Common Variable Immunodeficiency - atypical presentation

SANTA MARIA HOSPITAL
LISBON
PORTUGAL

Sara Pereira da Silva,
Susana Lopes da Silva

Case report

- 63 years old
- Caucasian
- Woman

- Referred for

hypogammaglobulinemia

Case report

- **29 years old - Left supraclavicular lymphadenomegaly**
  - Histological examination – inconclusive (sarcoidosis?/tuberculosis?)
  - Treatment with antituberculous agents during 2 years
- **30 years old – allergic rhinosinusitis**
  - grass-polen sensitization
  - topical nasal corticosteroids and/or oral anti-H_1
  - < 1 episode/year

Case report

- 33 years old – easy bruising and petechial rash

THROMBOCYTOPENIA

- splenomegaly
- bone marrow aspiration and biopsy – normal

DIAG: IMMUNE THROMBOCYTOPENIC PURPURA

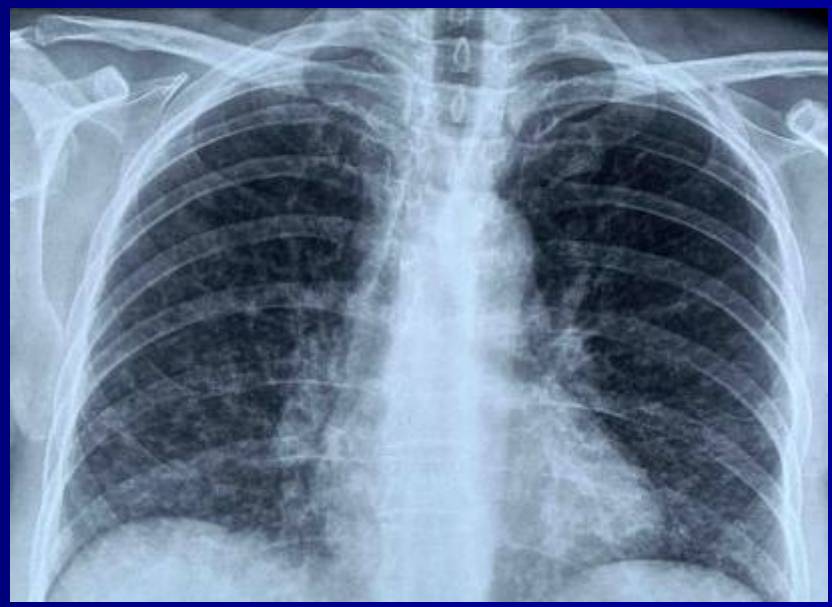
- treatment with prednisolone (dose?) during 2 years
- refused splenectomy

- continued prednisolone, intermitently untill 39 year old
- since 44 – normal and stable platelet count

