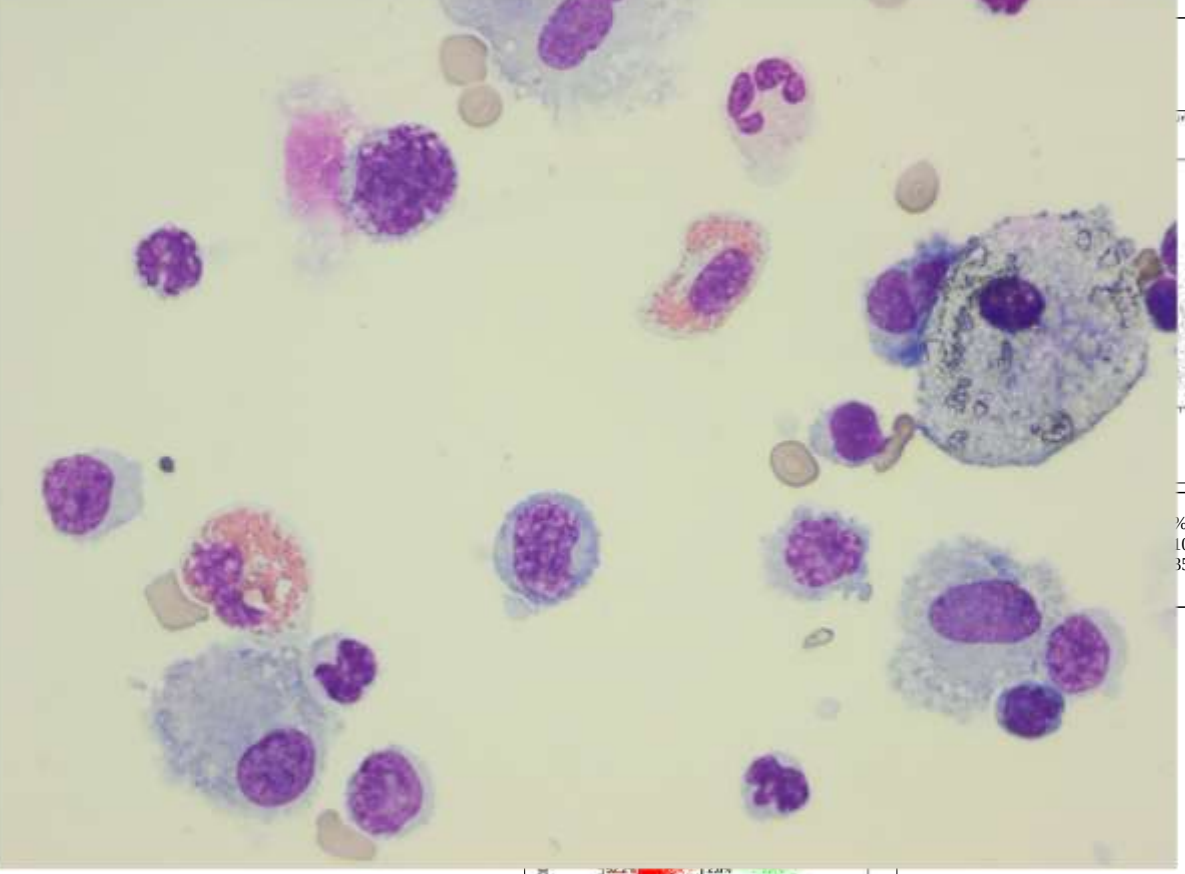
A distinctive clinicopathologic subtype of pulmonary MALT lymphoma

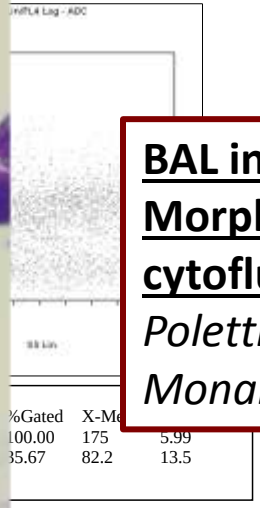
- No autoimmunity
- Normal LDH
- Typical histology
- Aberrant nuclear BCL10

Okabe-M, Inagaki-H, Ohshima-K et al. Nagoya, Japan

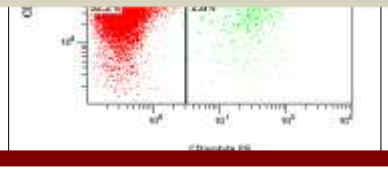
AP12-MALT1 fusion defines a distinctive clinicopathologic subtype in pulmonary extranodal marginal zone B-cell lymphoma of MALT. *Am J Pathol 162:1113,2003*

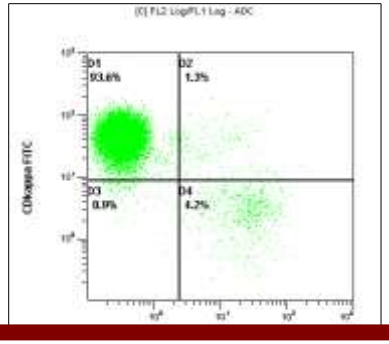






BAL in MALT lymphoma: Morphologic and cytofluorimetric analysis
Poletti V, et al
Monaldi Arch Chest Dis 1995





*Clonality and phenotyping analysis of alveolar lymphocytes is suggestive of pulmonary MALT lymphoma
Borie R, et al. Respir Med 2011
*Detection of MALT1 gene rearrangements in BAL fluid cells for the diagnosis of pulmonary MALT lymphoma.
Kido T, et al. Chest 2012

Respiratory Medicine (2011) 105, 1231–1237

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Clonality and phenotyping analysis of alveolar lymphocytes is suggestive of pulmonary MALT lymphoma

Raphael Borie [a,b], Marie Wislez [a,c,*], Martine Antoine [d], Jocelyne Fleury-Feith [c,e], Gabriel Thabut [f,g], Bruno Crestani [b,g], Isabelle Monnet [h], Hilario Nunes [i,j], Marie-Helene Delfau-Larue [k,l], Jacques Cadranel [a,c]

Table 1 Main clinical and bronchoalveolar lavage (BAL) data for patients with mucosa-associated lymphoid tissue (MALT) lymphoma in the global population and associated or not with a connective tissue disease. Data are number (percentage) for categorical variables or median (range) for continuous variables. * is *p* test between with and without connective tissue disease.

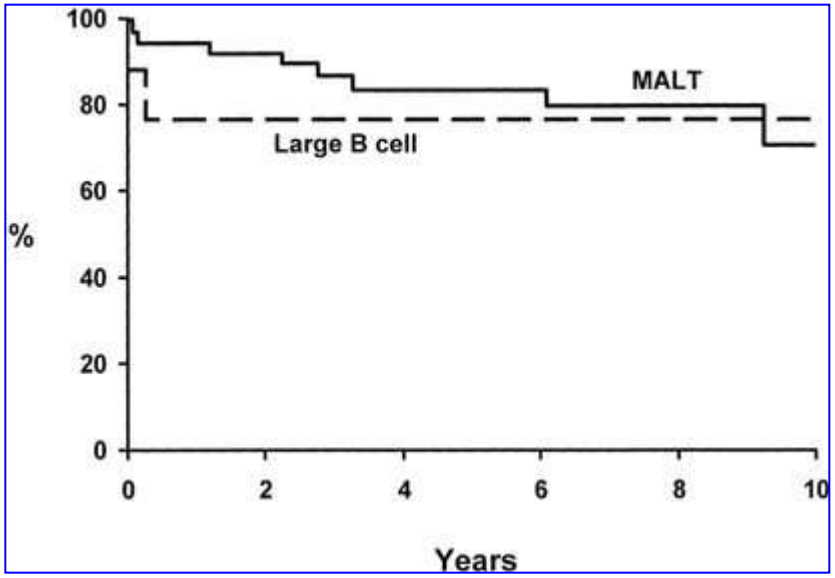
Malt lymphoma				
	Global population ($n = 44$)	Without connective tissue disease ($n = 33$)	With connective tissue disease ($n = 11$)	p*
Age	57.9 (30–76)	56.8 (36–83)	60 (30–79)	
Female	21 (46%)	12 (36%)	9 (81%)	0.02
Smoker	18 (40%)	17 (51%)	1 (9%)	0.03
Bronchoalveolar lavage				
Cell (/mm^3)	370 (21–2300)	300 (21–2300)	250 (80–390)	NS
Macrophages %	52.5 (16–97)	48 (16–97)	70 (36–85)	NS
Neutrophils %	3.5 (0–66)	3 (0–66)	3 (0–15)	NS
Eosinophils %	0.5 (0–8)	0 (0–8)	0.5 (0–4)	NS
Lymphocytes %	31.5 (2–80)	34 (2–80)	26 (4–61)	NS
T cell (CD3) %	68 (7–92)	41 (18–80)	89 (63–93)	0.003
CD3+CD4+	27 (4–77)	24 (4–77)	34 (23–70)	NS
CD3+CD8+	25 (2–80)	17 (2–63)	38 (18–80)	0.006
B-cell (CD19) %	20 (1–88)	34 (2–80)	6.5 (1–30)	0.007
Dominant B-cell clone	19 (82)	15 (88)	4 (66)	NS

Leuk Lymphoma. 2003 May;44(5):821-4. **Extranodal marginal zone B-cell lymphoma of MALT-type of the lung: single-center experience with 12 patients**. Zinzani PL, Tani M, Gabriele A, Poletti V, et al. University of Bologna, Bologna, Italy

The lung is a relatively rare site for mucosa-associated lymphoid tissue (MALT) lymphomas: we report the largest available single-center series of patients with this presentation. From August 1992 to October 2000, 12 patients with untreated primary low-grade MALT lymphoma of the lung were submitted either to chemotherapy alone (n = 8), surgery alone (n = 2) or surgery plus chemotherapy (n = 2). At diagnosis, 6 (50%) were asymptomatic and 6 (50%) had nonspecific pulmonary symptoms. The most common radiologic findings were a pulmonary infiltrate (7 cases) and a mass lesion (5 cases). Histological diagnosis was obtained with transbronchial lung biopsy/ broncho-alveolar lavage (BAL) (6 cases), with transthoracic needle biopsy (1 case), or an open thoracotomy (5 cases). **All patients had stage IE. All 12 (100%) achieved complete remission;** 3 (25%) local recurrences were observed. **The global 6-year survival rate was 100% with a relapse-free survival rate of 50%.** In conclusion, these data underline the diagnostic utility of BAL and the therapeutic efficacy of a chemotherapeutic strategy based on regimens such as N-CVP in the context of localized MALT lymphoma of the lung.

Linfoma MALT del polmone
Caratteristriche Cliniche

- Linfoma indolente ad ottima prognosi
- Anche le rare forme a grandi cellule hanno buona prognosi



Lymphoma-specific survival of patients with low-grade MALT lymphoma compared with those with diffuse large B-cell lymphoma complicating low-grade MALT lymphoma.
There is no difference in survival ($p = 0.624$).

Lymphomatois Granulomatosis (LYG)

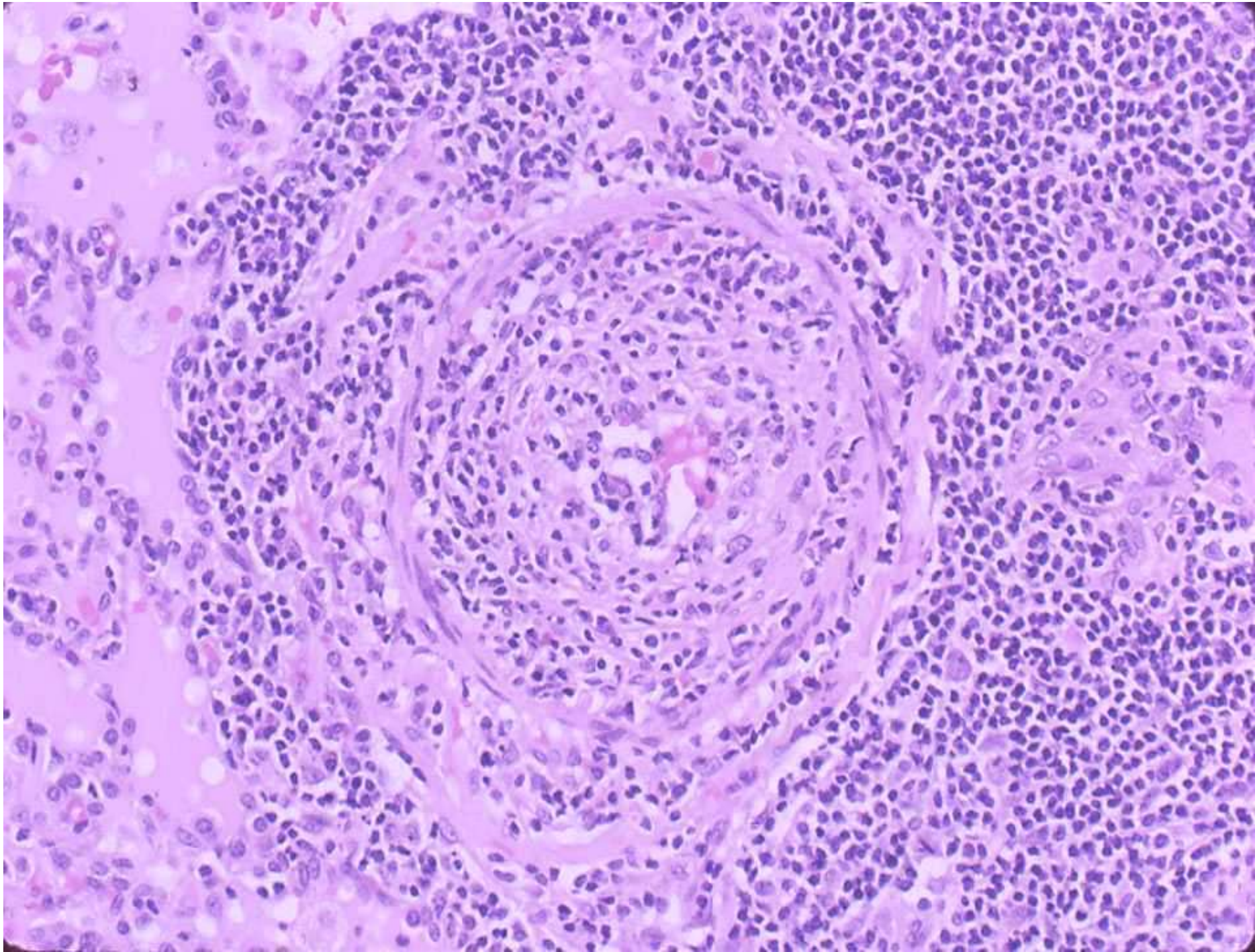
"... an angiocentric and angiodestructive lymphoreticular proliferative and granulomatous disease involving predominantly the lungs."

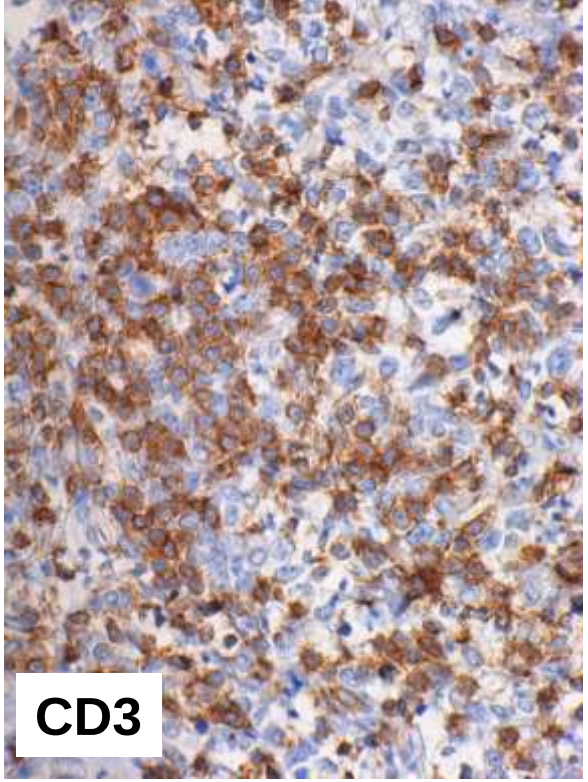
Liebow AA, Carrington CR, Friedman PJ: Lymphomatoid granulomatosis. Hum Pathol 1972;3:457–558.

