U. Mickys

Case No. 10

CLASSICAL DISEASE WITH PROTEAN APPEARANCE

L. Griškevičius
I. Vengalytė
R. Stulpinas

VALSTYBINIS PATOLOGIJOS CENTRAS

UNIVERSITÉ DE GENÈVE

SGPath SSPath
Société Suisse de Pathologie
Schweizerische Gesellschaft für Pathologie
Swiss Society of Pathology

European Association for Haematopathology

9th **International Course on Bone Marrow Pathology** May 7–9 2009   Geneva, Switzerland

CLINICAL DATA

Clinical history:

+ 74 year old woman;

+ No history of other disorders, surgery, trauma, drug or any other kind of allergy;

+ Two normal pregnancies;

+ Lower back pain irradiating to both legs lasting for one month;

+ Treatment with NSAIDs had no effect;

+ On OCT 10 2008 fell down, became immobile and was hospitalized due to extensive back pain.

Physical examination:

+ Palor;

+ Hyperaesthesia in lower extremities;

+ No pathological reflexes found;

+ Lasego symptom about 70° >;

+ Painful lumboscral part of the spine;

+ Decrease of muscle strength in legs.
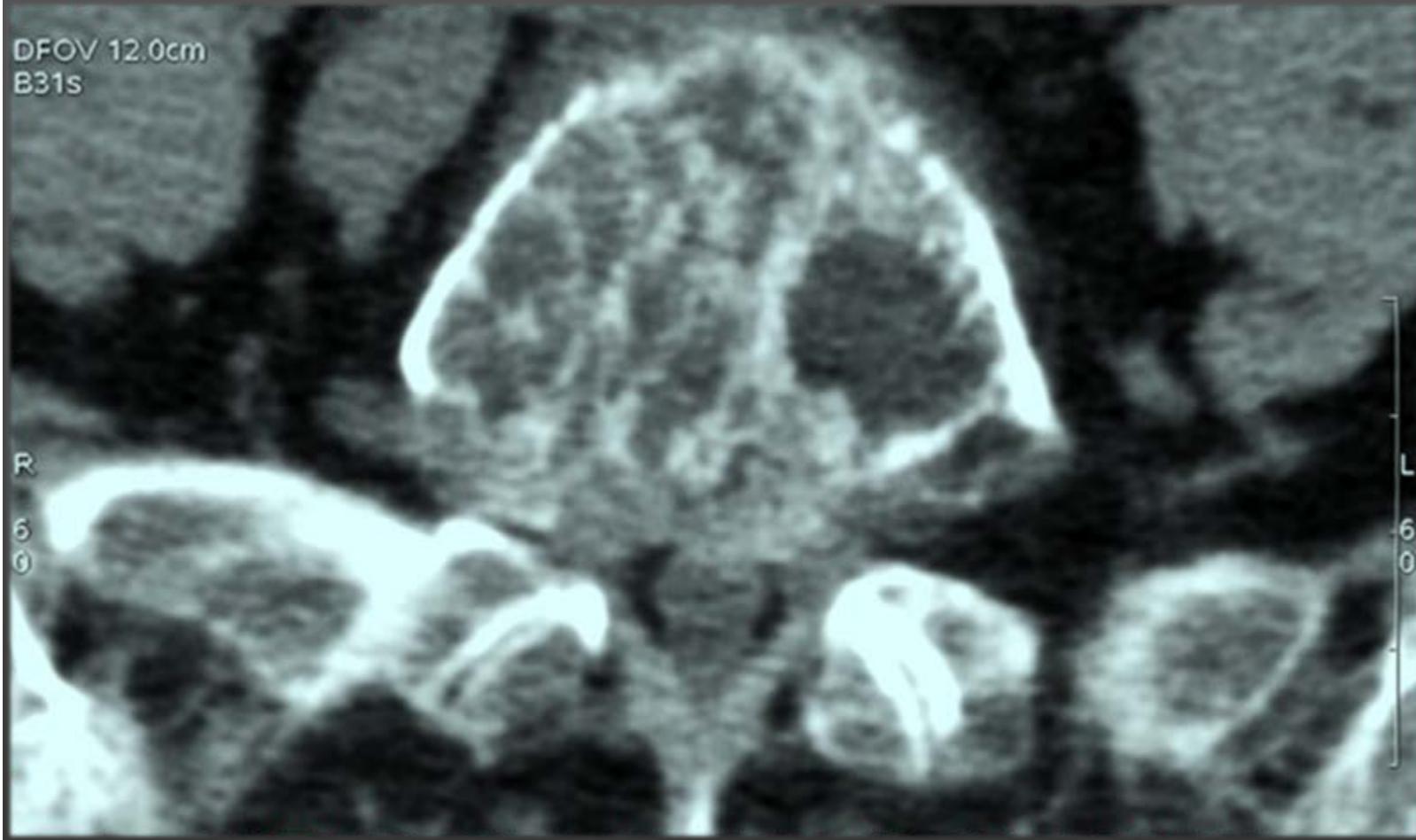
CT scan