Case report

- 62 years old - episode of acute rhinosinusitis ⇒ ENT evaluation

- proposal for sinus surgery



- pre-surgery evaluation

Chest Radiography: Reticulonodular opacities

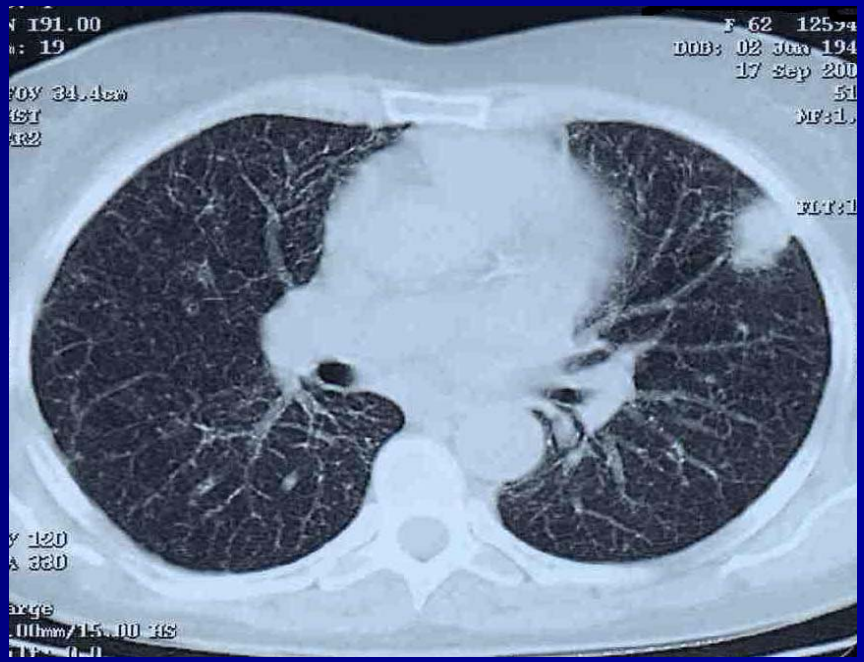
Referred to Pneumology

Case report

Pneumology

Chest CT

Reticular pattern with
multiple, diffuse nodules and
patchy ground glass opacification
in both lungs



Pulmonary Function Test

Discrete restrictive pattern (TLC – 83,2%)

Reduced diffusing capacity for carbon monoxide (DLco - 58%),
but normal when adjusted for lung volume (DL,co/VA – 87,3%)

Case report

Pneumology

Flexible broncoscopy

Endobronchial generalized inflammatory signs

Bronchoalveolar lavage (BAL)

- no infection or malignancy
- Cell count
  - Macrophages - 68% ↓ (74-98)
  - Lymphocytes - 23% ↑ (8-16)
  - Neutrophils - 9% ↑ (0-1,2)

  - CD_4 - 66% ↑ (37-53)
  - CD_8 - 26% (17-31)
  - CD_4/CD_8 - 2,5 ↑ (2)

Case report

Pneumology

Transbronchial Biopsy

"Interstitial inflammation and diffuse lymphoid infiltration with aggregates and lymphoid follicles, some with germinal centres"

A specific diagnosis was not possible

Open Lung Biopsy

"Dense interstitial lymphoid infiltrate with areas of interstitial fibrosis and lymphoid follicles. Alveolar septa extensively infiltrated, some with collapse of the air space."

Case report

Pneumology

- Diagnosis ???

  - during the investigation…

complaining of progressive fatigue

ORAL STEROIDS

(45 mg deflazacort/day – 3 months)

Case report

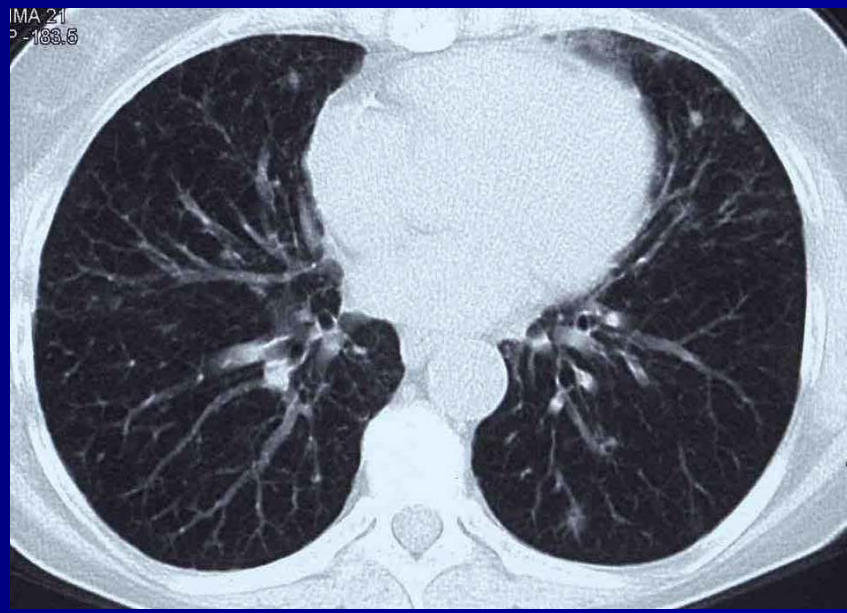
Pneumology

- 63 years old – evaluation after 1 year of steroids treatment

  - considerable clinical improvement

  - Chest CT

    Clear regression of infiltrates and nodules
    Discrete reticular pattern
    Multiple traction bronchiectasis