The lesion mimicked lymphoma and Wegener's granulomatosis = LYG

Lymphomatoid granulomatosis
Clinical features

- **IV-VI decade**
- **males > females (2-3:1)**
- **Symptomatic patients**
  - **cough, dyspnoea, fever, generalized malaise, weight loss, arthralgia**
- **Lab: lymphopenia, ESR ⬆**
- **Extrapulmonary involvement:**
  - **Skin (50%), CNS (25%), kidney, liver,……**

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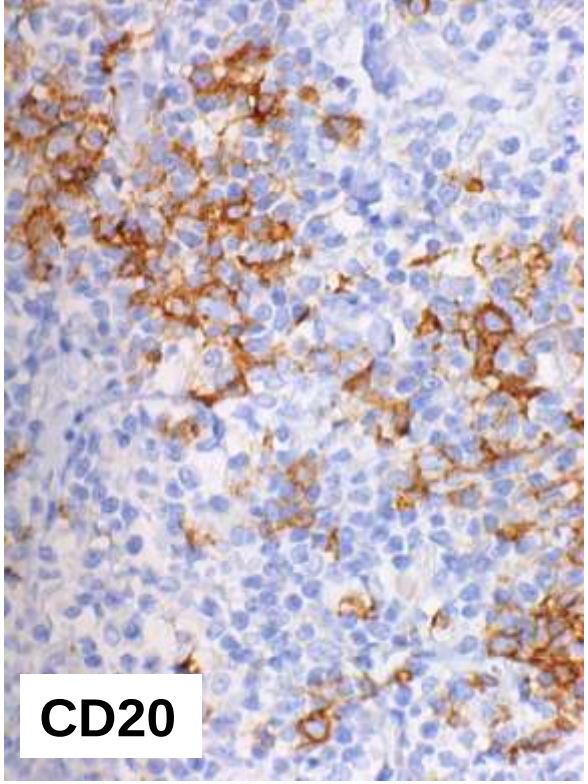
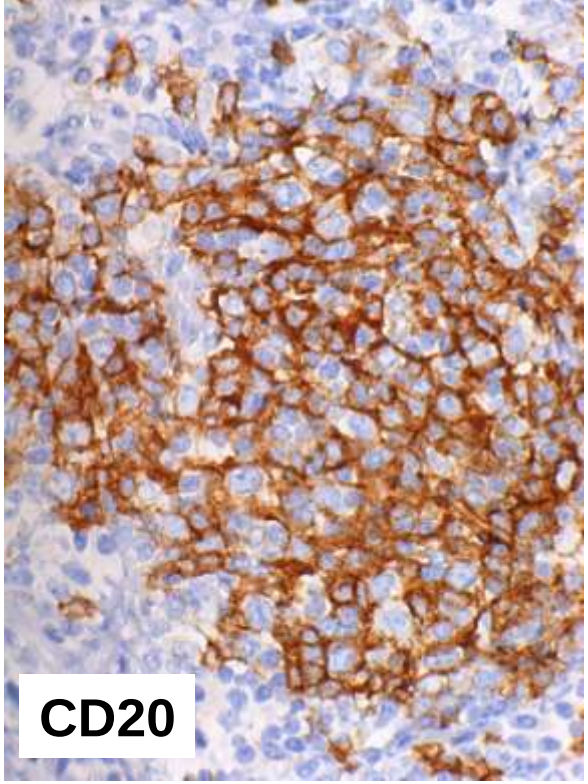

CD20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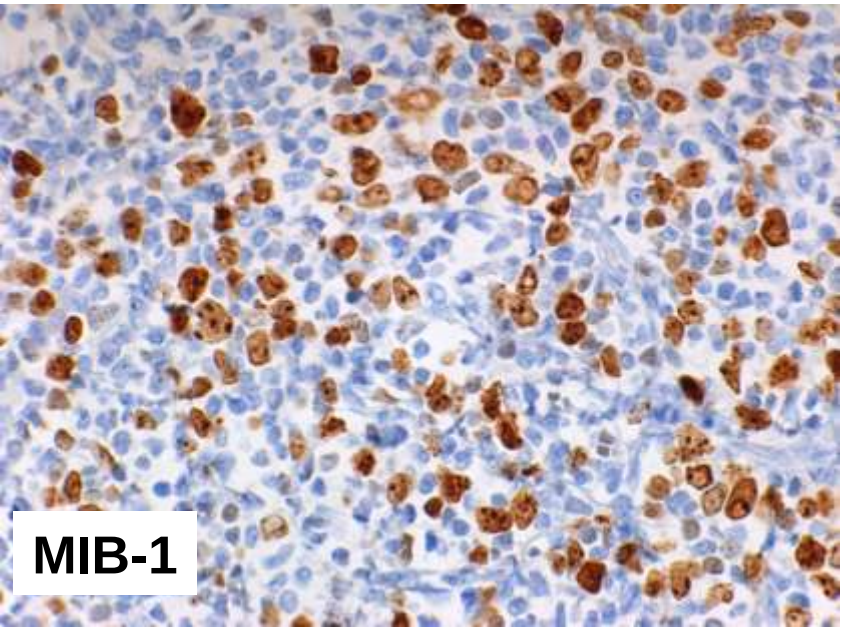
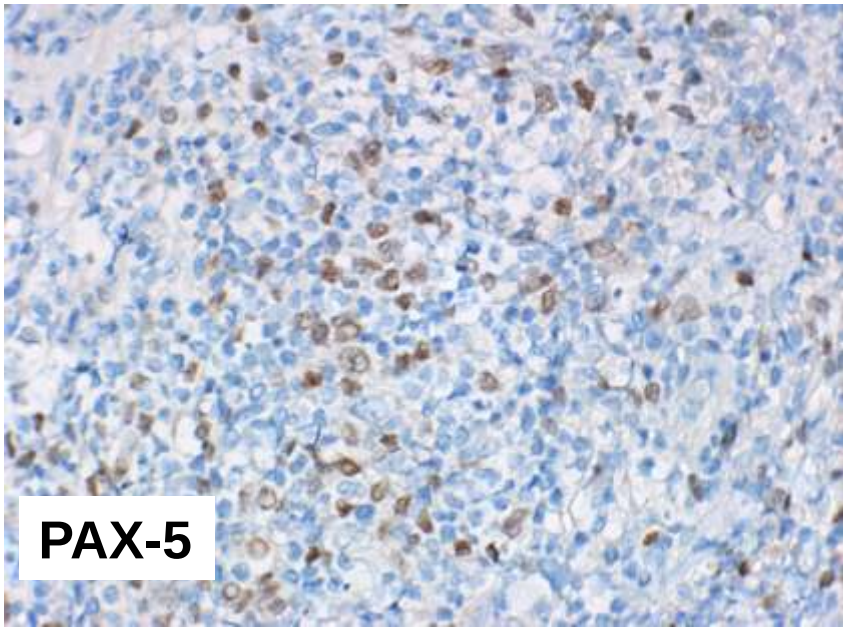

MIB-1


PAX-5

The American Journal of Surgical Pathology *18(8): 753–764, 1994*

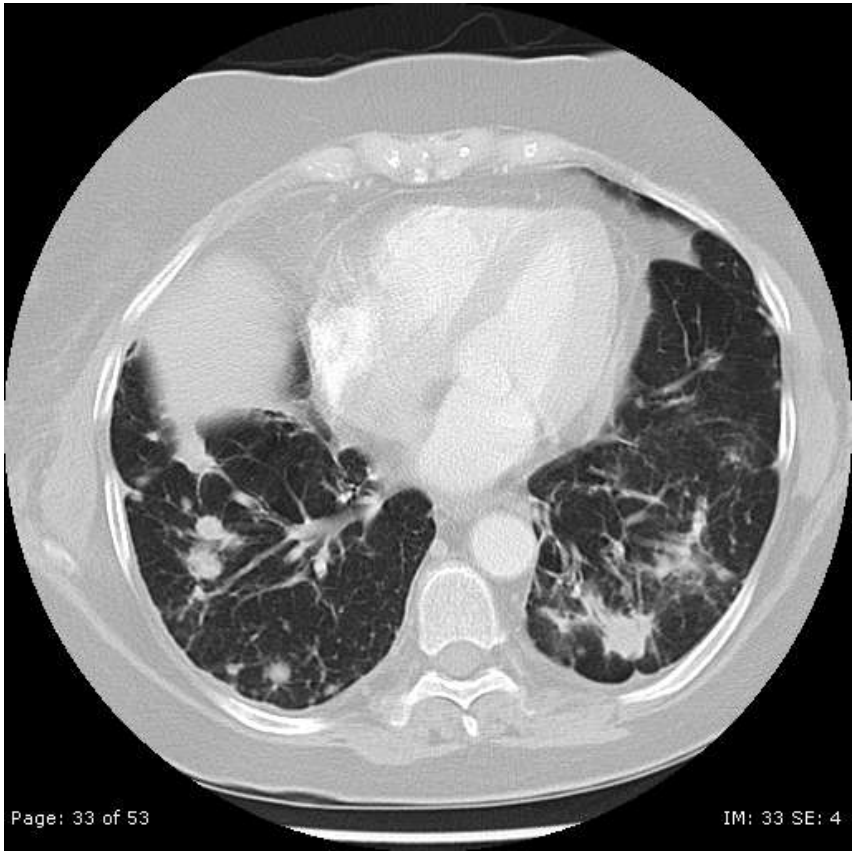
Pulmonary Lymphomatoid Granulomatosis

Evidence for a Proliferation of Epstein-Barr Virus Infected B-Lymphocytes with a Prominent T-Cell Component and Vasculitis

D. Guinee, Jr., E. Jaffe, D. Kingma, N. Fishback, K. Wallberg, J. Krishnan, G. Frizzera, W. Travis, and M. Koss

Multidetector CT: key features

- Bilateral, round, poorly marginated nodules 0.5–8 cm in diameter.
- Basal predominance.
- Peribronchovascular distribution.
- Can coalesce and cavitate.
- ‘‘Reversed halo sign’’.
- ‘‘Migratory’’ nodules due to ‘‘waxing and waning’’.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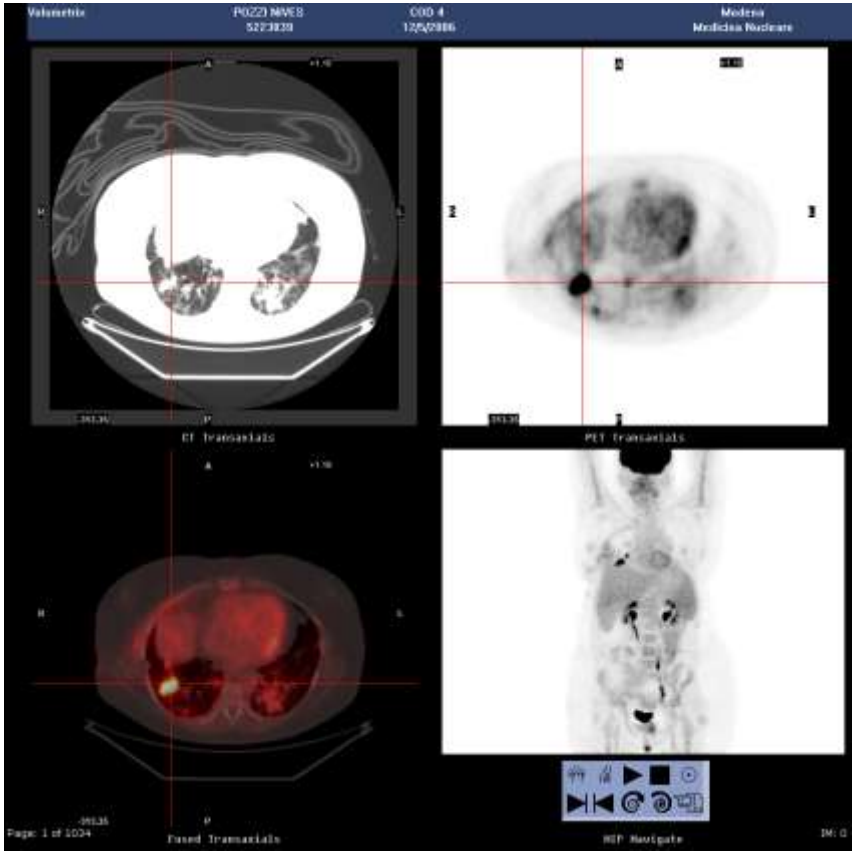

CT Transaxials
PET Transaxials
Fused Transaxials
MIP Navigate

Associated Conditions
- Hematological malignancies
  - Acute lymphoblastic leukemia
  - Chronic lymphocytic leukemia
  - Lymphoma
  - Hodgkin lymphoma
  - Myelofibrosis
- Wiskott-Aldrich syndrome
- Common variable immunodeficiency
- Acquired immune deficiency syndrome
- Carcinoma and chemotherapy
- Renal transplantation
- Autologous stem-cell transplantation
- Rheumatoid arthritis treated with methotraxate
- Sarcoidosis
- Liver disease
  - Biliary cirrhosis
  - Chronic hepatitis
- Retroperitoneal fibrosis
- Skin disease
  - Psoriasis
  - Dermatitis herpetiformis

Predictors of Poor Prognosis
- Central-nervous-system involvement
- Presence of numerous large atypical lymphoid cells
- Young age (< 25 y)
- Leukocytosis
- Hepatomegaly

Patient's history can be a clue !!!

