Case report

A. Dizdari

Istituto di Ematologia" Seràgnoli" - Bologna

- Male, 41 years old, from Romania

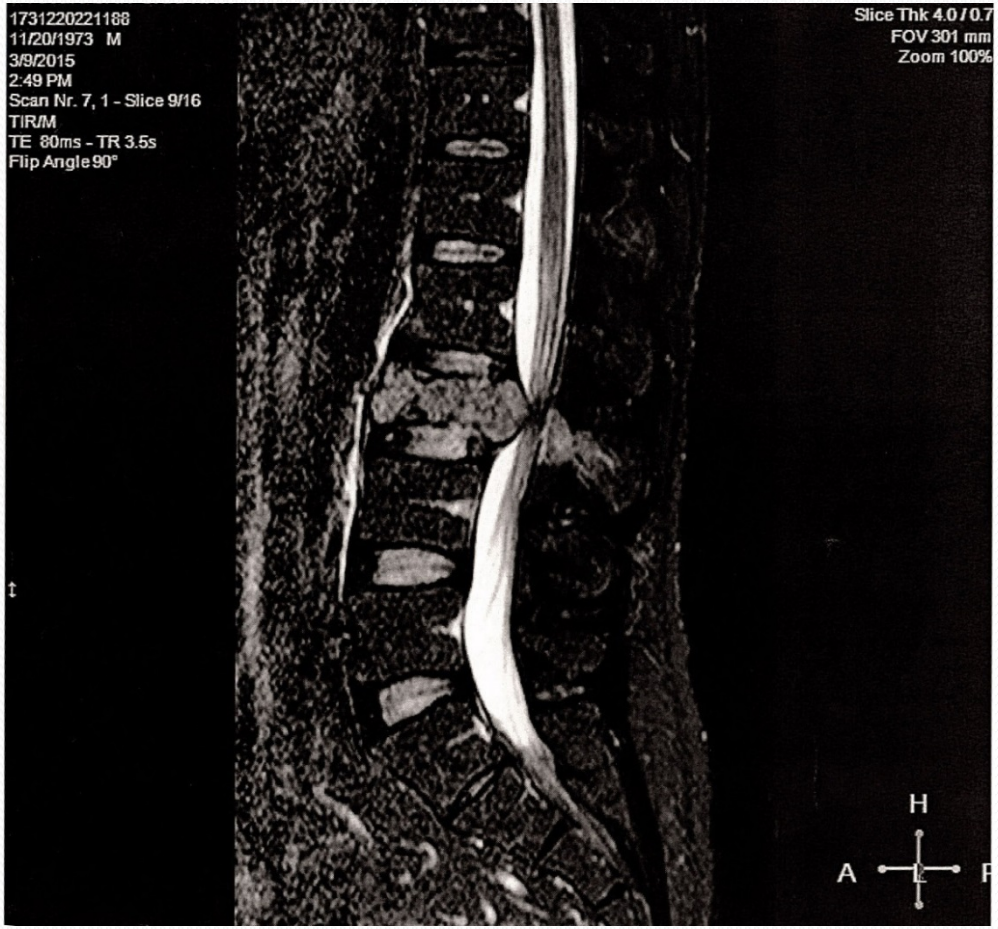
February 2015 - Lombar pain – Rx – L3 lytic lesion –biopsy- Plasmacytoma (Romania – confermed at Seragnoli's Istitute)

IgG /k 1200mg/l (5% CM, FLC k -19,4mg/l, k/λ - 1,1 B2M-1,4mg/l, LDH-110 U/l.

April 2015

- BM : non infiltrated plasmacells
- BO: 40% -cellularity, little PC infiltrate, with regular k/λ
- FISH : not valutable (CD 138+<5%)
- Pet/TC: Lesion of L3 with total bone destruction and infiltrated bone tissues into the left paravertebral region
- MRI: Tumor mass on L3 compressing the dural sac, intraforaminal compression of L3, on the left

Dg: Solitary Plasmacytoma May-June 2015: Radio-Therapy L2-L4 (VMAT– volumetric-modulated arc therapy radiation) 40Gy + vertebroplasty



Solitary plasmacytoma of bone (SPB)

5yr (OS -75%, DFS-45%) and 10yr(OS:45%, DFS:25%)