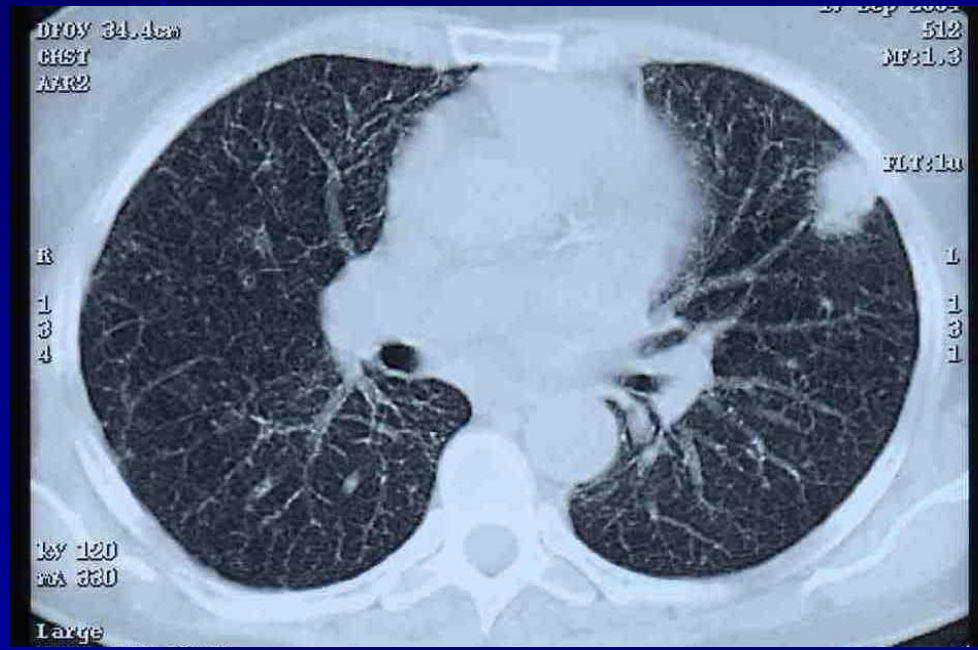
- Pulmonary Function Test

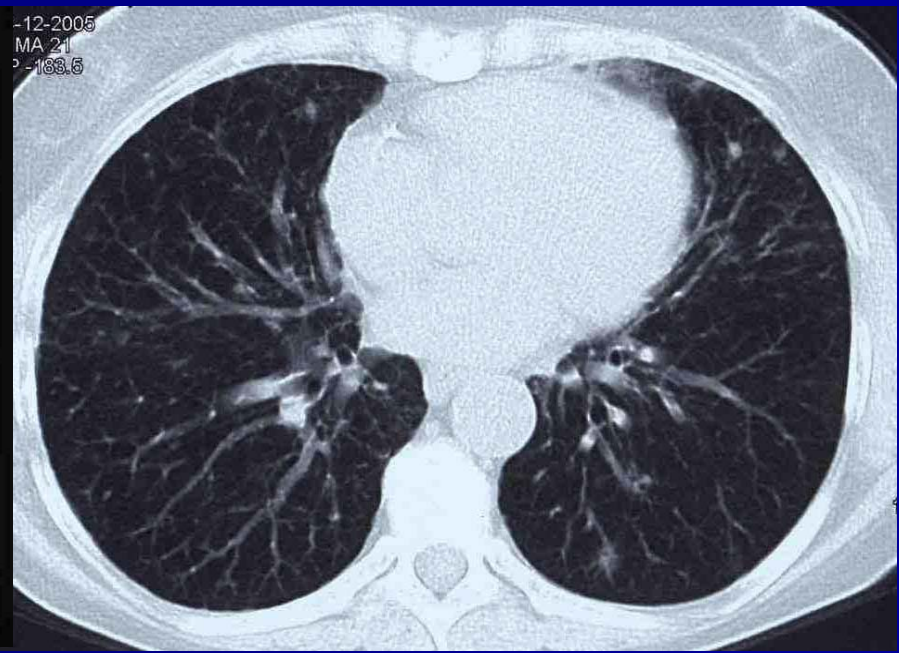
  Discrete restrictive pattern (TLC – 87,9%)
  Diffusing capacity for carbon monoxide - not performed

