CASE PRESENTATION

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PRESENT SITUATION

K. Fr. Date of birth: 26/04/1993

- 17 year old female
- **Skinny** constitution, **prepuberal habitus**, short height
- W: 27Kg, H: 140cm
- **Breasts**: stage I Tanner
- **Abdomen**: Liver (+2cm), Spleen - spleenctomy
- **Urogenital/ext genitals**: stage I Tanner
- Speenectomy (due to hypersleenism hematological findings))
- Unidentified immunodeficiency
- Currently under treatment with γ- globulin (sc)

REVIEW OF THE PATIENT'S PAST MEDICAL HISTORY

MEDICAL HISTORY

- Full-term gestation
- Normal delivery
- Medical history referred as uneventful until the age of 7

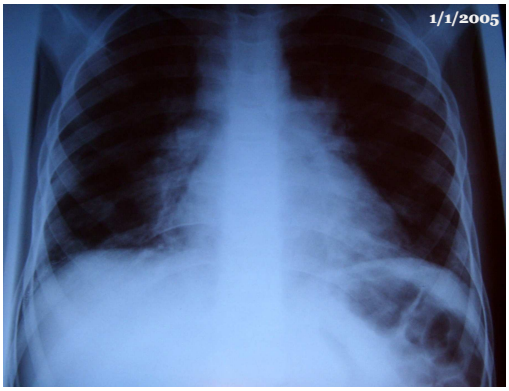
April 2000 -7 years old MOTORBIKE ACCIDENT

cachexia

Chest X-Ray: suspicious dispersed foci on both lungs

Abdominal U/S:

- mild increase of the spleen (longitudinal diameter 10,5cm)
- Diffuse mild heterogeneity -multiple suspicious foci (not traumatic)



April 2000 CT (chest- abdomen)

- Multiple nodular foci in lungs.
- Lymphnodes with pathological dimensions (mediastinum, carina, left axilla, periaortic and inguinal area)
- Hepatosplenomegaly.

May 2000 DATA

- Generalized lymphadenopathy
- Hepatosplenomegaly
- Diffuse nodular foci in both lungs
- Anemia (mild microcytosis, few spherocytes, elliptocytosis)
- Thrombocytopenia (PLT: 130-160k/μL)
- LDH > 320
- IgG subclasses lower than normal

June 2000 Immunological evaluation

- Findings compatible with immunological abnormalities, especially of the T cells and the macrophages.
- Suggestion:

✓determination of **lymphocyte immune phenotype**

✓**IgG, IgA, IgM** and **subclasses IgG** levels

June 2000 Bone marrow aspiration

- Bone marrow rich with mainly small megacaryocytes, non mature (dysplastic)
- **Red blood cells**: normal
- **Granulocytes** on maturation

June 2000 Bone marrow biopsy

- All cell types present
- Myeloid cellular line: formation of small or medium aggregations of non-nuclear cellular elements (identified as MPO+ and rarely as CD34+)
- Limited diffuse presence of small lymphocytes- presence of an activated lymphoid follicle
- Red cells: normal cell number- dysplastic variations
- Megacaryocytes :small increase in number- dysplastic

2001 Bone marrow aspiration

- **Karyotype** : normal (46XX)
- Dysplastic findings
- **Cell cultures**

Presence of Epo: increased presence of colonies (78/ plate) CFU-GM and abundant cluster G or G+ GM. No growth of BFU-E

Presence of Epo + SCF + G+GM- CSF: increased presence of CFU-GM+ increased presence of clusters. Relatively increased growth of BFU-E

Indications of spontaneous overgrowth of CFU-GM colonies reminding **MPS.**

May 2004 Bone marrow biopsy

- Bone marrow: normal
- Megacaryocytes: quantitatively normal, dysplastic.
- Platelet aggregates
- Granulocytes:60% (mainly at the stage of myelocyte.)
- Eosinophiles increased 6%.
- Red blood cells 20% -abnormal erythropoiesis.

August 2000 ABDOMINAL U/S

- Splenomegaly (13,3cm) -multiple hypoechogenic areas
- Lymphnodes: liver hilus (1,23 cm the largest)
  mesenteric (up to 1,5cm)
  periaortic (1.3cm)

July 2004 ABDOMINAL U/S

- Normal liver dimensions. Multiple, diffuse small hypoechogenic foci [granulomas(?) mycetomas (?)].
- Kidneys with increased size
- Lymphnodes: multiple large parahilus (1,69cm)
  mesenteric – paraaortic (1,88cm)
  left kidney hilus (2,43cm- 3,25cm)

August 2000 Lymphnode biopsy

- Intense hyperplasia of the lymphoid follicles with accumulation of voluminous activated lymphoid follicles

2002 Lung biopsy

- Pulmonary parenchyma:

✓lymphocytic/lymphoid follicle hyperplasia (interalveolar septal (interstitial) and bronchial distribution).

✓No necrosis/ granular inflammation

- Histological findings **compatible with** lymphocytic interstitial pneumonia **(LIP)**

July 2003 Spleenectomy (1)

- **Splenic parenchyma**: normal cellular architecture
- **White pulp**: lymphoid follicle hyperplasia,expanded T areas due to identification of T lymphocytes and expression of cytotoxic cells
- **Lymphnodes** : splenic / liver hilus, iliac bifurcation, par aortic, pancreatic, celiac tripod - paracortical zone expanded (T lymphocytes)
- **Lymphoid follicle** hyperplasia.