- 5% of plasma cells disorders are SPB
- Small M-protein: present in 30-75% of cases, may not disappear with treatment. The last one: a significant predictor of progression to MM (about 10% progression in 3 years)
- SPB with **minimal marrow involvement** (about 40% of patients) with 0-10% clonal PC. 60% of these have high risk of progression in 3 years.
- SPB meeting **criteria for MM** > 10% marrow clonal PC – treatments differs only in the case of additional lesions or CRAB (Hb<10, Ca>11,5, IR:creatinine>2mg/dl)
- **Multiple Plasmacytomas**: 30-50% of pts with SPB

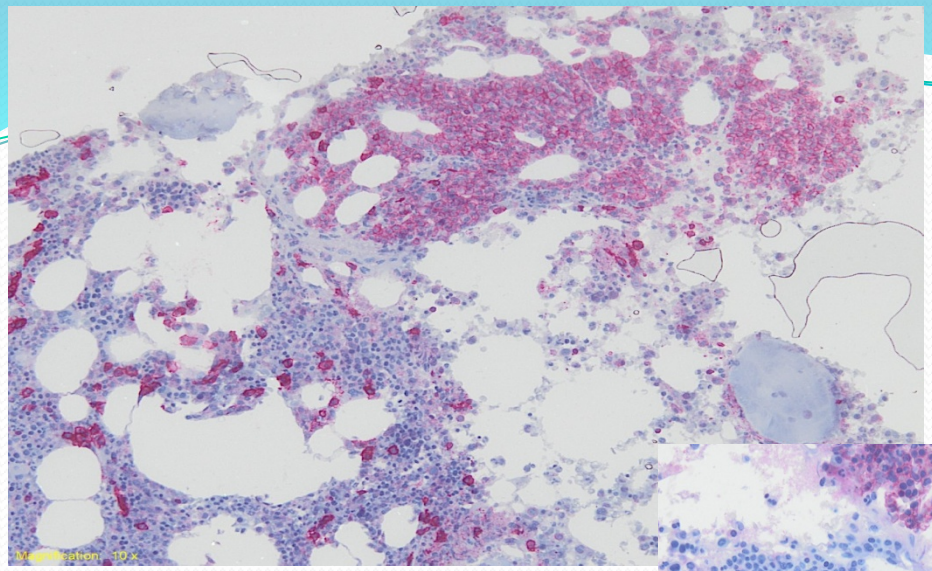
  (2 concurrent distinct, more than 2, 2 or 3 apparently solitary lesions in 1-2yr)

Rajkumar V et al, Lancet Oncology 2014-updated Jul. 2016

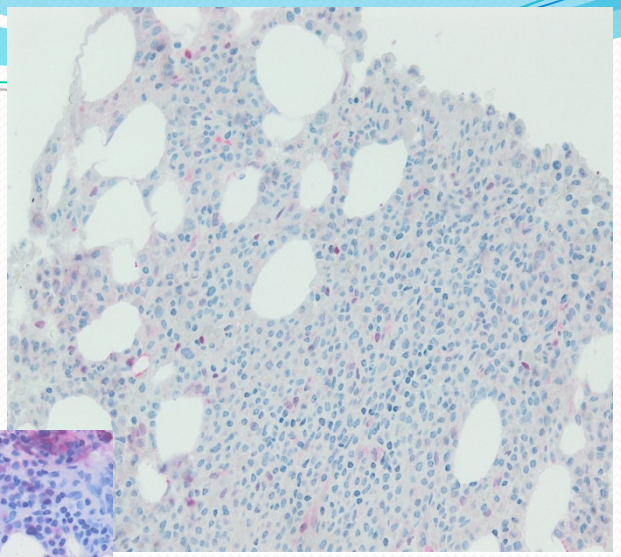
July 2015: MRI- progression L3 – canalicular stenosis, infiltration of m. psoas on the left, suspicious C3-C4 lesions

November '15 : 2° opinion at Seràgnoli's Istitute:

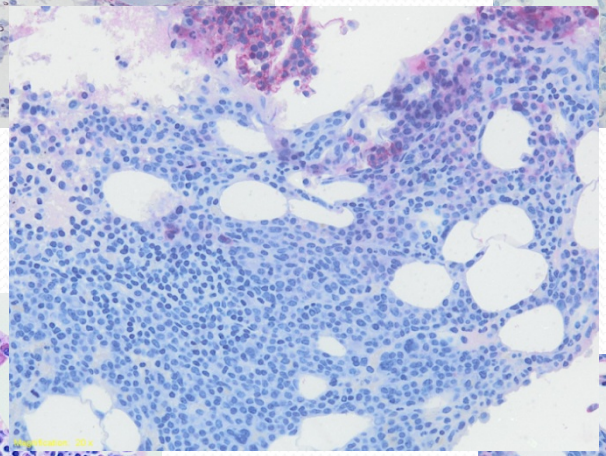
- IgG /k : 1318mg/l (5% CM, k -50,3mg/l , B_2M -1,4mg/l, LDH -144mg/l,
- BM < 5% plasma-cells
- BO: 20% cellularity, low grade Plasmacytoma ??, interstizial 10-15% PC, and *nodular* : CD 38+, negative for : FLC(non secretory), CD56+/BCL1 e Citocheratine
- *Pet/TC*: increased uptake of FDG throughout the skeleton, major lesion in sternum, VI, X left rib with adjacent soft tissues, left scapula, C3, C4 vertebral bodies. Pathological uptake in liver, IV, VII, VIII hepatic segments
- *MRI* of the spine: Multiple osteolytic lesions (cervical and dorsal vertebrae)
- Needle biopsy of sternal lesion (2,7cm): Plasmocitoma –G° intermediate PC–nucleolated, CD38+, Ki67/MIB-1 (15-20%)
- Echo *liver*: Hypo-echogenic lesions (0,7-1 e 1,2cm)
- Liver biopsy – negative for plasma-cells