Case report

Pneumology

- 63 years old – evaluation after 1 year of steroids treatment





Case report

Pneumology

- 63 years old – evaluation after 1 year of steroids treatment

  – Laboratory evaluation:
    - Haemoglobin: 16,2g/dl
    - Leucocyts: 6 100/mm^3 (N - 64,4%, E – 1,4%, B – 0,4%, L – 22,8%, M – 11,1%)
    - Platelets: 217 000/mm^3
    - **Serum protein electrophoresis - γ - 2,2% - 0,1 g/dL**
    - **IgA - 12 mg/dL** (70-400)
    - **IgG - 106 mg/dL** (700-1600)
    - IgM – 44 mg/dL (40-360)
    - **bone marrow aspiration and biopsy - normal**

Referred to Primary Immuno Deficiency

Case report

PID

DENIED

- Fatigue, dyspnoea or cough
- Recent weight loss or oedema

Past History

- 62 years old - laparoscopic cholecistectomy
- No smoking habits
- 6 pregnancies, 4 deliverys

- NO HISTORY of
  - Frequent or severe infections
  - Gastrointestinal diseases
  - Recurrent inflammatory arthritis

Case report

PID

Family History

Sister – Rheumatoid Arthritis
Sister – Arthritis, not characterized
Sister – Thyroid disease, submitted to surgery

Descendents - 2 ♀ and 2 ♂

♀ 34 years old – frequent diarrhea and uveitis

Physical Examination

BMI =19 (height - 161 cm, weight - 50 kg)

Splenomegaly, slightly painful at palpation

Laboratory evaluation

Before steroids

After 1 year of steroids treatment

	18/06/1998 56 years old	20/04/2002 60 years old	30/06/2004 62 years old	20/10/2005 63 years old	
Hb (g/dL)	13,7	13,3	13,7	16,2	
Leuc (/mm3)	**3 500**	**3 300**	4 900	6 100	
N (%)	51	66	57	61,9	
E (%)	6	2	7,8	1,5	
B (%)	0	0	0,2	0,2	
L (%)	35	23	26,2	25,2	
M (%)	8	9	8,8	11,2	
Plat (/mm3)	**146 000**	**141 000**	163 000	217 000	
Total Proteins (g/L)	65	59	60	64	
Albumin (g/L)	46	37	38,6	68,4%	
α1/α2	2,1%/10%	8,9%/13%	0,44/0,95	3,2%/14%	
β	10,8%	9,2%	0,45	12,2%	
γ (%/g/dL)	**5,0% - 0,33**	**6,2% - 0,37**	**4,2% - 0,25**	**2,2% - 0,10**	