Extensive osteoporosis. Compressive deformations (I –II degree) of L2-L4 vertebrae. Left protrusion of L4/5. Focal destructive changes of L3, L5 vertebra bodies.

Blood test:

Analysis	Result	Standard
WBC (*10e9/l)	7.960	4.0 - 9.0
NEU (*10e9/l)	5.31	2.0-6.93
LYM (*10e9/l)	2.22	1.0-2.5
MON (*10e9/l)	0.31	0.12-0.9
EOS (*10e9/l)	0.09	0.02-0.45
BAS (*10e9/l)	0.02	0-0.09
RBC (*10e12/l)	3.291	Mal.:4.5-5.5, Fem.:4.0-5.1
HgB (g/l)	108.70	Mal.:135-160, Fem.:120-150
Hct (l/l)	0.315	Mal.:0.40-0.48, Fem.:0.36-0.42
MCV (fl)	95.67	82-95
MCH (pg)	33.03	25-35
MCHC (g/l)	345.2	330-348
RDW (%)	14.78	11.6-13.7
Plt (x10e9/l)	207.90	180-320
MPV (fl)	7.60	7.4-10.4

Biochemical blood test:

Analysis	Result	Standard
Urea (mmol/l)	8,4	2,5-7,5
Creatine (mkmol/l)	92	M:62-115, F:53-97
K (mmol/l)	3,9	3,8-5,3
Na (mmol/l)	134	134-145
Cl (mmol/l)	100	98-107
Glucose(Serum) (mmol/l)	5,3	4,2-6,1
Total protein(g/l)	89.0	66-83
Albumin (%)	38,2 (34 g/L)	53-63
Globulin (%)	61,8	
Alfa 1 (%)	2	2-4,5
Alfa 2 (%)	6,7	6-11
Beta 1 (%)	4	5-8
Beta 2 (%)	2,5	3-5
Gama (%)	46,6	11-19
ß2 microgobulin (mcg/ml)	7,83	0,97-2,64

Blood protein test:

Analysis	Result	Standart
B2 microglobulin (mg/L)	7,83	0,97-2,64
Immunoglobulin A (g/L)	0,49	Mal.: 0,7-3,7 Fem.: 0,88-4,1
Immunoglobulin G (g/L)	49,36	7,0-16,0
Immunoglobulin M (g/L)	0,16	Mal.: 0,40-2,40 Fem.: 0,34-2,10

Paraprotein – IgG lambda

Serum protein electrophoresis:

Total protein = 89.0 g/l
A/G = 0.62
Globulins   61.8%
Comments:
monoclone in gamma fraction