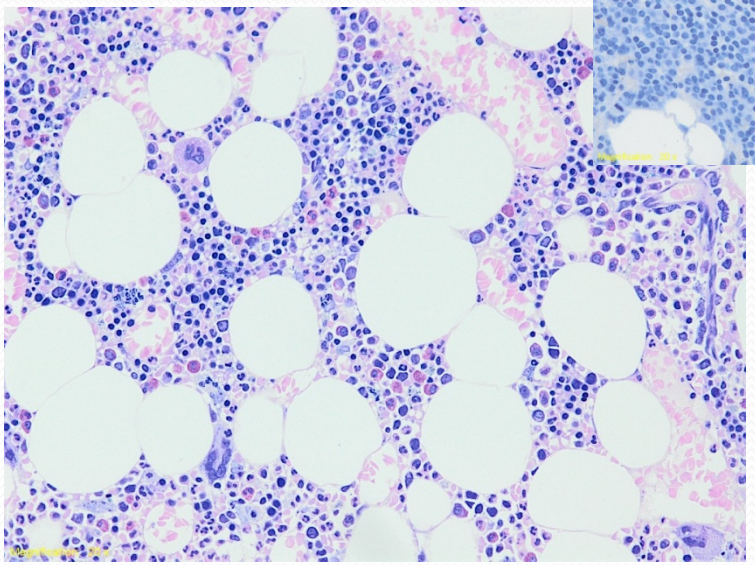
Nodulo BOM CD38+

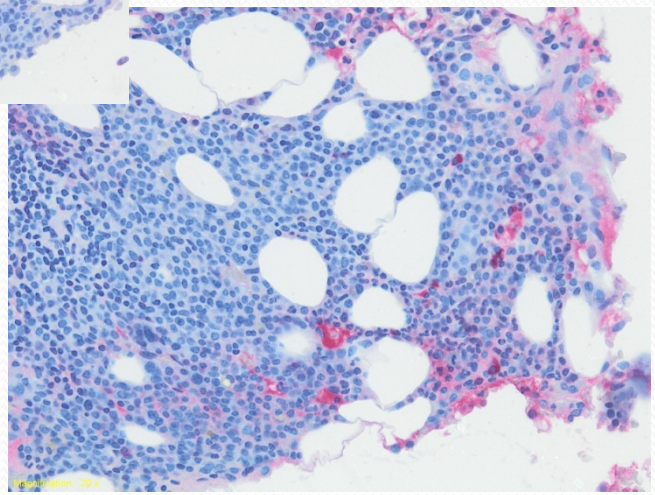


Bcl 1



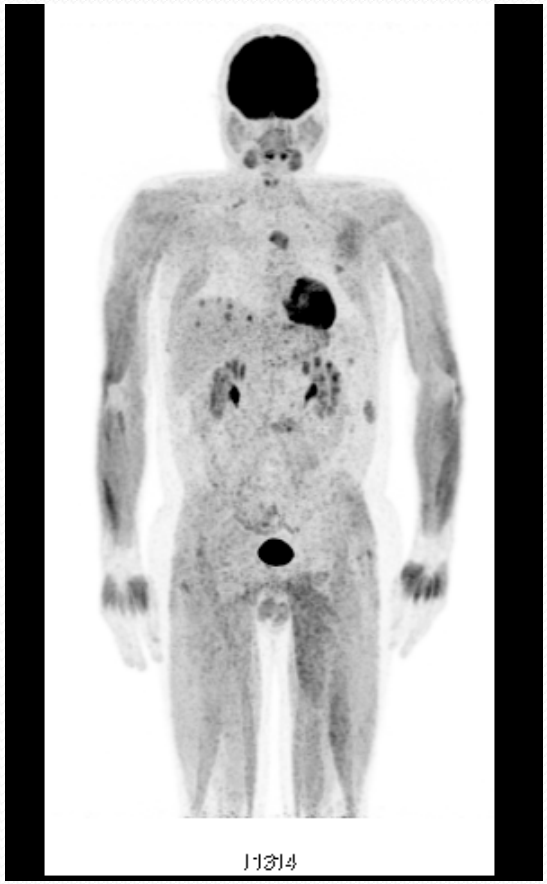
Kappa
(k)

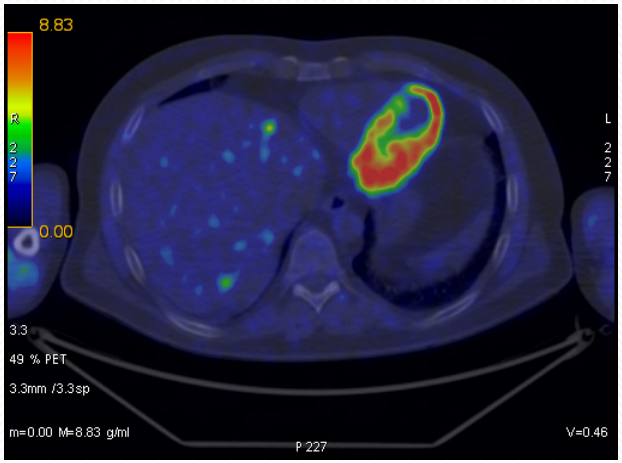


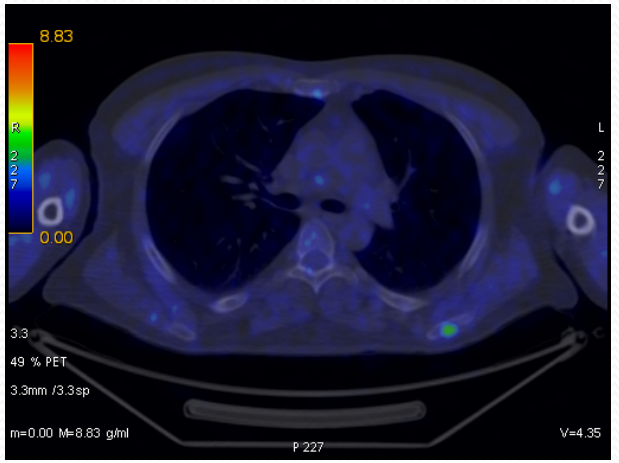


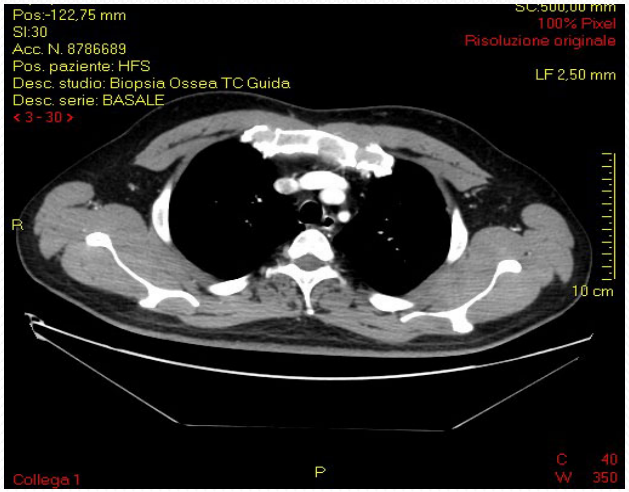
Lambda (λ)