LYG and IgG4

- IgG4-related lesions and LYG-G1 are morphologically indistinguishable from one another in the lung

- Given the absence of EBV-positive cells, atypia, and monoclonality, what has been described as LYG-G1 may not actually be part of the spectrum of LYG-G2/G3 and may actually correspond to IgG4-related disease

Lymphomatoid granulomatosis
Take home messages

- **LYS is a T-cell rich, large B-cell lymphoma (grade 2 & 3)**

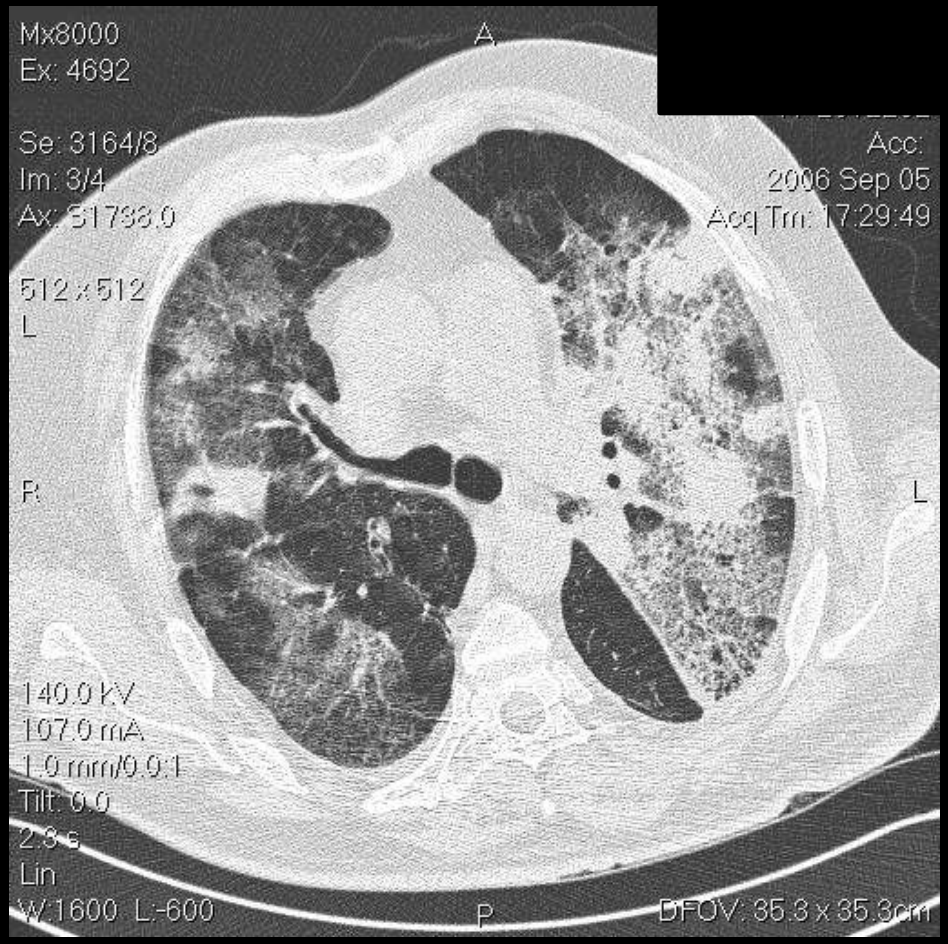
- **Histologic grading is based on the number of EBV+ large B-cells x high-power-field**

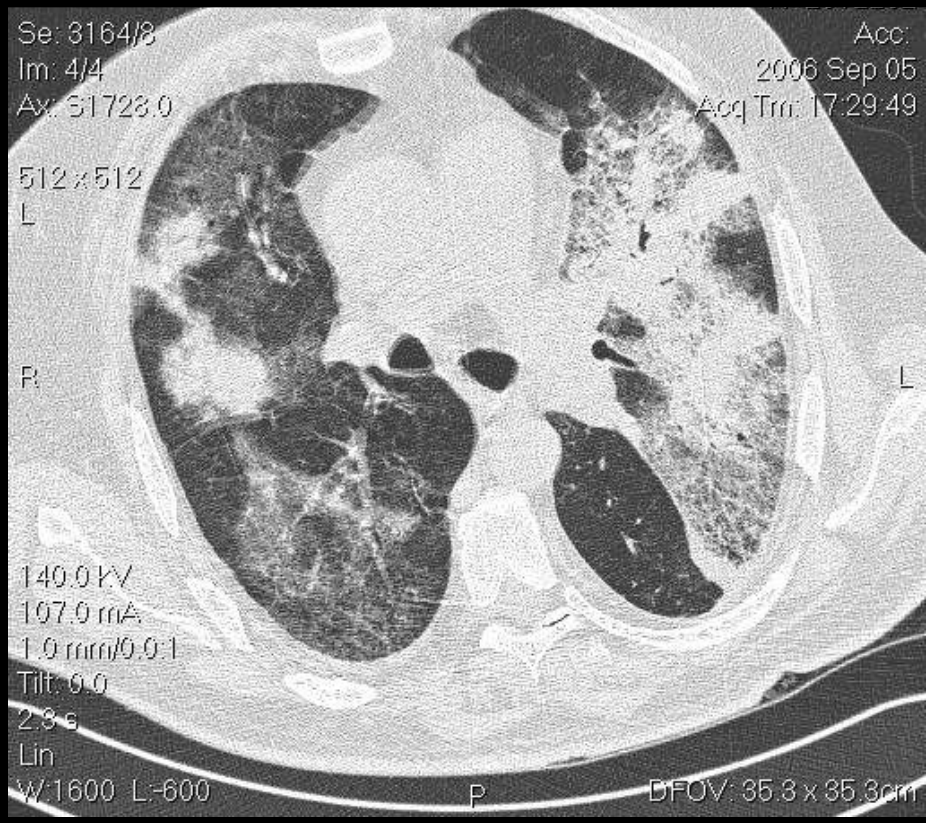
G1= < 5 / G2= 5-20 / G3= >20

- **Grade 1 might be an other entity (IgG4 related disorder) and may spontaneously regress**

Colby TV, Mod Pathol 2012

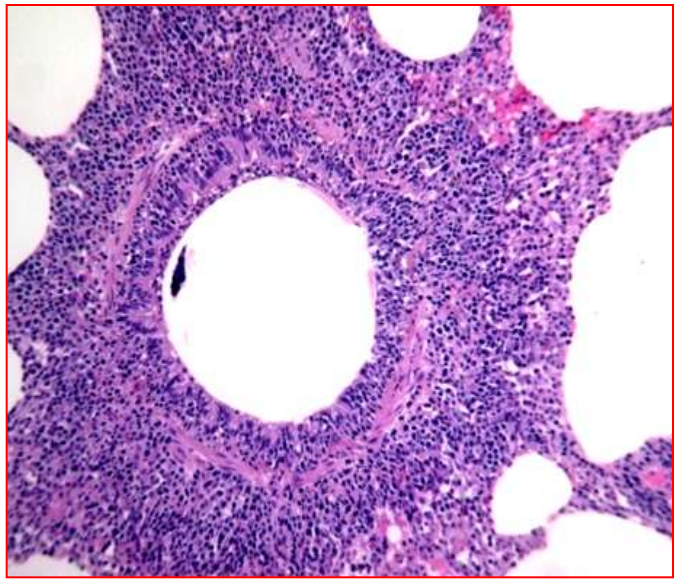
58 y/o male;acute respiratory failure, hemophagocytic syndrome

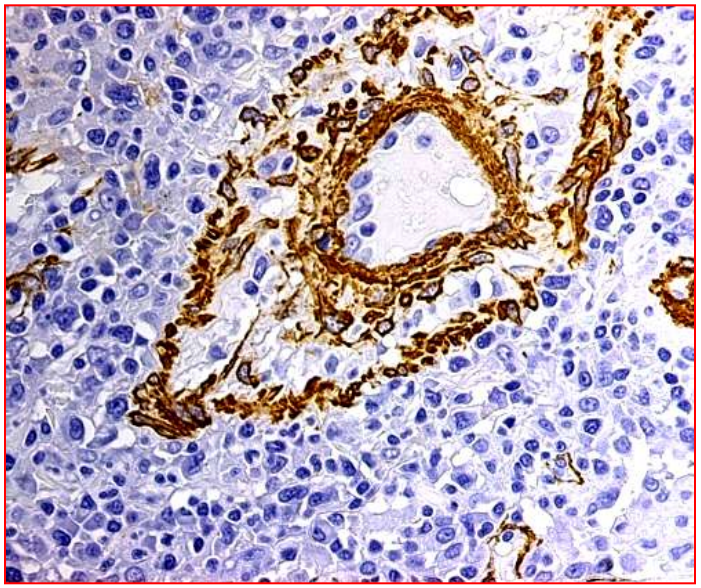


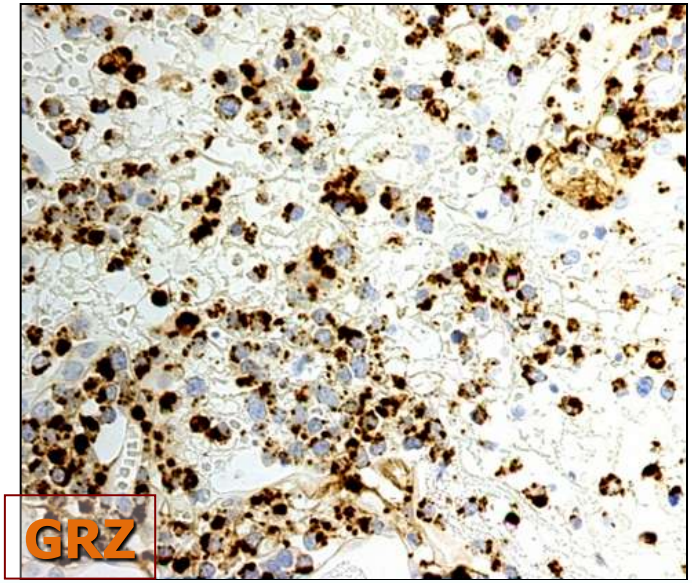


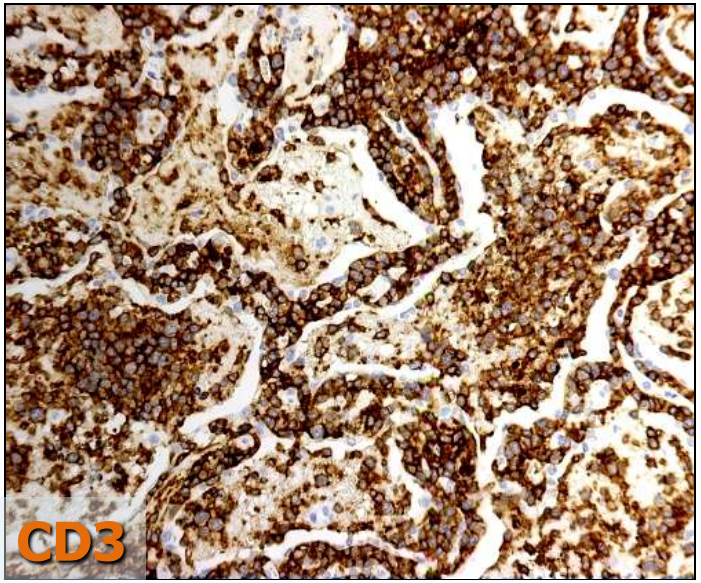
#98-1074 #IST 98-5672A F.S. Coinvolgimento polmonare; linfocitopenia

Caso 1

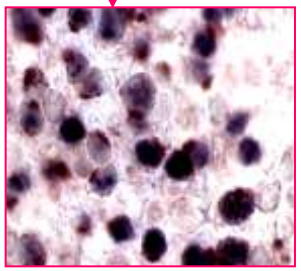




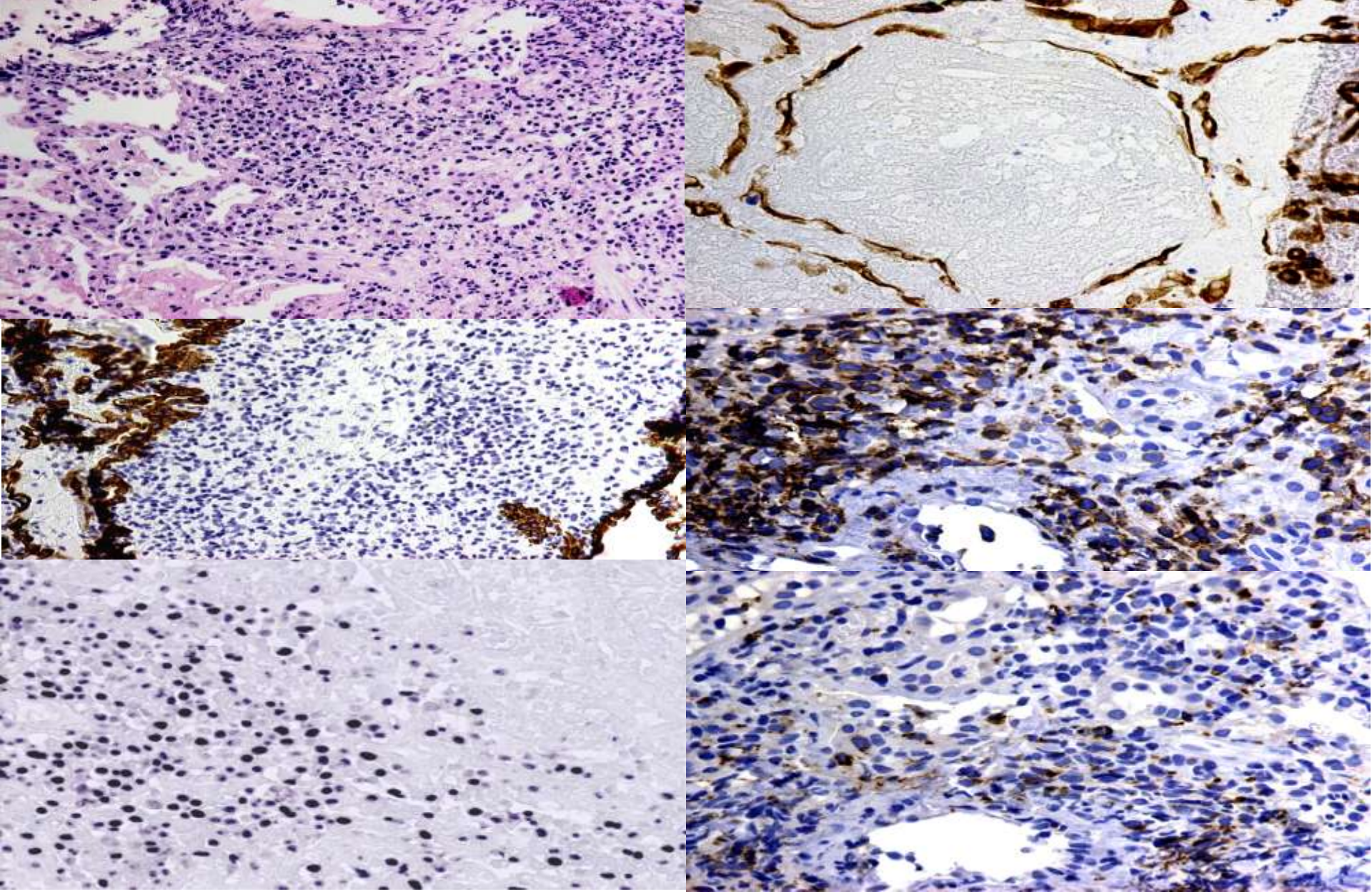




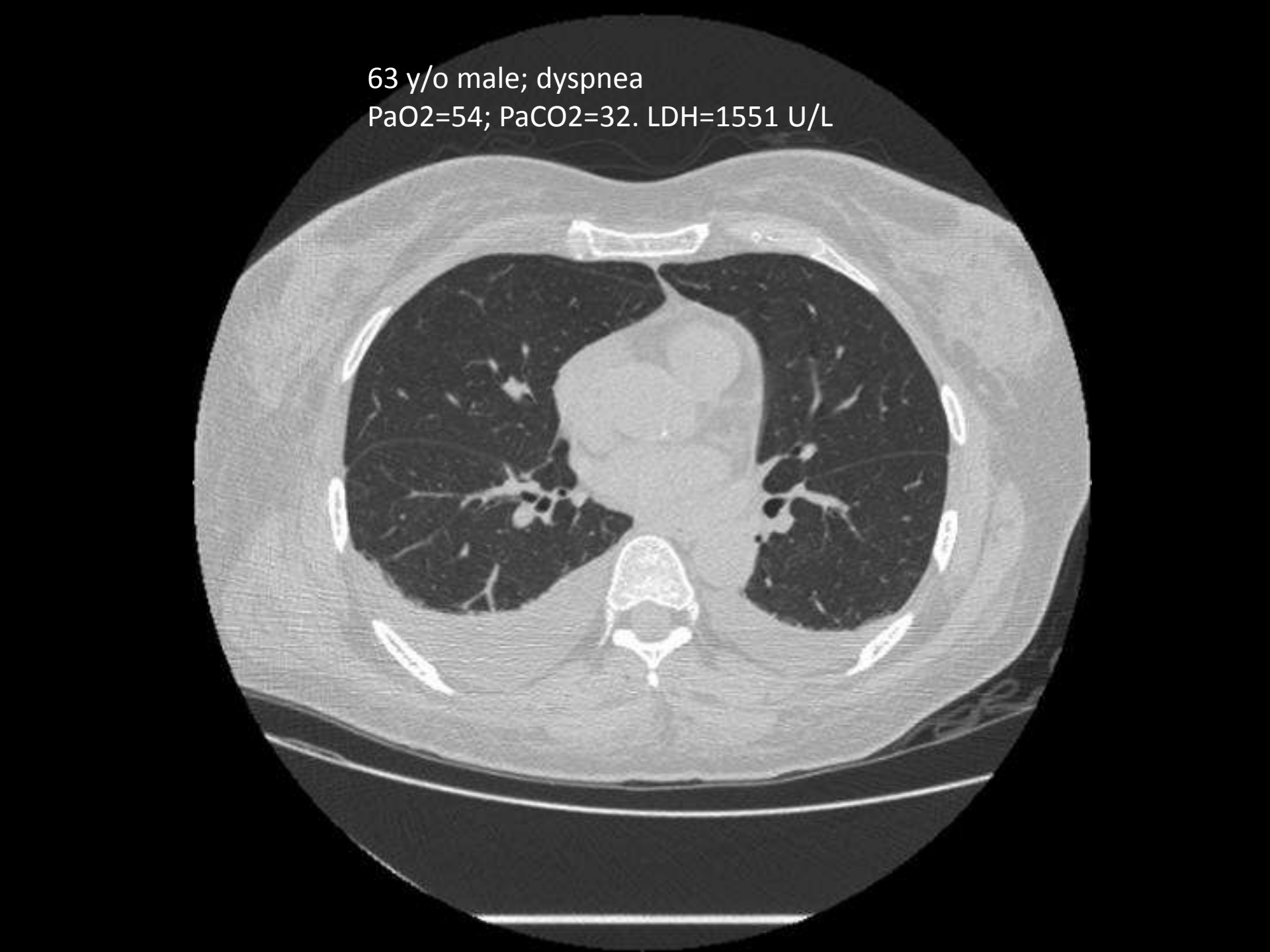
CD3+
CD5-
CD4-
CD8-
CD16-
CD30-/+
CD56-
CD57-
GRZ++
Ki67>80%
P53-
TCR$\alpha\beta$-
TCR$\gamma\delta$+
EBER++