July 2003 Spleenectomy (2)

- **Lymphatic sinuses**: significant histiocytosis with heterogeneous hemophagocytosis
- **Segments of subcapsular parenchyma** : significant lymphocytic infiltration of portal spaces (as in chronic hepatitis) with predominance of expression of indexes of T cellular differentiation and immunophenotypic characteristics as in T population of spleen and lymphnode areas
- ***Possible autoimmune lympho-hyperplastic syndrome with disturbances in the mechanism of apoptosis of the lymphocytes***

Further laboratory evaluation		Further laboratory evaluation	
T3	141(60-220 ng/dl)	ANA	(-)
T4	8.3(4.5-12 μg/dl)	ASMA	(-)
Anti TG	<20	AMA	(-)
Anti TPO	18	ANCA	(-)
FSH	9 mIU/ ml	SACE	(-)
LH	7.9 mIU/ ml	C3	Normal
PRL	12 ng/mL (1.9-25)	C4	Normal
IGF-1	50.8 ng/mL (237-996)		

2001 lymphocyte immunophenotype in bone marrow sample	
Erythroblasts	16.4% nucleated
lymphocytes	9%
granulocytes	77%
CD46+, CD16+	50.3%
monocytes	3%
BCD 19+	7.4%
Plasmocytes CD38bright	0%
CD34+/ CD117+ stem	0.6%
DC2	0.45%
T4	3.5%

2006 Lymphocyte immunophenotype in peripheral blood

- Normal % of T lymphocytes with normal rate of helper/suppressors and inversed rate of naïve/ memory cells. Normal % of B and NK lymphocytes. Relatively increased rate of stimulated T lymphocytes.

Immunoglobulin levels through all these years

	IgA mg/dl	IgM mg/dl	IgG mg/dl	IgG1 mg/dl	IgG2 mg/dl	IgG3 mg/dl	IgG4 mg/dl
4/2000	23	85	429				
9/2003	5.53	85	229				
8/2006	8.05	22.9	334				
9/2006	6.28	30.1	360	135	129	7	6
2/2008	5	118	889				
10/08	6	59	653				

HLA- identity

- The patient is HLA identical / compatible with her sister :
- **Patient**: A*02, *11, B*35, *39, DRB1*01, *16
- **Sister**: A*02, *11, B*35, *39, DRB1*01, *16

	00	01	02	03	03	04	05	06	08	09
Hct	34.7	37,2	37,7	36,4	45,8	32,2	25,3	30	30,4	31,1
Hb(g /dl)	11.4	12,5	12,2	12	14,8	10,5	8,3	9,2	8,3	9,4
WBC (k/ µL)	7	8,2	5,9	6,3	13,5	38,2	31,8	24,4	10,3	19,25
PLT (k/ µL)	133	145	142	76	477	666	383	502	63	190

	6/8/03	16/1/04	27/9/04	3/1/05	19/5/06	30/1/08	30/6/09	10/12/09
Ur (mg/dl)		↑	42	20	42	35	43	60
Cr (mg/dl)		↑	1,0	0,9	0,9	1,3	1,7	2,0
sGOT (IU/l)	↑		146	106	58	38	32	55
sGPT (IU/l)	↑		140	78	50	21	21	24

Date	Infection	
06/2002	Fever and abdominal pain	Blood culture: staphylococcus
01/2003	Vertigo and abdominal pain	
02/2003	Periumbilical pain	
10/2004	Abdominal pain	
04/2005	pneumonia	
01/2006	Retrosternal pain	
04/2006	Periumbillical pain	
06/2006	Right knee arthritis	
12/2009	H1N1 infection	
04/2010	Respiratory infection	

- Start treatment with γ- globulin 400mg/ kg/ month on 03/2003

In Summary

- **A 17 year old girl**
- **Medical history referred as free** until the age of 7
- **7 years old: 1st hospital admission**
  - ✓Cachexia
  - ✓Hepatospleenomegaly
  - ✓Hypersleenism (anemia, thrombocytopenia)
  - ✓Lymphadenopathy
- **Progressive worsening of symptoms**

In Summary

- **Until today**
  - ✓Spleenectomy
  - ✓Spleen biopsy: ALPS
  - ✓Repeated BMA: normal
  - ✓Lymphnode biopsy: hyperplasia of lymphoid follicles
  - ✓Lung biopsy: LIP
- **Renal deficiency (GFR: 43mL/min/1.75m2)**
- **Immunoglobulins**: low levels
- **Cellular immunity:** increased rate of stimulated T lymphocytes
- **Treatment:** γ- globulin

DNT cells control (ALPS)

- Normal fraction of FOXP3 expressing T reg
- Leucocytosis with lymphocytosis. Normal distribution of lymphocyte subsets. Increased percentage of activated CD8+ cells. Very low naïve cells.
- Strongly reduced percentage of CD27 IgM and class switched memory B cells. Disturbed B cell differentiation
- Normal percentage of double negative T cells.
- Normal apoptosis after stimulation with CD 95L
- No indication of ALPS