Agarose gel (hydragel)
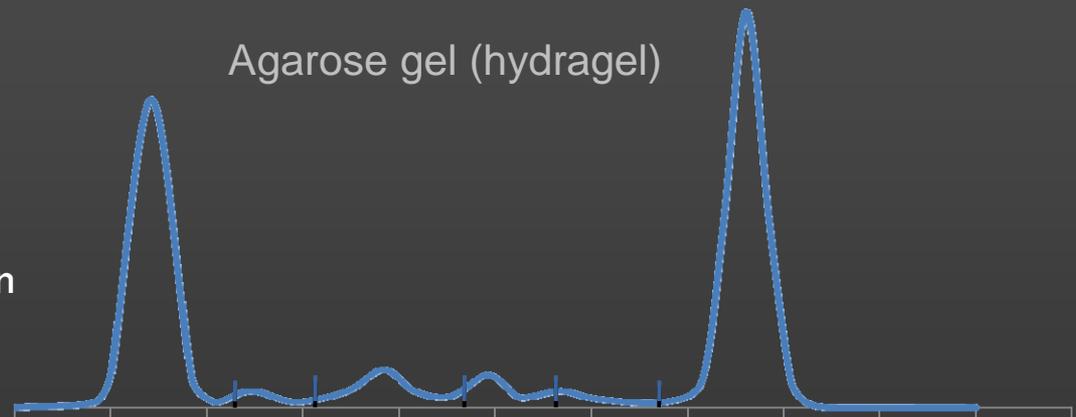
Fraction	%	g/l	Norm %	g/l
Albumin	38.2	34.0	60-70	43-51
Alpha 1	2.0	1.8	1.4-2.7	1-3
Alpha 2	6.7	6.0	7-11	5-8
Beta 1	4.0	3.6	6-9	4-6
Beta 2	2.5	2.2	2-5	1-4
Gamma	46.6	41.4	8-16	6-12

Bone marrow aspiration:

Type of cell	Normal range, %	BM aspirate	BM imprint	Comment
Lymphoid cells and lymphocytes	10,0-13,0	25	18	Pancytopenia, significantly increased amount of plasma cells, representing different stage of maturation, partialy with irregular forms. Decreased granulopoesis. Single megacariocytes. Anisocitosis. Rouleux formation of RBC.
Blasts	0,0-3,0	0	1	
Myelocyte	3,0-12,0	6	6	
Metamyelocyte	8,0-14,0	3	4	
Promonocyte	0,2-0,5	0	0	
Monocyte	1,0-2,0	4,5	0	
Plasma cells	0,4-1,6	12	38	
Megakaryocites	38,8-150	11,4	Singles	

Clinical diagnosis:

+ Multiple myeloma IgG lambda;
+ ISS stage III:
    + Albumin 34 g/l;
    + β 2 microglobulin - 7,8 mcg/l;
+ Compressive deformations of L2 - L4 vertebrae.

TREATMENT

Response to given treatment:

- 6 courses of Melphalane + Prednisolone administered.

- Reduced back pain;

- Starting to walk (minor improvement);

- Reduction of M protein by 68% (partial remission achieved);

- Treatment with MP will be continued untill plato phase is reached (stabile M protein level for 2 months).

Tests after treatment:

| Analysis	Result post	Result pre	Standard
Immunoglobulin A (g/L)	0,29	0,49	Mal.: 0,7-3,7 Fem.: 0,88-4,1
Immunoglobulin G (g/L)	26,55	49,36	7,0-16,0
Immunoglobulin M (g/L)	0,28	0,16	Mal.: 0,40-2,40 Fem.: 0,34-2,10
Total protein (g/l)	77	89	66-83
β 2 microglobulin (mg/L)	3,1	7,83	0,97-2,64
Alfa 1 (%)	2,2	2	2-4,5
Alfa 2 (%)	9	6,7	6-11
Beta 1 (%)	5,3	4	5-8
Beta 2 (%)	2,5	2,5	3-5
Gama (%)	20,7	46	11-19
M gradient (g/l)	13,7	41	