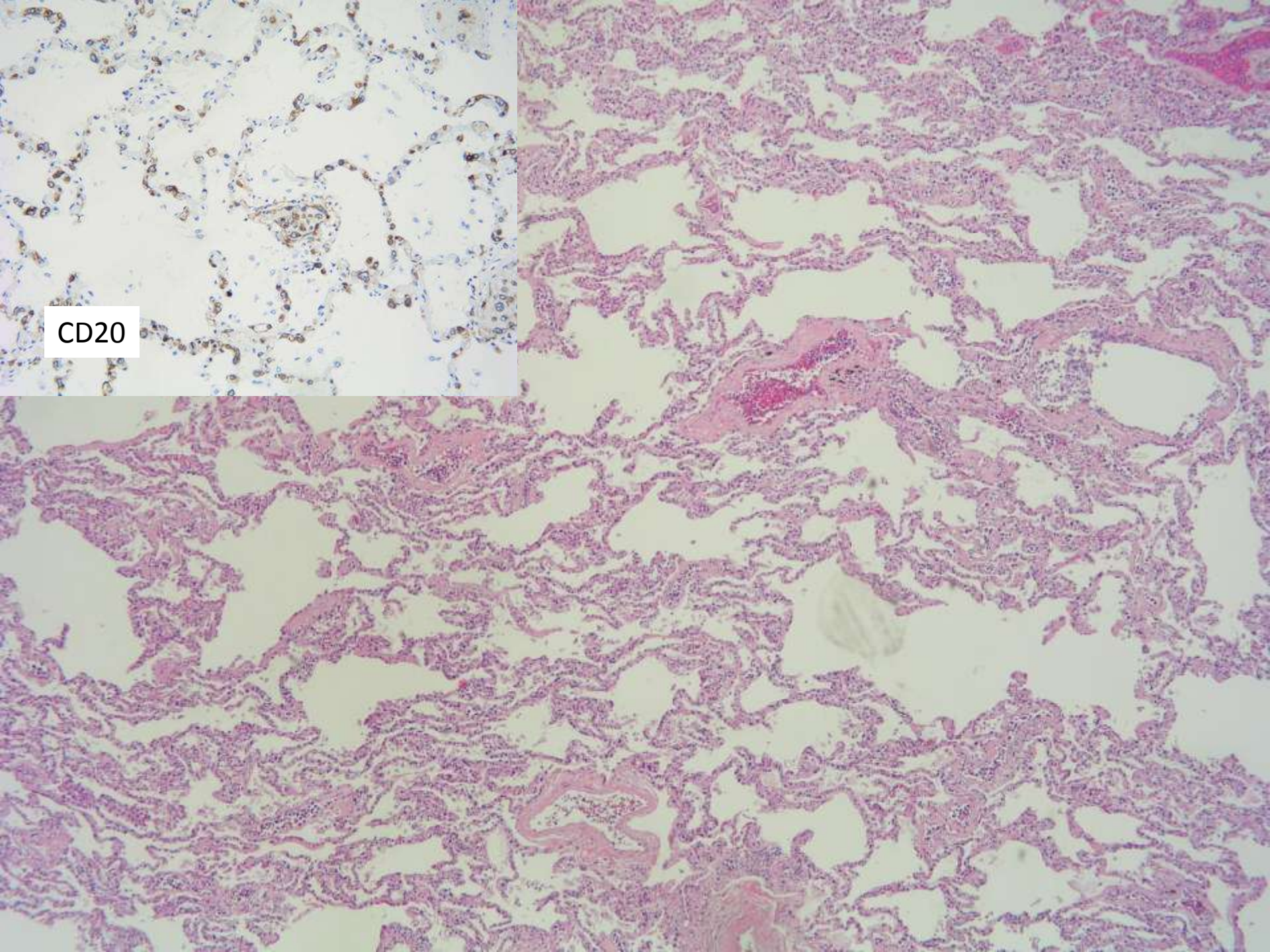


Pulmonary, angiocentric, nasal type lymphoma, T/NK



Transbronchial biopsy from a patient with **pulmonary T-cell lymphoma, nasal type**. The precise diagnosis was obtained on scarce material by demonstrating a large lymphoid infiltrate characterised by a T-cell, cytotoxic immunophenotype with evidence of EBV infection cells and extensive necrosis. E&E (a), cytokeratin 8/18 (b,c), CD3 (d), EBER (e), granzyme (f).


63 y/o male; dyspnea
PaO2=54; PaCO2=32. LDH=1551 U/L


CD20

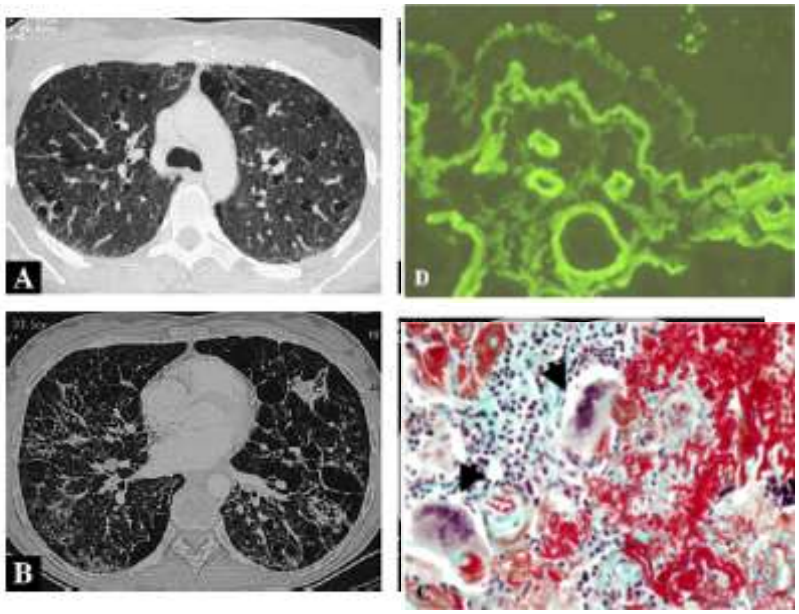
Case Report

Pulmonary Cystic Disorder Related to Light Chain Deposition Disease

Magali Colombat, Marc Stern, Odile Groussard, Dominique Droz, Michel Brauner, Dominique Valeyre, Hervé Mal, Camille Taillé, Isabelle Monnet, Michel Fournier, Serge Herson, and Claire Danel

Service d'Anatomie Pathologique and Service de Pneumologie–Hôpital Beaujon, Clichy; Service de Pneumologie–Hôpital Foch, Suresnes; Service d'Anatomie Pathologique–Hôpital Saint-Louis, Service de Médecine Interne–Groupe Hospitalier Pitié-Salpétrière, and Service d'Anatomie Pathologique–Hôpital Européen Georges Pompidou, Paris; Service de Radiologie and Service de Pneumologie–Hôpital Avicenne, Bobigny; and Service de Pneumologie–Hôpital Intercommunal, Créteil, France

Light chain deposition disease (LCDD) is a rare disorder that very uncommonly affects the lung. We report three cases of severe cystic pulmonary LCDD leading to lung transplantation. Such a presentation has never been previously reported. The three patients present with a progressive obstructive pulmonary pattern associated with numerous cysts diffusely distributed in both lungs. The disease was histologically characterized by non–amyloid amorphous deposits in the alveolar walls, the small airways and the vessels. It was associated with emphysematous-like changes and small airway dilation. Monotypic κ light chain fixation was demonstrated on the abnormal deposits and along the basement membranes. Electron microscopy revealed coarsely granular electron-dense deposits in the same localizations. Mild extrapulmonary deposits were found in salivary glands in one patient. No immunoproliferative disorder was identified. We conclude that LCDD may primarily affect the lung, present as a pulmonary cystic disorder, and lead to severe respiratory insufficiency.



Drugs (immunosuppressive) and lymphoproliferative disorders

Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
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Mod Rheumatol, 2014; Early Online: 1–3

DOI: 10.3109/14397595.2013.878016

informa
healthcare

ORIGINAL ARTICLE

Clinical characteristics and incidence of methotrexate-related lymphoproliferative disorders of patients with rheumatoid arthritis

Yuji Yoshida[1], Yuko Takahashi[2], Hiroyuki Yamashita[2], Toshikazu Kano[2], Hiroshi Kaneko[2], and Akio Mimori[2]

Table 3. Characteristics of the patients with MTX-LPDs.

Patient no.	Sex	Age	RA duration (years)	MTX duration (years)	Total dosage of MTX (mg)	Biologics	Pathology status	EBER	Prognosis
1	M	77	6.6	5.3	1772	None	DLBCL	–	CR
2	F	54	6.0	4.3	1970	ETN	HL	+	PR→CT
3	F	72	5.5	2.4	671	Non	T-cell	+	No change→OP
4	F	71	0.8	0.5	155	TCZ	DLBCL	–	No change→CT

CR, complete remission; PR, partial remission; CT, chemotherapy; OP, operation; EBER, Epstein-Barr virus-encoded RNA; ETN, etanercept; TCZ, tocilizumab

The Journal of Rheumatology Volume 34, no. 2

Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication.

Yoshihiko Hoshida, Jing-Xian Xu, Shigeki Fujita, Itsuko Nakamichi, Jun-Ichiro Ikeda, Yasuhiko Tomita, Shin-Ichi Nakatsuka, Jun-Ichi Tamaru, Atsushi Iizuka, Tsutomu Takeuchi and Katsuyuki Aozasa

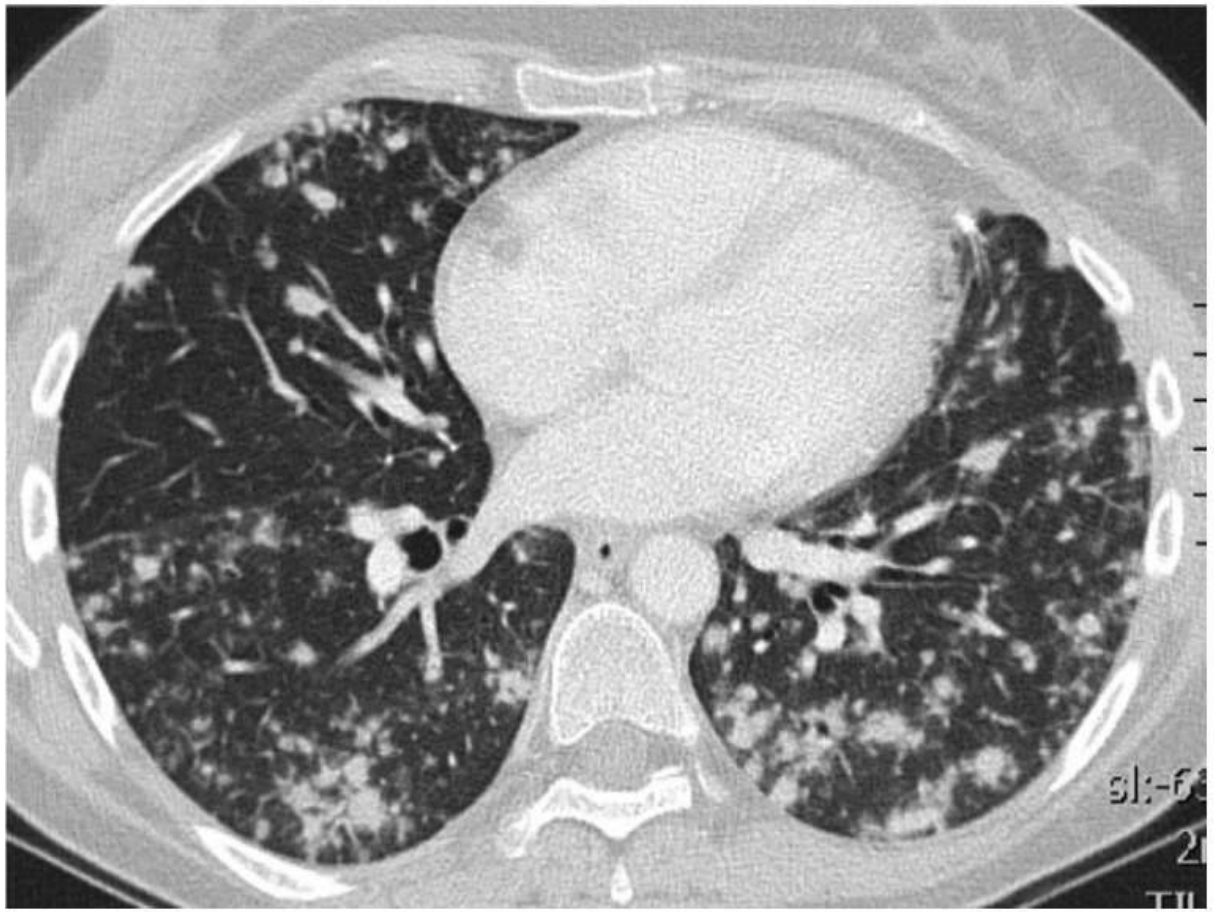
J Rheumatol 2007;34;322-331

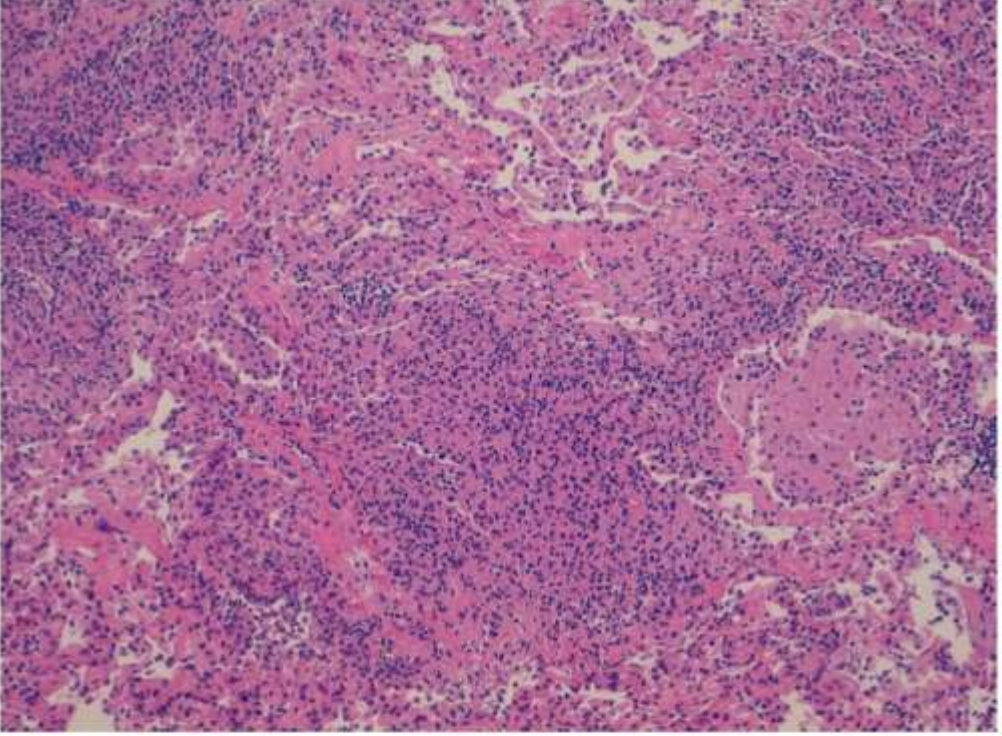
Table 2. Histologic classification of MTX-LPD and non-MTX-LPD.