NR: 10 - 19% / 0,6 - 1,6g/dL

Laboratory evaluation

Before steroids

After 1 year of steroids treatment

6 month without steroids

	18/06/1998 56 years old	20/04/2002 60 years old	30/06/2004 62 years old	20/10/2005 63 years old	27/04/2006 63 years old
Hb (g/dL)	13,7	13,3	13,7	16,2	14,6
Leuc (/mm3)	**3 500**	**3 300**	4 900	6 100	6 600
N (%)	51	66	57	61,9	71,6
E (%)	6	2	7,8	1,5	0,5
B (%)	0	0	0,2	0,2	0,2
L (%)	35	23	26,2	25,2	17,3
M (%)	8	9	8,8	11,2	10,4
Platelets (/mm3)	**146 000**	**141 000**	163 000	217 000	171 000
Total Protein (g/L)	65	59	60	64	62
Albumin (g/L)	46	37	38,6	68,4%	37,9
α1/α2	2,1%/10%	8,9%/13%	0,44/0,95	3,2%/14%	**8,2% / 16,1%**
β	10,8%	9,2%	0,45	12,2%	11,1%
γ (%/g/dL)	**5,0% - 0,33**	**6,2% - 0,37**	**4,2% - 0,25**	**2,2% - 0,10**	**3,4% - 0,21**

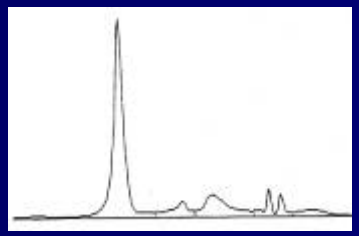
NR: 10 - 19% / 0,6 - 1,6g/dL

Laboratory evaluation

6 month without steroids

Serum protein electrophoresis

Total protein	(g/L)	- 62
Albumin	(g/L)	- 37,9
α1/α2	(%)	- 8,2 /16,1
B	(%)	- 11,1
γ	(%/g/dL)	**- 3,4% - 0,21**



CRP: 0,29 mg/dL
ESR: 16 mm

renal and hepatic biochemistry - normal
thyroid function - normal

- Ig G -160 mg/dL (700-1600)
  - Ig G_1 - 137 mg/dL (700-1600)
  - Ig G_2 - 9 mg/dL (490-1140)
  - Ig G_3 - 27 mg/dL (20-110)
  - Ig G_4 - 0 mg/dL (8-140)
- Ig A - 8 mg/dL (70-400)
- Ig M - 32 mg/dL (40-360)
- Total Ig E << 3,9 U/mL

Immunoelectrophoresis - normal

B_2-microglobulin: 3,93 mg/L (0,8-2,2)
LDH: 453 U/L

ACE: 49 U/L
α_1-antitripsin: 36 UI/L

Laboratory evaluation

6 month without steroids

- Autoimmunity
  - Antinuclear Ab
  - Anti-DS-DNA Ab
  - Anti-RO (SS-A) Ab
  - Anti-LA (SSB) Ab
  - Anti-sm Ab
  - Anti-scl 70 Ab
  - Anti-Jo 1 Ab
  - Antiribosome Ab
  - Anti RNP-Sm Ab
  - Anticentromere Ab
- Serum Immune-complex

NEGATIVE

- Cultural test
  - sputum
  - feces
  - urine

NEGATIVE

- Virology
  - HIV, HBV, HCV

Ø

Skin prick test positive for:

- *Iolium perene*
- *parietaria officinalis,*
- *parietaria judaica*
- tree polen mixture

Specific IgE - Negative

Laboratory evaluation

6 month without steroids

- Specific/vaccine antibodies production:
  - anti – *H. influenzae* Ab - after vaccination → NEGATIVE
- Blood Type: B Rh+
  - isohemagglutinin anti-A (titre) - 1 → Very Low
- **Lymphocytes Immunophenotype**
  - $CD3^+$ - 74,4% / 805,7 /µL (p10)
  - $CD4^+$ - 39,5% / 427,7 /µL (p5)
  - $CD8^+$ - 30,5% / 330,3 /µL (p25)
  - **$CD19^+$ - 6,7% / 72,6 /µL (<p5)**
  - **$CD3^-$ $CD56^+$ - 4,2% / 45,5 /µL (<p5)**