HISTOLOGY

Histology

Part 1:
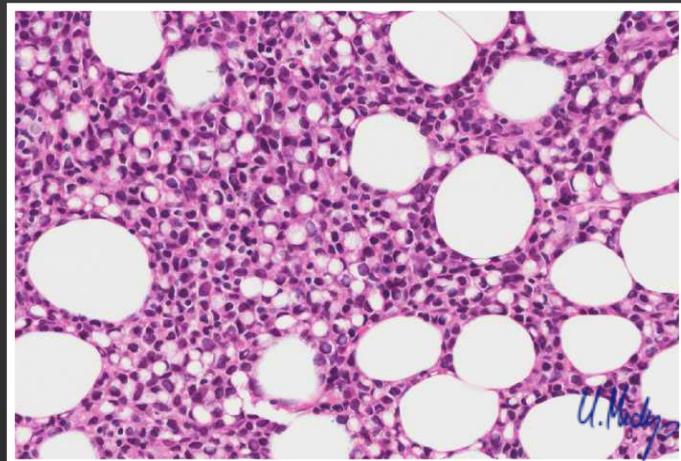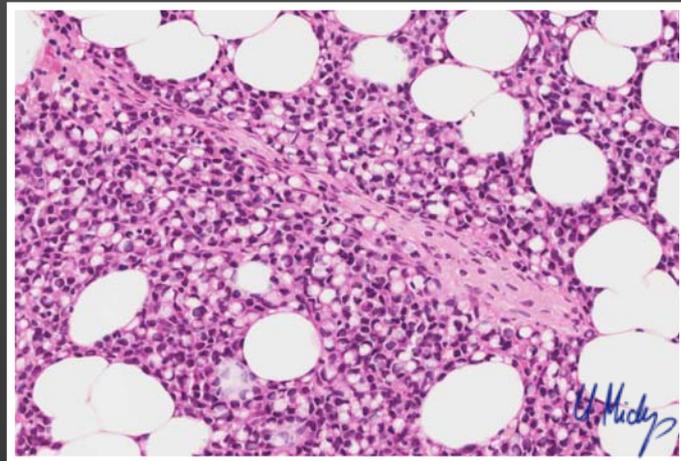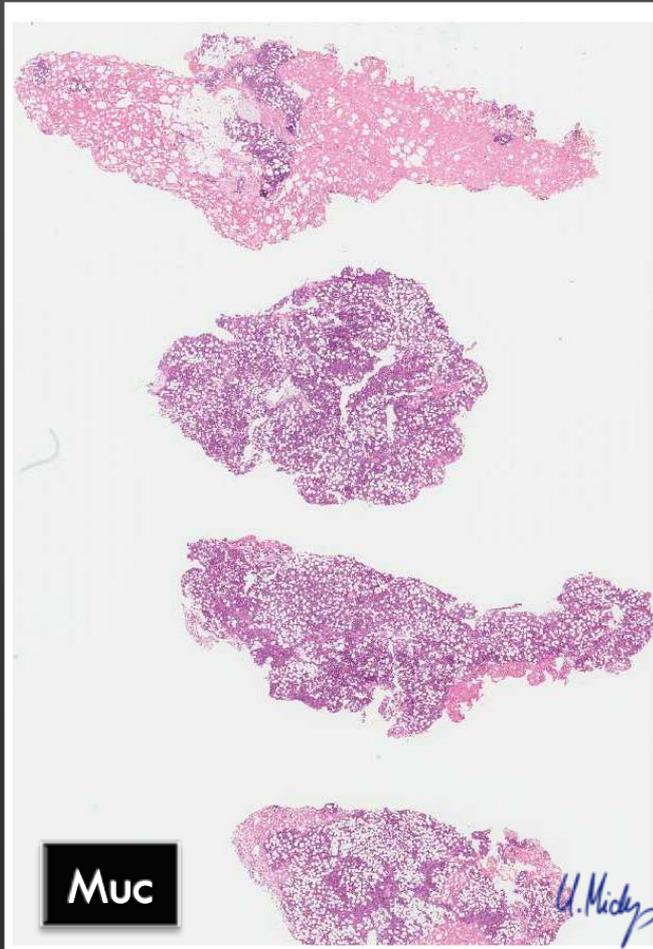
Histology

Part 2:

Histology

Part 3:

CD20

Pax-5

CD117

CD79a

Histology

Part 4:

Ig lambda

Ig kappa

CyclinD1

CD138
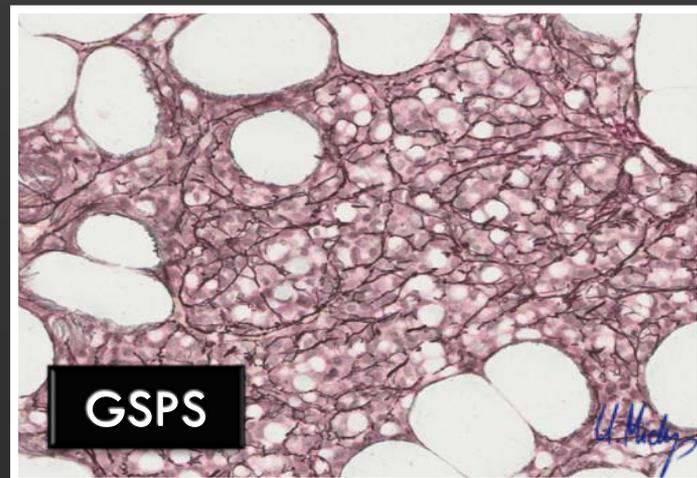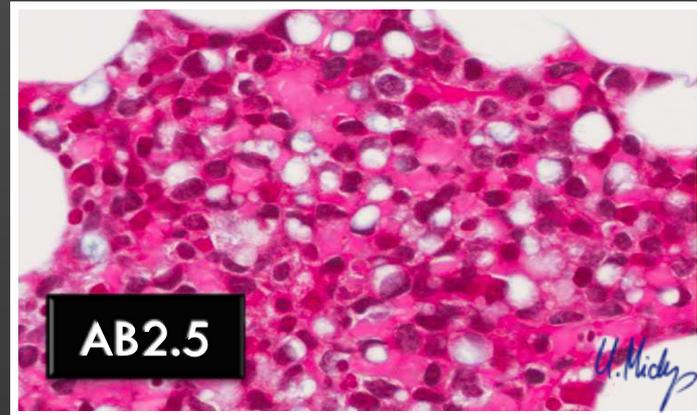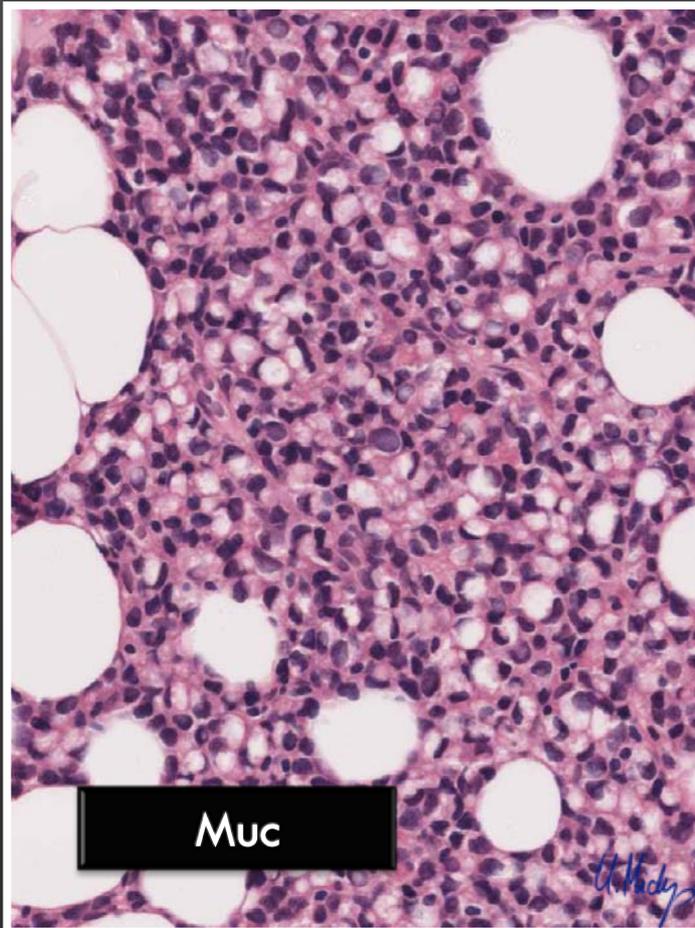