	MTX-LPD (%)	Non-MTX-LPD (%)	RA (%)	Sporadic LPD (%)
Total	48	28	76	150
B cell LPD	38 (79.2)	22 (78.6)	60 (78.9)	111 (74.0)
DLBCL	29 (60.4)	15 (53.6)	44 (57.9) *	64 (42.7) *
Follicular lymphoma	3	2	5	23
Lymphoplasmacytic	2	0	2	4
Plasmacytoma	0	2	2	1
Mantle cell lymphoma	0	1	1	3
Diffuse polymorphic	2	1	3	0
HL-like LPD	1	0	1	0
Others	1	1	2	16
T cell LPD	3 (6.3)	4 (14.3)	7 (9.2)	16 (10.7)
Natural killer/T cell LPD	1 (2.1)	0 (0)	1 (1.3)	6 (4.0)
HL	6 (12.5)	2 (7.1)	8 (10.5)	16 (10.7)

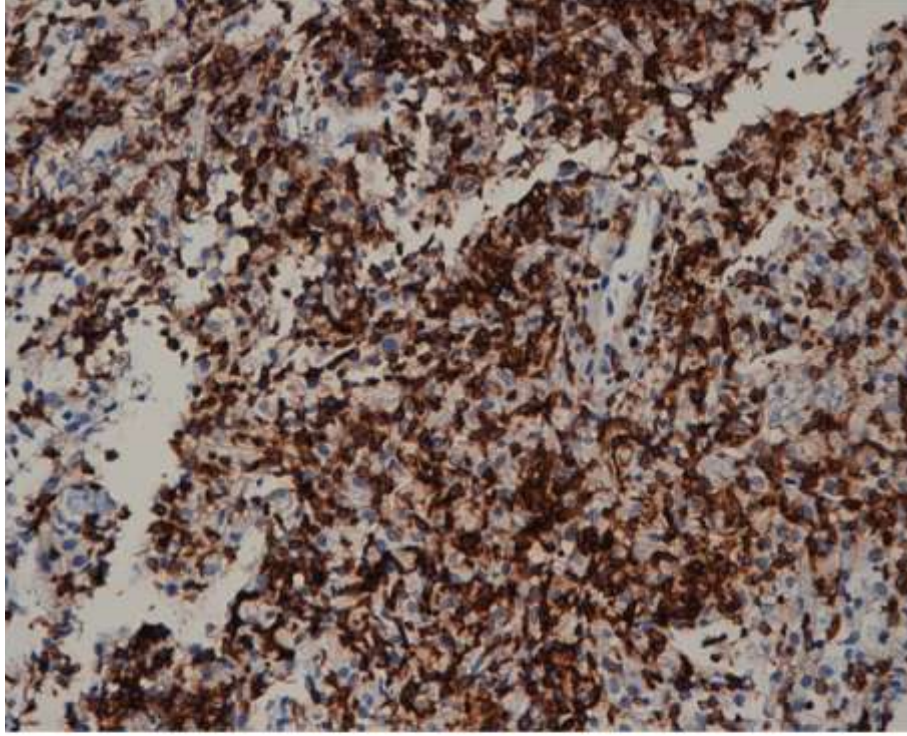
MTX: methotrexate, DLBCL: diffuse large B cell lymphoma, HL: Hodgkin's lymphoma. * $p < 0.05$.

32 female under treatment with natalizumab for multiple sclerosis
Asthenia , SOB





H&E



CD3

CD4 (EBER--)

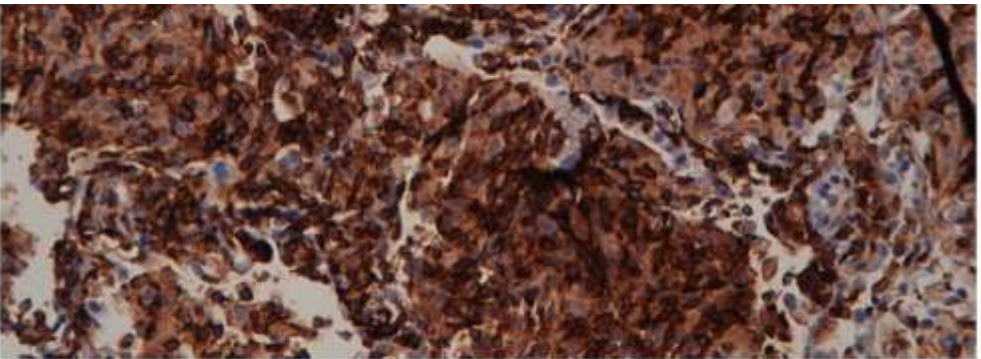


TABLE 3 Summary of the computed tomography features in the malignant spectrum of pulmonary lymphoproliferative disorders

Lymphoproliferative lung disorders	Computed tomography features
MALT lymphoma	Nodules or consolidation Peribronchovascular Multiple/bilateral (70%) Hilar/mediastinal nodes (30%) Ground-glass attenuation (halo sign) Rarely cysts, pleural effusion, tree-in-bud
High-grade primary large pulmonary B-cell lymphomas	Nodule or mass cavitation in 50% Rarely pleural effusion
Lymphomatoid granulomatosis	Bilateral nodules/masses Peribronchovascular Coalescence and/or cavitate Pleural effusion (30%) Hilar adenopathies (<25%) Migratory Uncommon: single nodules, alveolar opacities and reticulonodular diffuse lesions
Follicular lymphoma	Ground-glass opacities (crazy paving) Nodules
Intravascular large B-cell lymphoma	Bilateral reticular shadows Reticulonodular or nodular shadows Ground-glass opacities Wedge-shaped subpleural opacities Pleural effusion
Nasal-type T-/NK-lymphomas	Nodules or excavated masses Pleural effusion
Anaplastic large cell lymphoma, T-cell type	Masses or single nodules
Mycosis fungoides	Nodules with halo signs Peripheral consolidation Crazy paving pattern
Primary pulmonary Hodgkin disease	Solitary mass or multinodular disease Air bronchograms or cavitation Pleural effusion, lymphadenopathy

MALT: mucosa-associated lymphoid tissue; NK: natural killer cell.

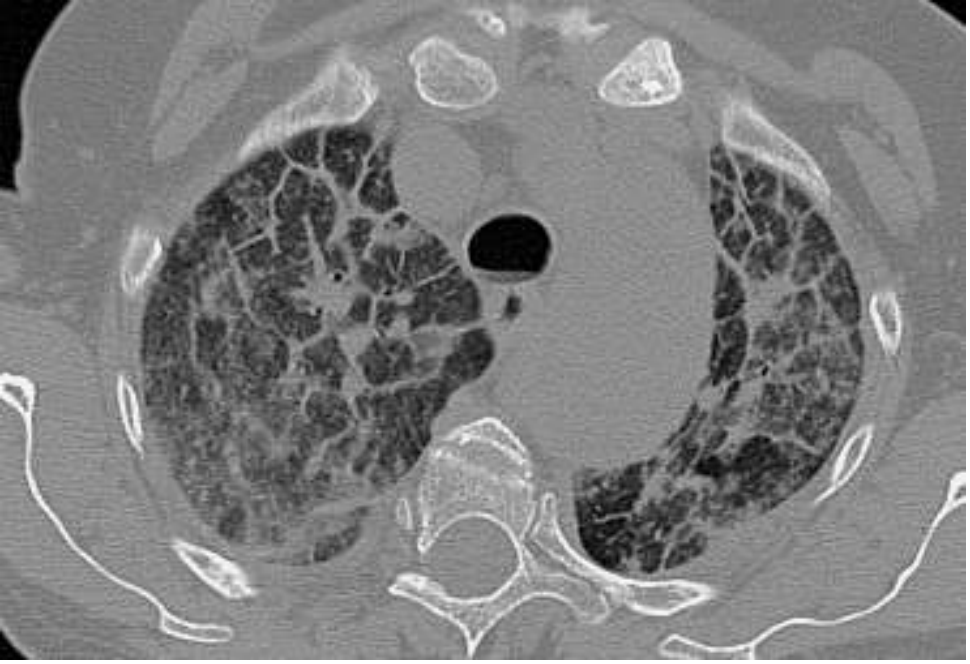
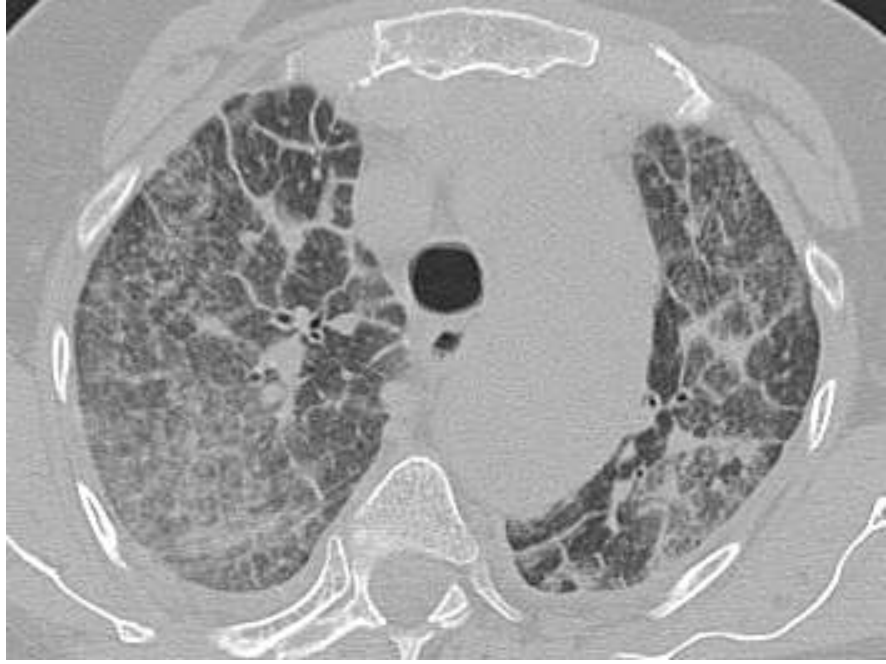
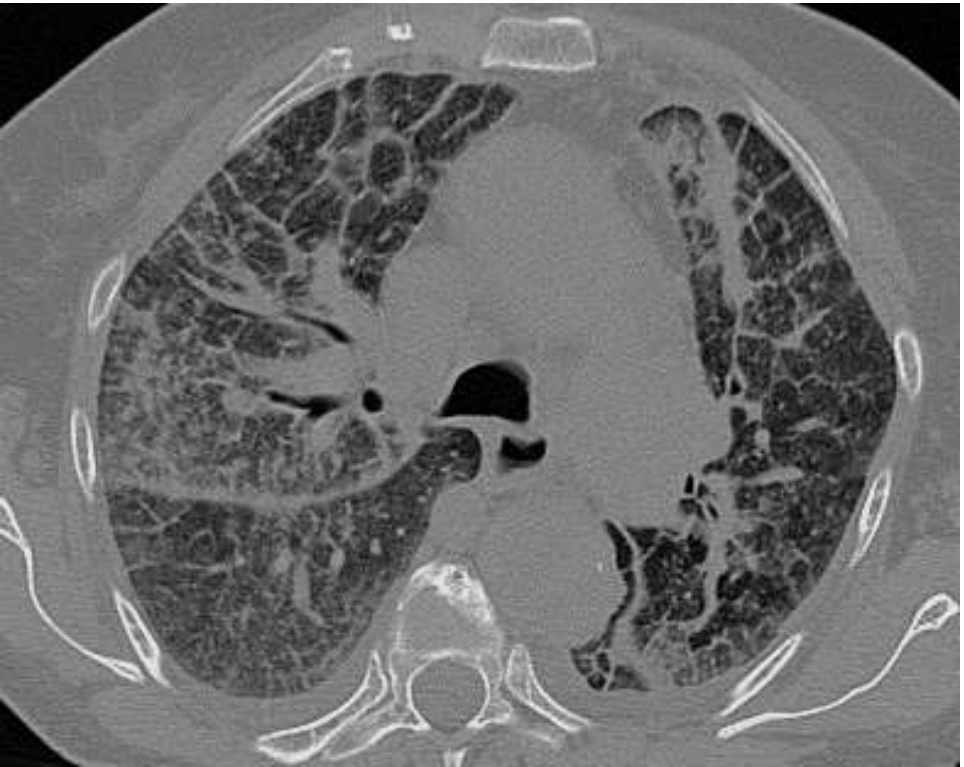
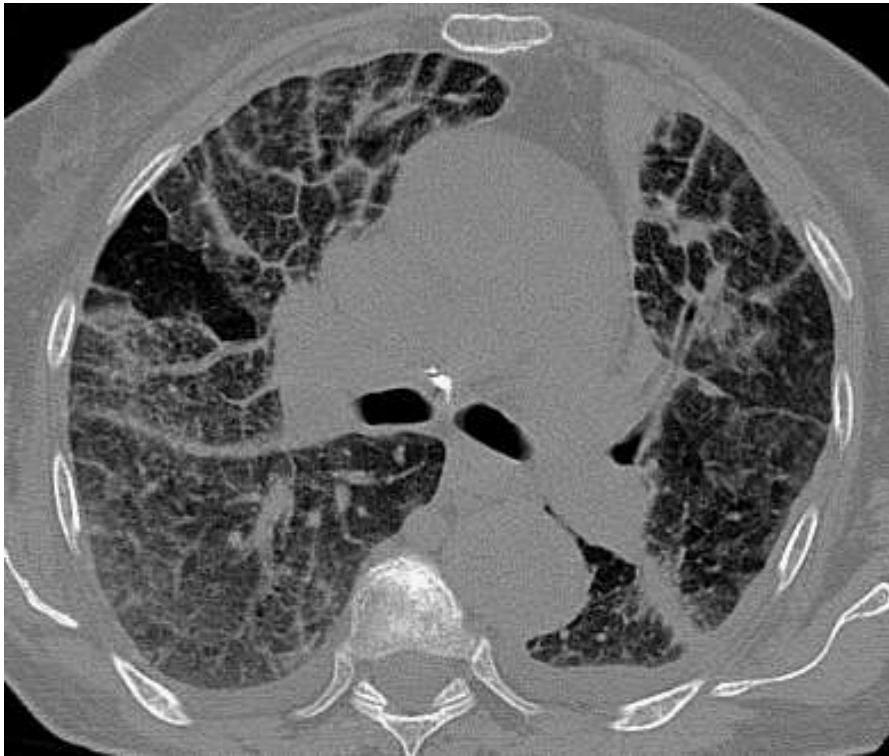
TABLE 2 Clinical profile and laboratory syndromes: red flags for clinicians