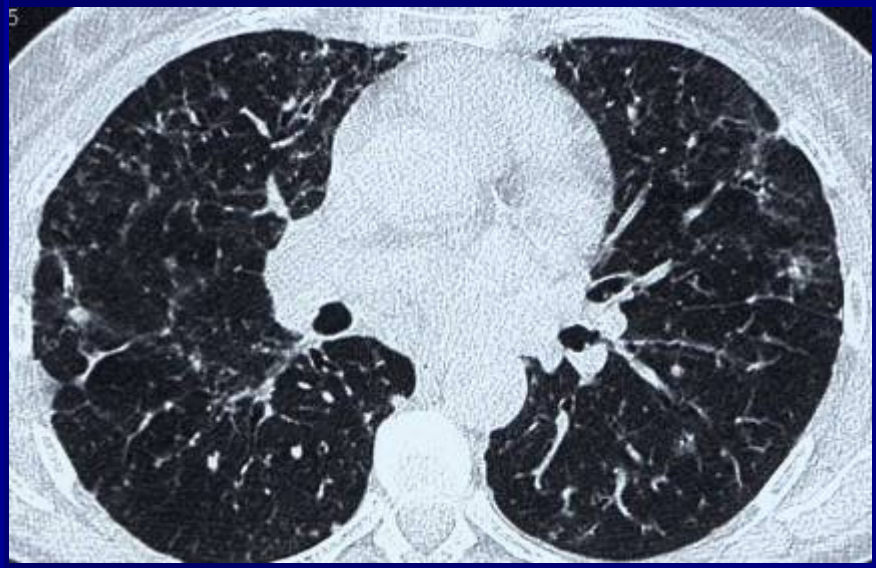
B lymphocytes (*Gate* at $CD19^+$)
$CD27^+IgD^+$ → 7%
$CD27^+IgD^-$ → 5%

6 month without steroids

Chest CT

Traction bronchiectasis in peripheral areas of more intense fibrosis

Diffuse interstitial infiltrates, in both lungs



Abdominal ultrasonography

Splenomegaly (14,7 cm X 8,4 cm)

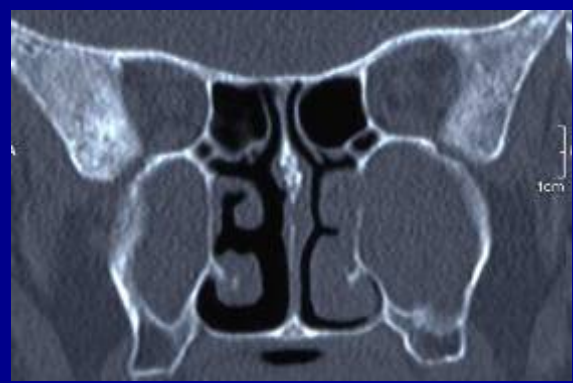
Pulmonary Function Test

Diffusing capacity for carbon monoxide - **72,1 %**

Sinus CT

Hyperthophic rhinitis

Chronic bilateral maxillary sinusitis



Diagnosis

- **CVID**
  - **Lymphoid Interstitial Pneumonia**
  - **Chronic Allergic Rhinosinusitis**
  - **Immune Thrombocytopenic Purpura –** in remission
  - **Splenomegaly**

Evolution

- No significative infections
  - February/06 – *Herpes varicela-zoster* cutaneous infection
- No respiratory complaints

Evolution - Therapeutics

1 Postpone beginning immunoglobulin replacement therapy

2 worsening documented by chest CT

pneumology decided to restart steroids, in August/06:

- deflazacort – 21 mg/day
- budesonido – 400μg, 2 twice/day

November/06 to January/07– 4 episodes of acute rhinosinusitis, treated with antibiotics

3 **January/07 - Began intravenous immunoglobulin replacement therapy (400 mg/Kg)**

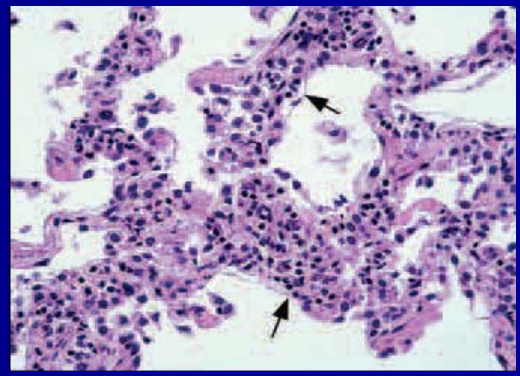
Lymphocytic Intersticial Pneumonia (LIP)