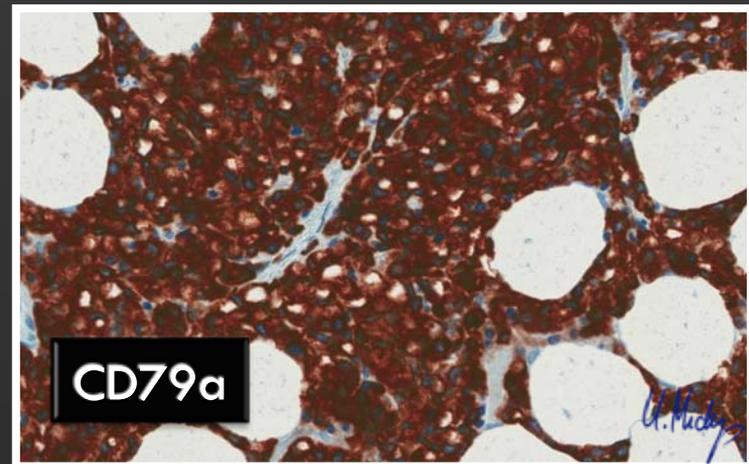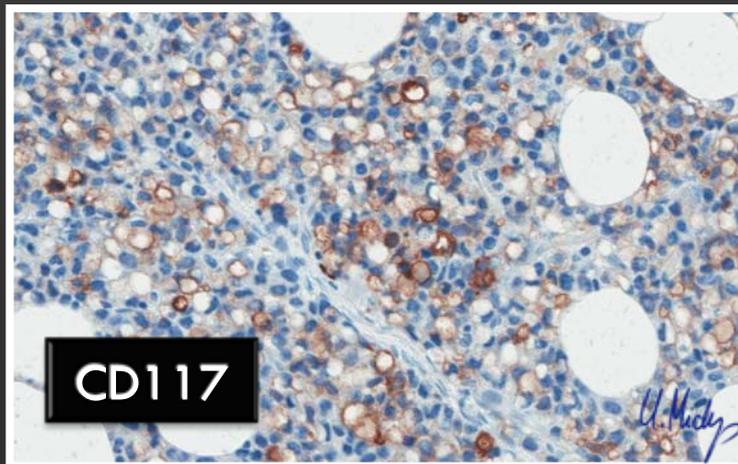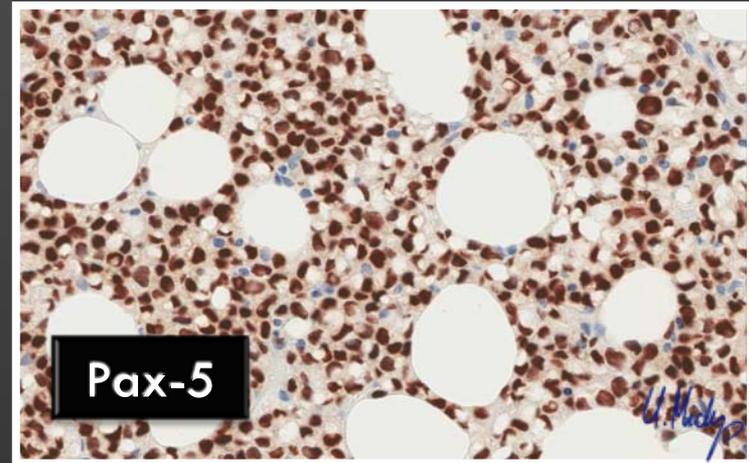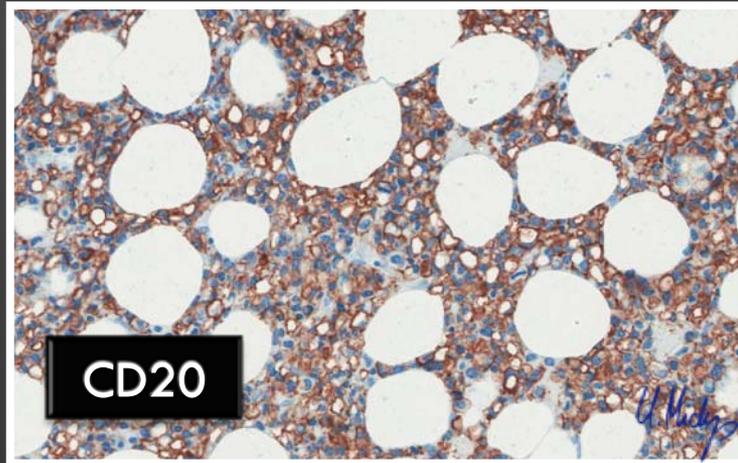