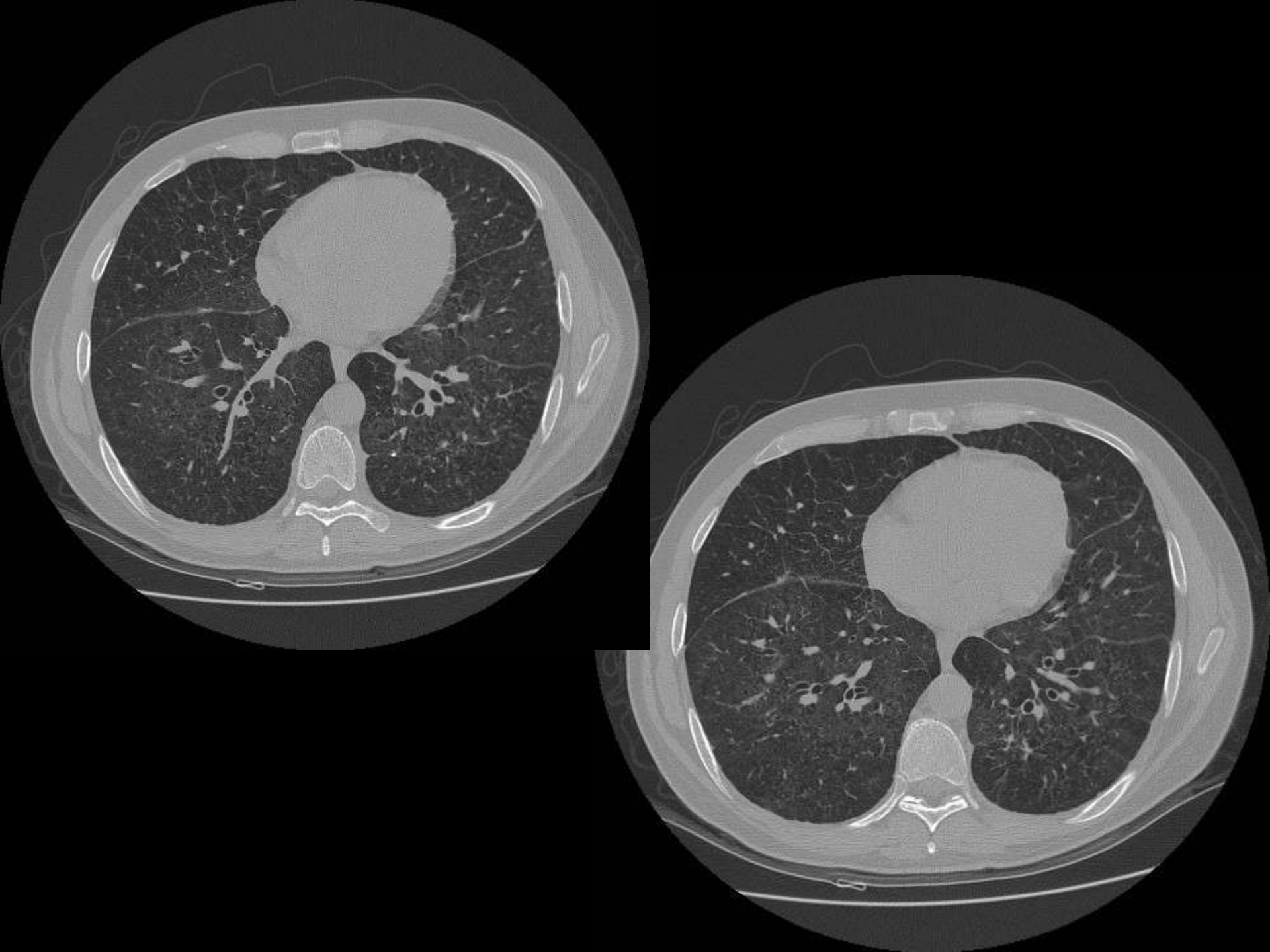
Asymptomatic lesions	MALT lymphoma
Serum para-proteins and/or increased LDH	
Collagen-vascular disease	MALT lymphoma in collagen-vascular disorders (*e.g.* Sjögren)
Immunodeficiency	Lymphomatoid granulomatosis in HIV
	Lymphomatoid granulomatosis in Wiskott–Aldrich syndrome
Transplantation	Post-transplant lymphoproliferative processes
Respiratory symptoms	T-cell lymphomas
Lymphopenia and/or eosinophilia	Granulomatous mycosis fungoides
	Hodgkin lymphoma
Thromboembolism	Intravascular lymphoma
Acute pulmonary hypertension-like onset	
Increased LDH and/or hypercalcaemia	
Haemophagocytic syndrome[#]	NK-/T-cell lymphoma, nasal type
	T-cell lymphoma
Organising pneumonia	Hodgkin lymphoma
	Lymphomatoid granulomatosis
Treatment with methotrexate, natalizumab or other drugs	Atypical lymphoproliferative processes

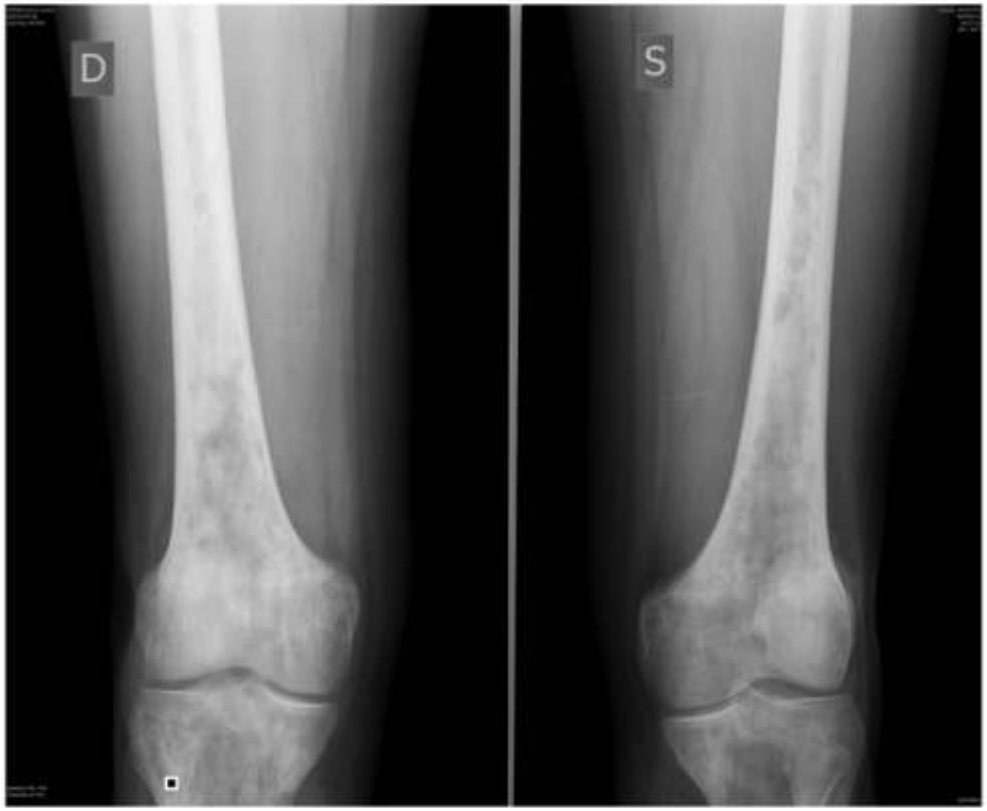
MALT: mucosa-associated lymphoid tissue; LDH: lactate dehydrogenase; NK: natural killer cell. [#]: abrupt onset, increased triglycerides, increased ferritin, coagulation abnormalities, increased transaminases, and decreased fibrinogen and cytopenia/pancytopenia.

LYMPHOMAS, PRIMARY IN THE LUNGS: DIFFERENTIAL DIAGNOSIS

- Unresolving “pneumonia”
- Lung Tumors
- Organizing pneumonia (cryptogenic)
- Vasculitis
- Carcinomatous Lymphangitis
- Neoplastic thrombotic microangiopathy
- ILDs (sarcoid, LIP, …….)
- Metastatic tumors (lung cysts):carcinomas, sarcomas, LAM, ……)
- Rare entities (Erdheim Chester Disease, ….)
- ……..

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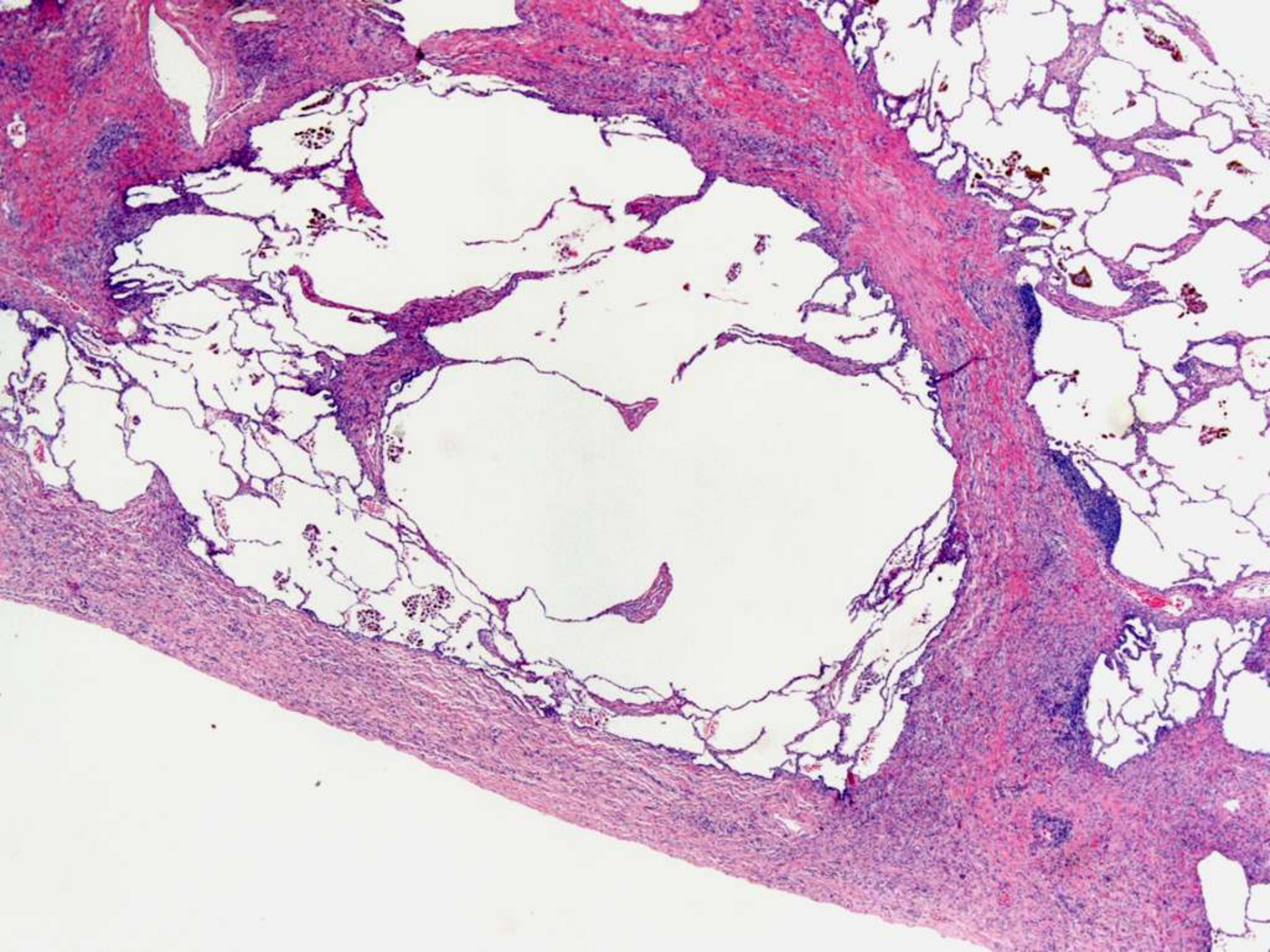
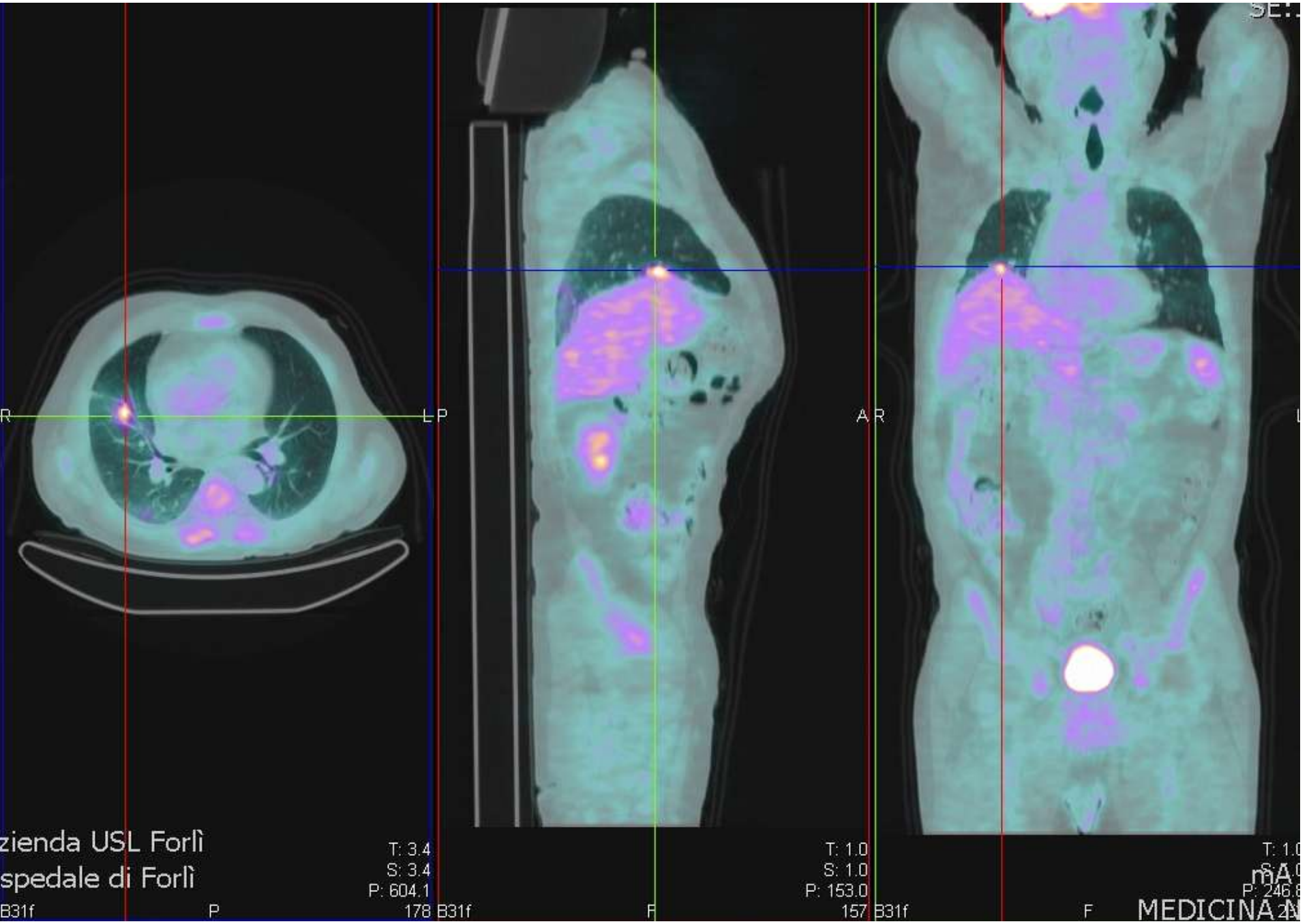