- Uncommun
- 1969 - Liebow and Carrington originally classified as an idiopathic interstitial pneumonia
- Removed from that category - belongs within a **spectrum of pulmononary lymphoproliferative disorders**
- 2002 – ATS/ERS consensus – classification of IIP
  - LIP included because of its clinical, radiographic and pathologic features

Diffuse hyperplasia of bronchus-associated lymphoid tissue

Microscopic dominant features

diffuse, polyclonal lymphoid cell infiltrates surrounding airways and interstitium



Lymphocytic Intersticial Pneumonia (LIP)

- ++ ♀
- 5th decade
- Idiopathic?
- Infections (*Pneumocystis jeruveci,* HBV, EBV)
- Systemic diseases
  - Autoimmune diseases (**Sjogren,** RA, SLE)
  - Immuno deficiencies (HIV, **CVID**)
- Late complication of allogenic bone marrow transplantation

Association 1st described in 1973, by Liebow e Carrington

++ T CD_4^+ cell infiltration

Lymphocytic Intersticial Pneumonia (LIP)

- 80% - serum dysproteinemias ⟶ **10% hypogammaglobulinemia**
- **Symptoms**: progressive cough and dyspnea
  - **VERY INSIDIOUS**
- Great variability in clinical course
  - Spontaneous resolution
  - Progressive respiratory failure and death
- **Steroids are the mainstain of the therapy**
  - Response is unpredictable
  - 50-60 % - stabilization or improvement
- 33 - 50% - die within 5 years
- 5% transform to lymphoma

Prednisone

0,75 - 1 mg/Kg/day - 8 to 12 weeks
0,25 mg/Kg/day - 6 to 12 weeks

References

- Notarangelo, L, Casanova,JL, Conley, ME,Chapel H, Fisher A, Puck J *et al.* **Primary imunodeficiency diseases: An update from the International Union of Immunological Societies Primary Immunodeficiency diseases Classification Commitee Meeting in Budapest, 2005.** J Allergy Clin Immunol 2006;117:883-96
- Mouthon L, Berezne A, *et al.* **Diagnostic des déficits immunitaires primitifs à l'âge adulte.** Press Med 2006; 35:903-11
- Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. **Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency.** J Allergy Clin Immunol 2004;114:415-21
- Swigris JJ, Berry GJ, raffin TA, Kuscner WG. **Lymphoid Interstitial Pneumonia – A Narrative Review.** Chest 2002;122:2150-2164
- **American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopatic Interstitial Pneumonias.** Am J Respir Crit Care Med 2002;165:277-304
- North ME, Spickett GP, Webster ADB, Farrant J. **Raised serum levels of CD8, CD25 and ß2-microglobulin in common variable immunodeficiency.** Clin.exp.Immunol. 1991; 86, 252-255
- Davies CH, Juniper MC, Gray W, Gleeson FV, Chapel HM, Davies RJ. **Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A.**Thorax 2000;55;88-90
- Lynch DA, Travis, WD, Muller NL, Galvin JR, Hansell DM, Grenier PA, King TE. **Idiopathic Interstitial Pneumonias: CT Features – Review** Radiology 2005; 236:10-21
- Swigris J,Berry G, Raffin G, Kushner W. **Lymphoid Interstitial Pneumonia – A Narrative Review.** CHEST 2002;122:2150-2164
- Brandt D, Gershwin M. **Common variable immune deficiency and autoimmunity.** Autoimmunity Reviews 2006; 465-470
- Bayry J, Hermine O, Webster D, Levy Y, Kaveri S. **common variable immunodeficiency: the immune system in chaos.** TRENDS in Mol Med 2005 (11) 8; 370-376