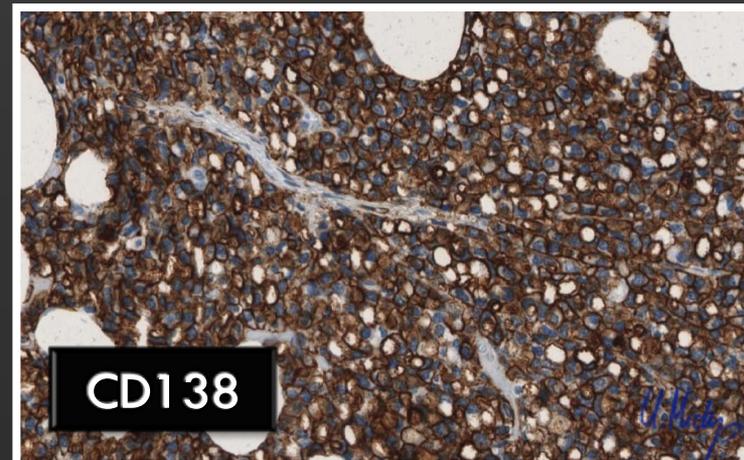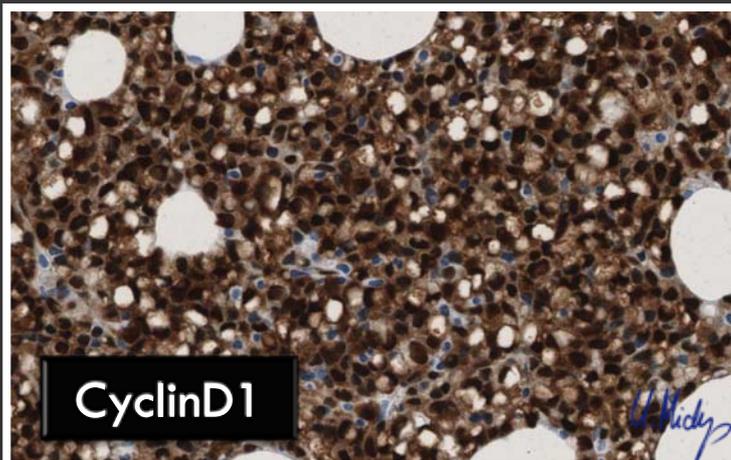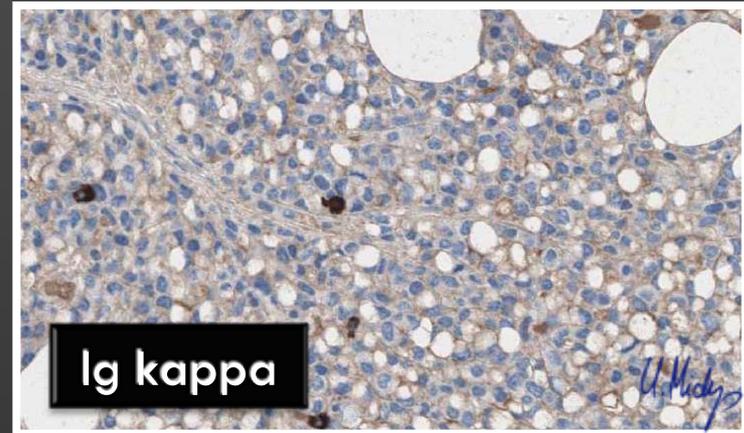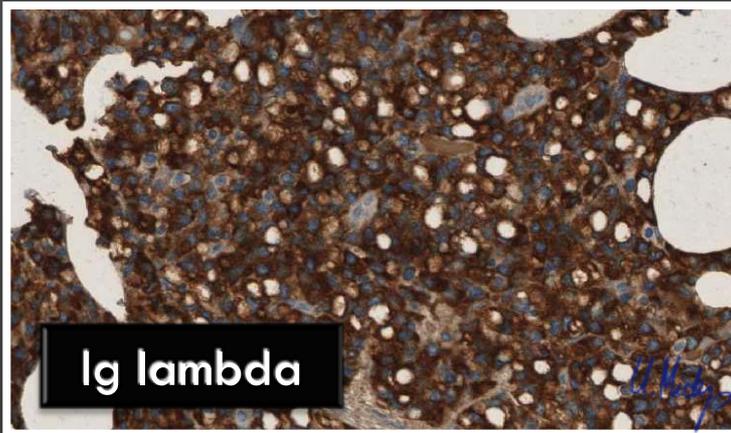
Histology