MORPHOLOGIC DIAGNOSIS OF LYMPHOPROLIFERATIVE DISORDERS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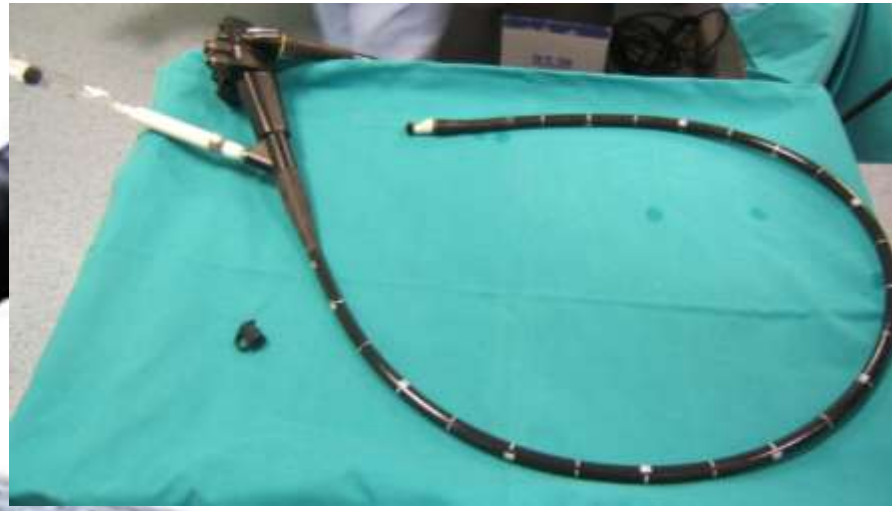
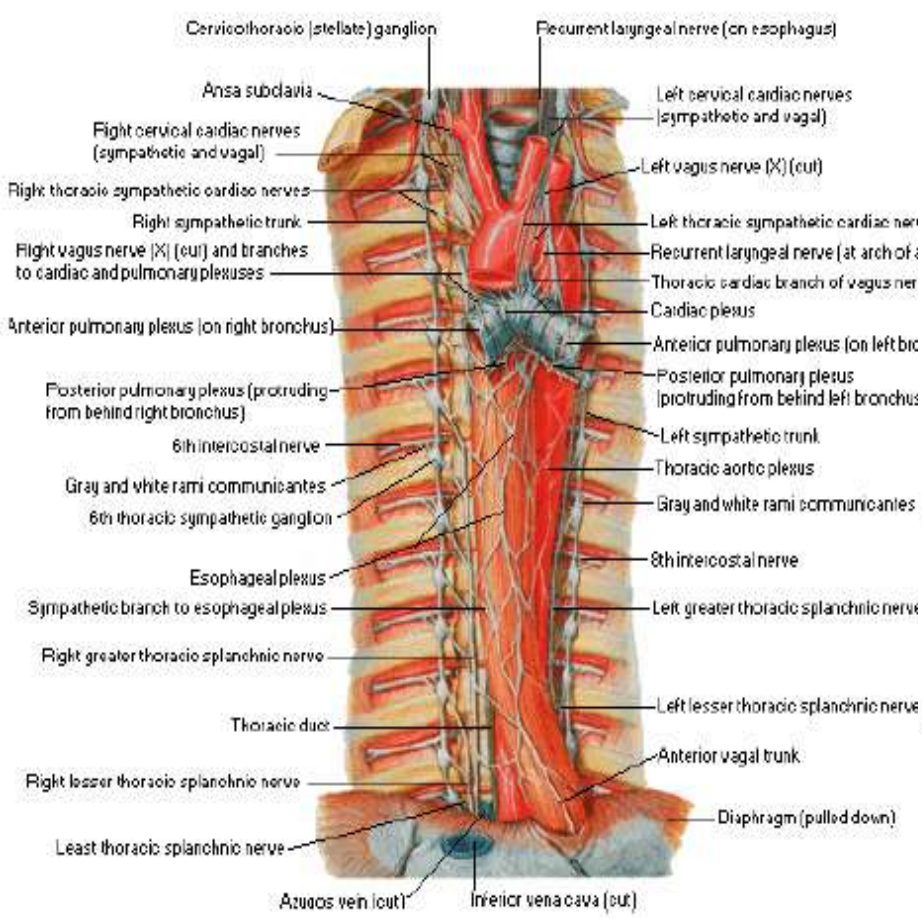
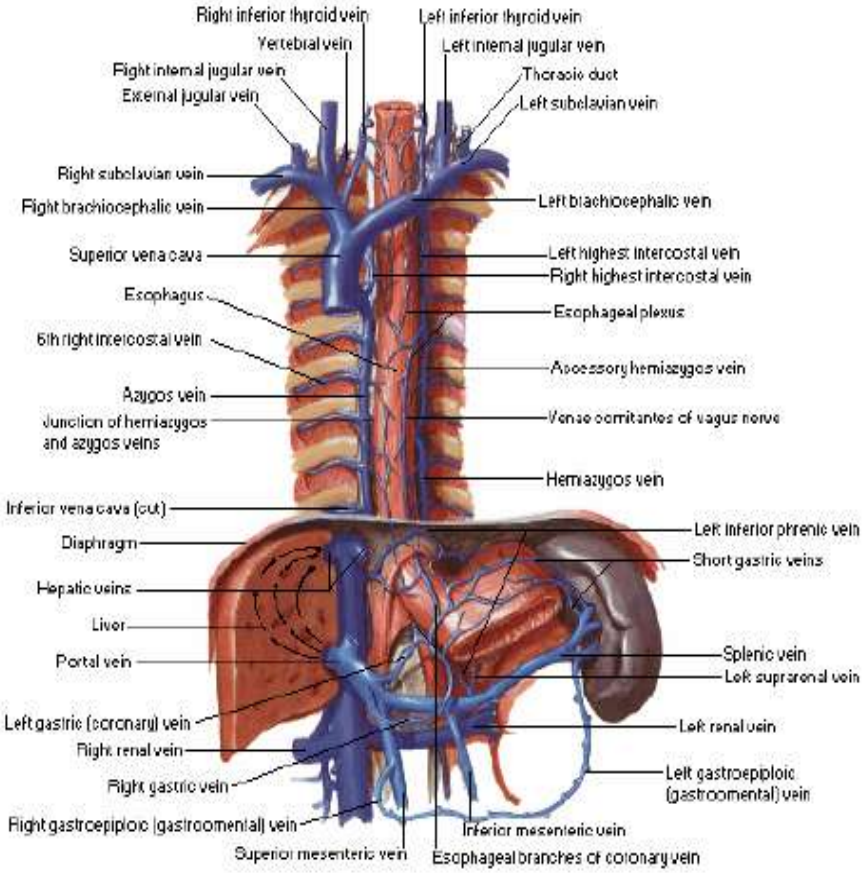
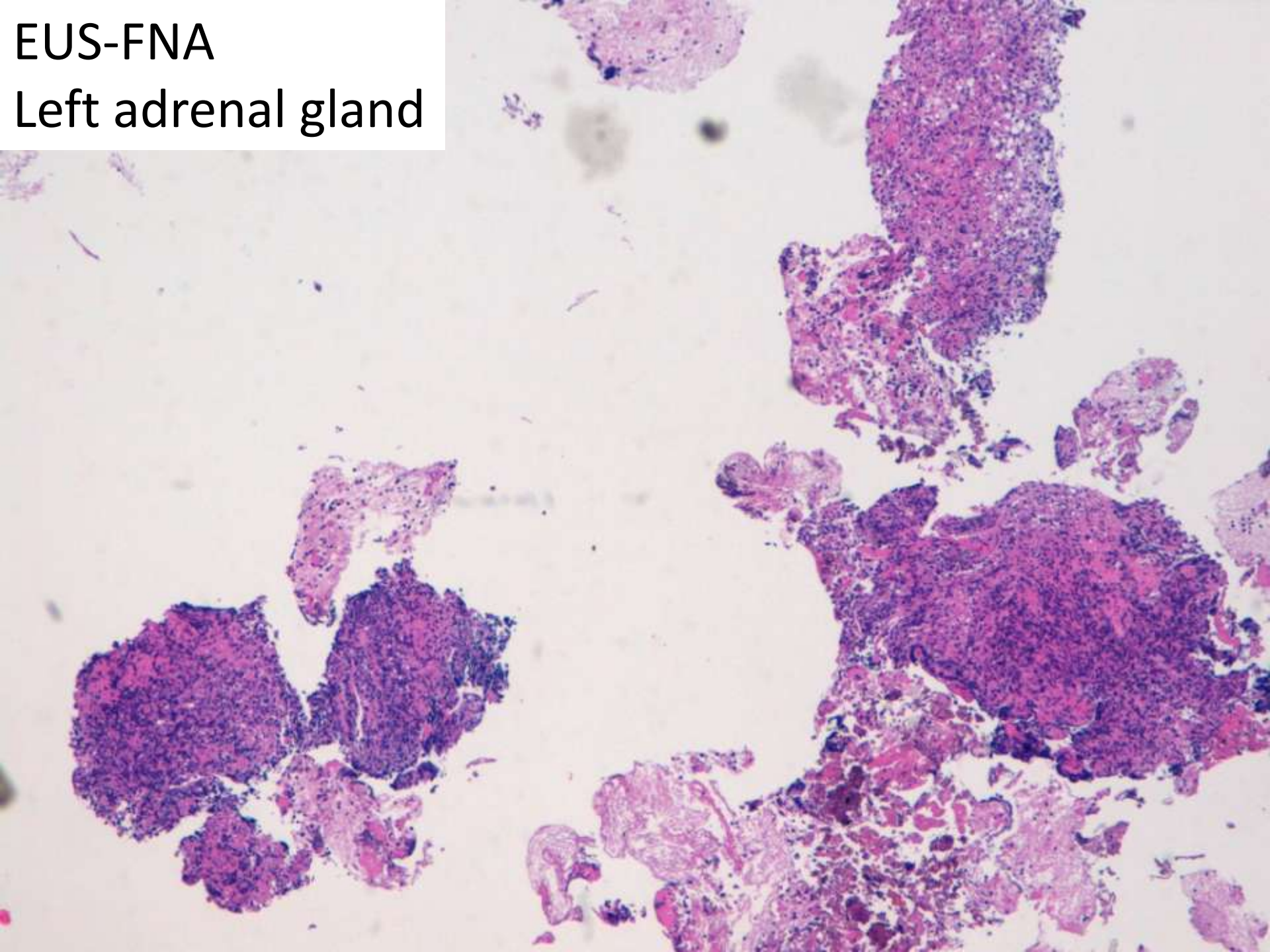


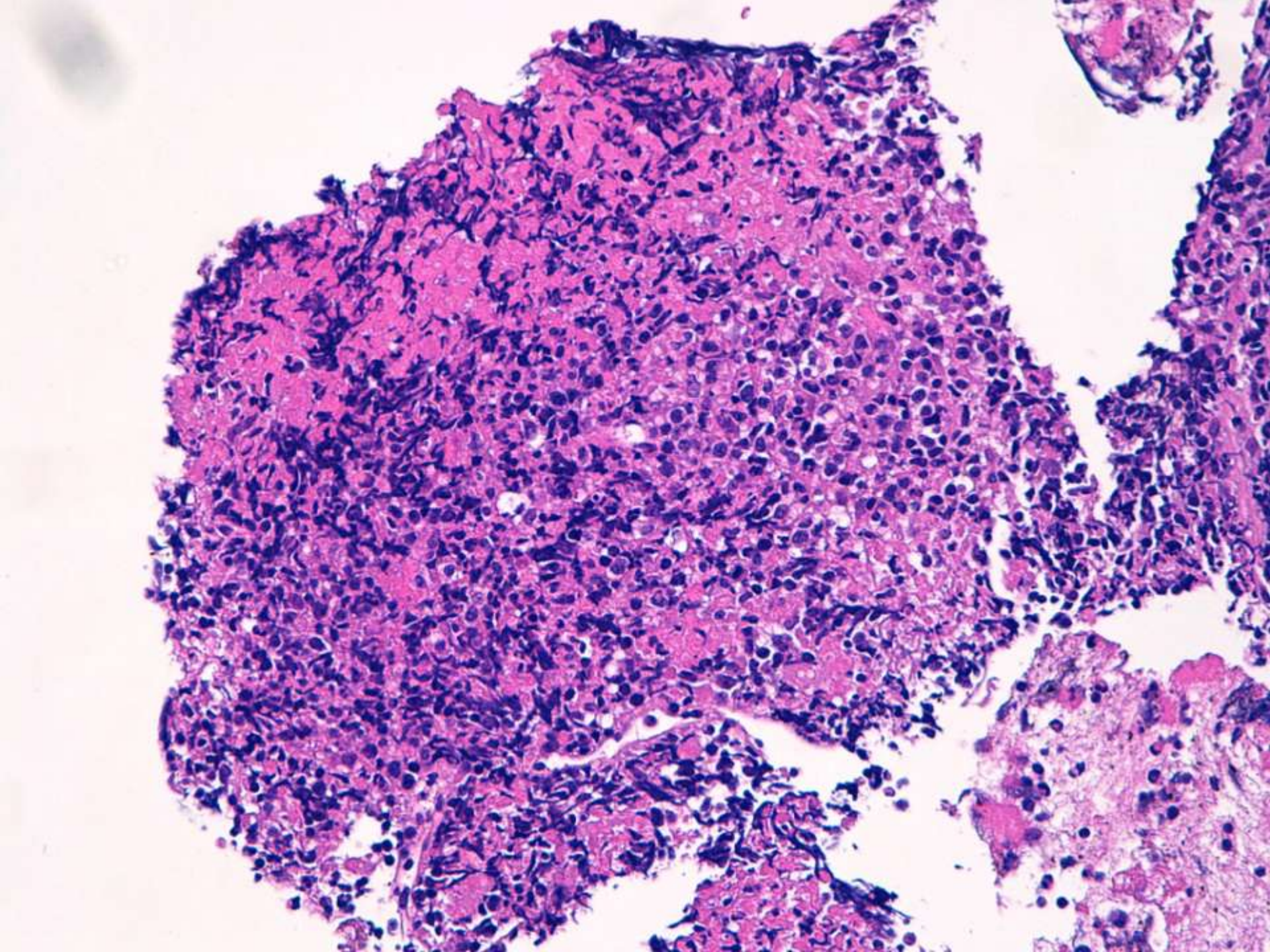
EUS: Olympus


Cervicothoracic (stellate) ganglion
Recurrent laryngeal nerve (on esophagus)
Ansa subclavia
Left cervical cardiac nerves (sympathetic and vagal)
Right cervical cardiac nerves (sympathetic and vagal)
Left vagus nerve (X) (cut)
Right thoracic sympathetic cardiac nerves
Right sympathetic trunk
Left thoracic sympathetic cardiac ner
Right vagus nerve (X) (cut) and branches to cardiac and pulmonary plexuses
Recurrent laryngeal nerve (at arch of
Thoracic cardiac branch of vagus ner
Cardiac plexus
Anterior pulmonary plexus (on right bronchus)
Anterior pulmonary plexus (on left bro
Posterior pulmonary plexus (protruding from behind right bronchus)
Posterior pulmonary plexus (protruding from behind left bronchus
6th intercostal nerve
Left sympathetic trunk
Gray and white rami communicantes
Thoracic aortic plexus
6th thoracic sympathetic ganglion
Gray and white rami communicantes
8th intercostal nerve
Esophageal plexus
Sympathetic branch to esophageal plexus
Left greater thoracic splanchnic nerve
Right greater thoracic splanchnic nerve
Left lesser thoracic splanchnic nerve
Thoracic duct
Anterior vagal trunk
Right lesser thoracic splanchnic nerve
Diaphragm (pulled down)
Least thoracic splanchnic nerve
Azygos vein (cut)
Inferior vena cava (cut)