Part 5:

Ki67 14,7%
(Apperio
Nuclear 9.0)

Trephine biopsy
OCT 21 2008:

- Fixation: Buffered 10% formalin
- Decalcification: „Mielodec" (Bio-optica): hydrochloric acid
- Processed ordinary and parafin embeded.
- Histochemical stains:
    - AB2.5/mucikarmin negative
    - Methyl Green Pyronin: negative
- IF:
    - IgG (+) 80%
    - IgA(-)
- Flow cytometry: Not done
- Molecular analysis: Not done
- Cytogenetics: Not done

- IH:
- PanCK/CAM5.2(-),
- CD138(+++) 100%
- CD20(++) 100%
- LCA(+++) 100%
- CD79a(+++) 100%
- PAX5(++) 100%
- Ig lambda(+++)100% and Ig kappa(-)
- CyclinD1(+++)100%
- CD117(+/++) 30%
- EMA(+/++) 10%
- IgM/IgD(-),
- CD56(-).
- Ki67 proliferative activity ~15%

Plasma cell cytological variants

- Conventional (Marchalko cells)
- Flaming cells (IgA)
- Mott, morular, grape cells
- Thesaurocytes
- With crystaline deposits
- With Russell and Dutcher bodies

- Cleaved, multilobated and monocytoid cells/ polymorphous
- Pleomorphic
- Blastic
- **Signet ring**
- Small
- Histiocytoid
- Clear
- Spindle
- Oncocytic

Banerjee SS, Verma S, Shanks JH. Morphological variants of plasma cell tumours. Histopathology. 2004 Jan;44(1):2-8.

Myeloma: IH variations

CyclinD1+ increased ~ CD20+ expression; lymphoplasmacytic morphology; amount of plasma cells; better survival;

Cook JR, Hsi ED, Worley S, Tubbs RR, Hussein M.
I mmunohistochemical analysis identifies two cyclin D1+ subsets of plasma cell myeloma, each associated with favorable survival. Am J Clin Pathol. 2006 Apr;125(4):615-24.

CD138 loss ~ Complicated IH diagnostics

Svrcek M, Meignin V, Brière J, Quillard J, Mariette X, Audouin J, Janin A.
Multiple myeloma with loss of CD138 expression in two rare metastatic localizations, peritoneum and skin. Histopathology. 2007 Jun;50(7):952-4.

CD117+ ~ Better prognosis?

The prevalence and clinical implications of c-kit expression in plasma cell myeloma.
Pruneri G, Ponzoni M, Ferreri AJ, Freschi M, Tresoldi M, Baldini L, Mattioli M, Agnelli L, Govi S, Mancuso P, Agazzi A, Bertolini F, Peccatori J, Bosari S, Gianelli U, Viale G, Neri A. Histopathology. 2006 Apr;48(5):529-35.

CD117 (c-kit) is aberrantly expressed in a subset of MGUS and multiple myeloma with unexpectedly good prognosis.
Bataille R, Pellat-Deceunynck C, Robillard N, Avet-Loiseau H, Harousseau JL, Moreau P. Leuk Res. 2008 Mar;32(3):379-82. Epub 2007 Sep 4.

Myeloma: IH variations

+ Pax-5+

Lin P, Mahdavy M, Zhan F, Zhang HZ, Katz RL, Shaughnessy JD Expression of PAX5 in CD20-positive multiple myeloma assessed by immunohistochemistry and oligonucleotide microarray. .
Mod Pathol. 2004 Oct;17(10):1217-22..

PubMed searches,

- ✚ Signet ring (cell) myeloma /plasmacytoma ~7 records
- ✚ CyclinD1(positive) myeloma ~13 records
- ✚ Signet ring (cell) lymphoma ~61 records
- ✚ Signet ring cell myeloma CyclinD1+ No records

Earliest detected: Dorfman RF. Multiple myeloma showing signet-ring cell change. Histopathology. 1991 Jun;18(6):577-8.

CLASSICAL DISEASE WITH PROTEAN APPEARANCE

✚ PROPOSED DIAGNOSIS:

IgG+ plasma cell myeloma (signet ring cell variant) with CyclinD1 positivity.

"Clear your mind must be if you are to discover the real villains behind the plot…"

Yoda, the Jedi Master