Right inferior thyroid vein
Left inferior thyroid vein
Vertebral vein
Left internal jugular vein
Right internal jugular vein
Thoracic duct
External jugular vein
Left subclavian vein
Right subclavian vein
Right brachiocephalic vein
Left brachiocephalic vein
Superior vena cava
Left highest intercostal vein
Right highest intercostal vein
Esophagus
Esophageal plexus
6th right intercostal vein
Accessory hemiazygos vein
Azygos vein
Junction of hemiazygos and azygos veins
Venae comitantes of vagus nerve
Hemiazygos vein
Inferior vena cava (cut)
Left inferior phrenic vein
Diaphragm
Short gastric veins
Hepatic veins
Liver
Splenic vein
Portal vein
Left suprarenal vein
Left gastric (coronary) vein
Left renal vein
Right renal vein
Left gastroepiploic (gastroomental) vein
Right gastric vein
Right gastroepiploic (gastroomental) vein
Inferior mesenteric vein
Superior mesenteric vein
Esophageal branches of coronary vein

EUS-FNA
Left adrenal gland





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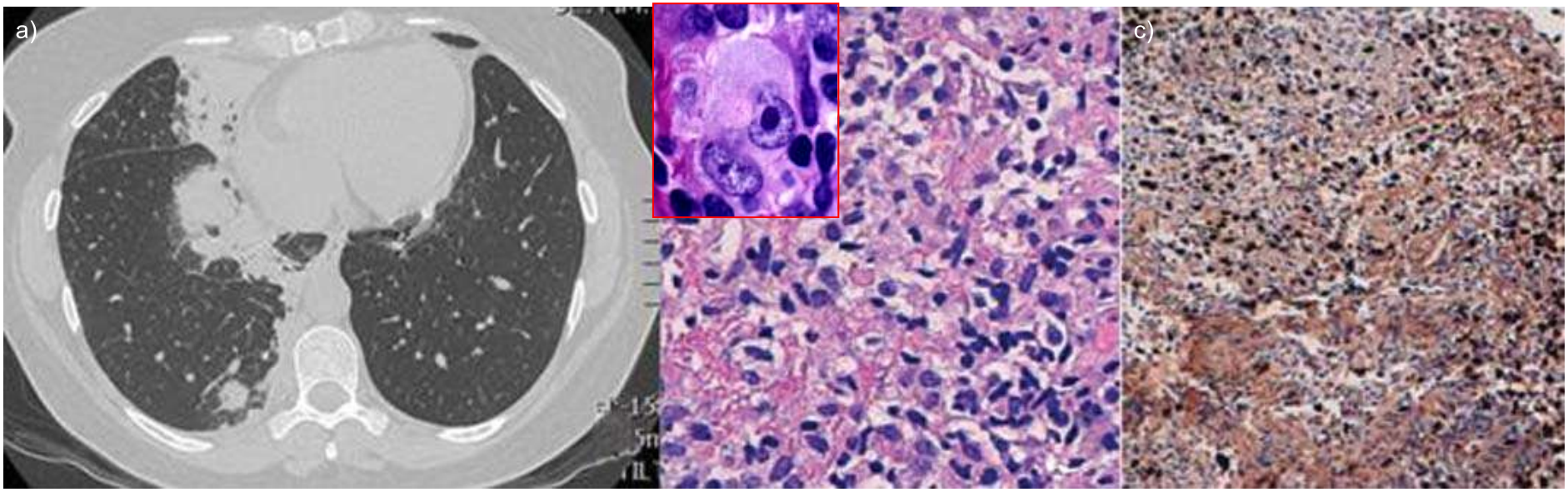
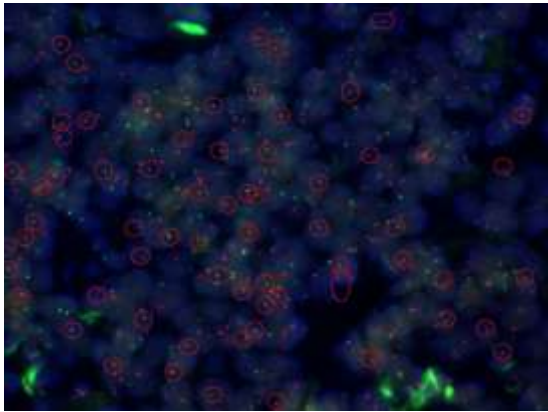
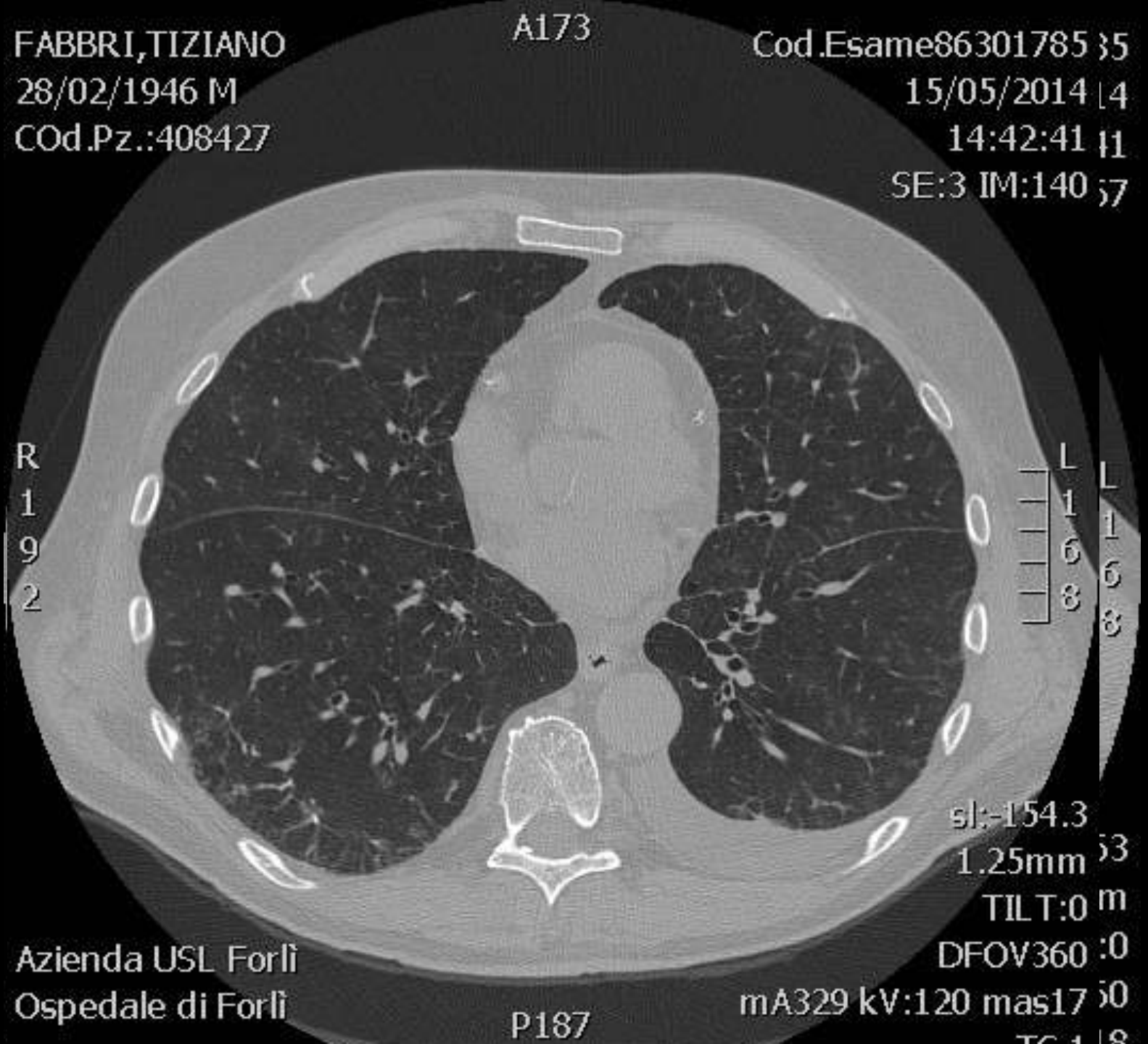


FIGURE 2 a) An axial multidetector computed tomography scan in a 43-year-old female, demonstrating consolidations with air bronchograms. b) Transbronchial biopsy of the consolidation revealed Hodgkin lymphoma. c) Immunophenotypic analysis revealed strong expression of activation markers (CD30).

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Ospedale di Forlì
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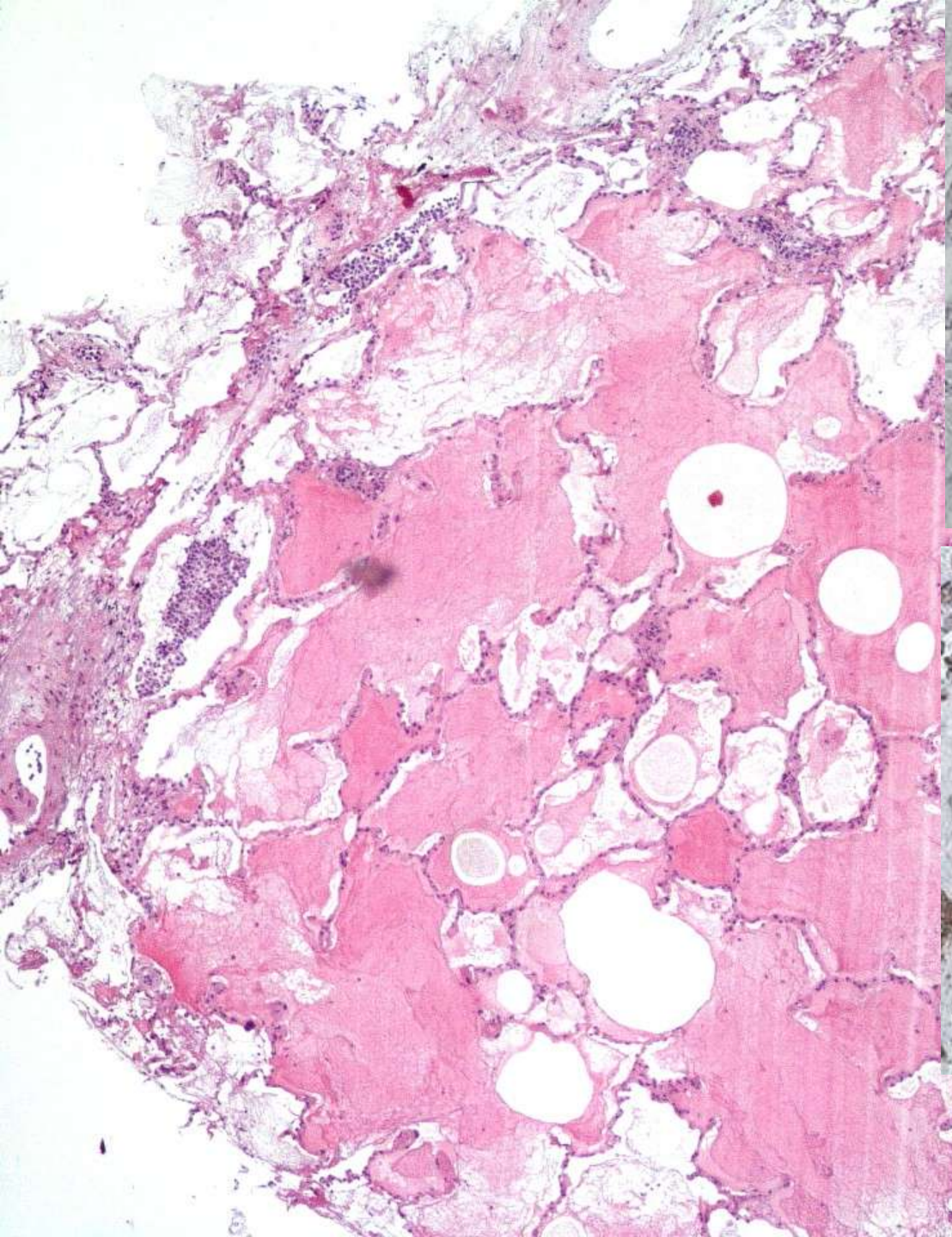

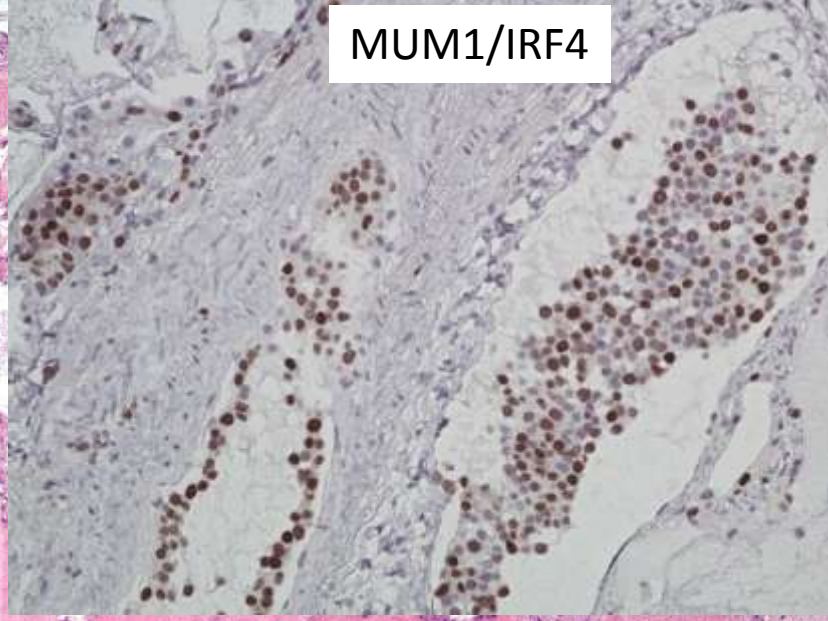
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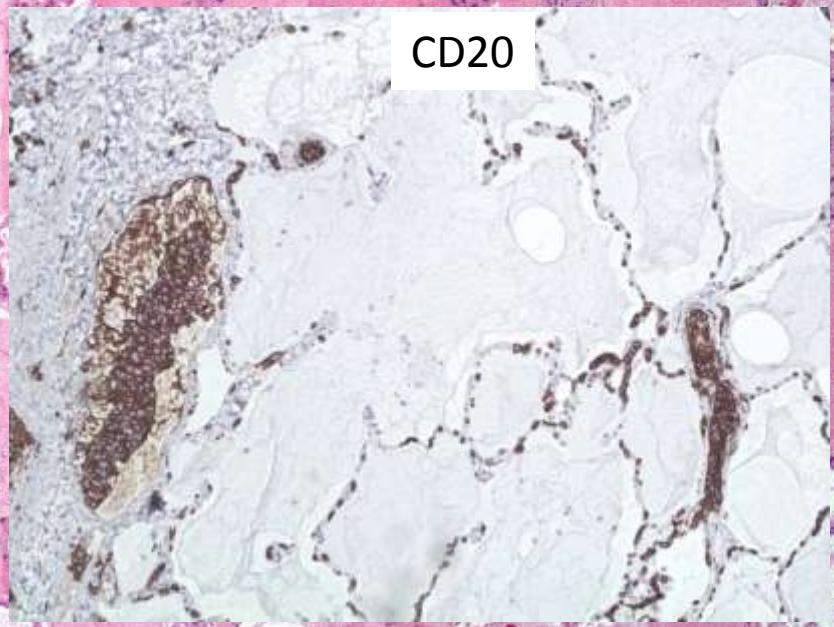
CD20

Haematologica 2008

Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

Pier Luigi Zinzani,[1] Maurizio Martelli,[2] Venerino Poletti,[3] Umberto Vitolo,[4] Paolo G. Gobbi,[5] Tommaso Chisesi,[6] Giovanni Barosi,[7] Andrés J.M. Ferreri,[8] Monia Marchetti,[7] Nicola Pimpinelli,[9] and Sante Tura[1]

The recommended first-line therapy includes anthracycline-based chemotherapy with CHOP or CHOP-like, MACOP-B or MACOP-B-like regimens (grade B).

Rituximab association with chemotherapy needs to be evaluated within approved clinical trials.

Response should be evaluated as for nodal DLBCL, including pulmonary function tests (grade D).