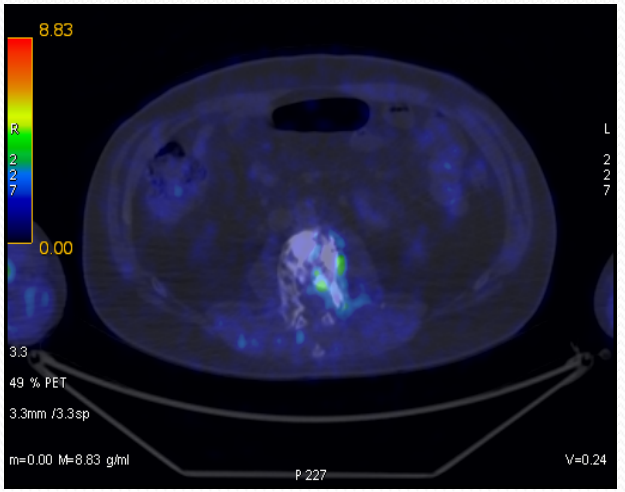
PET – TAC Relapes

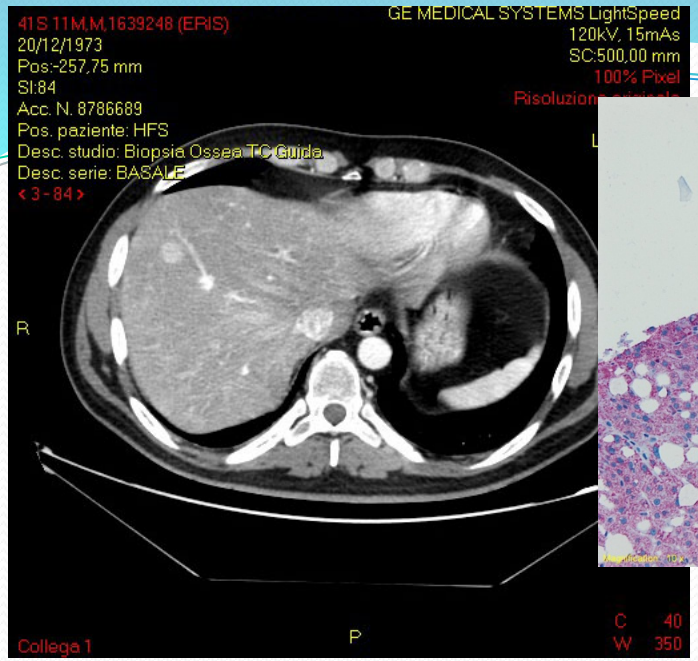


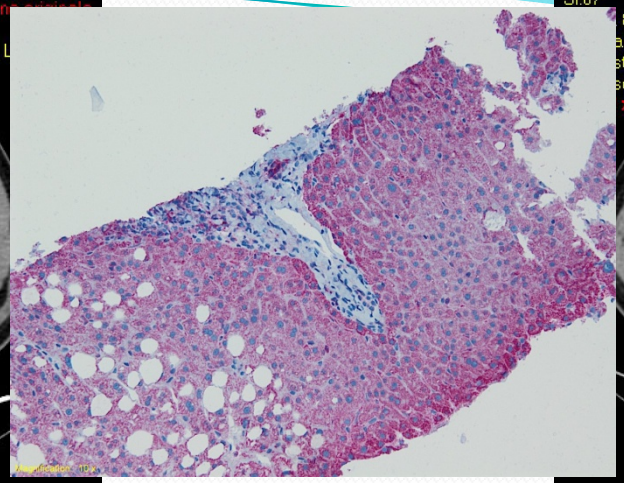


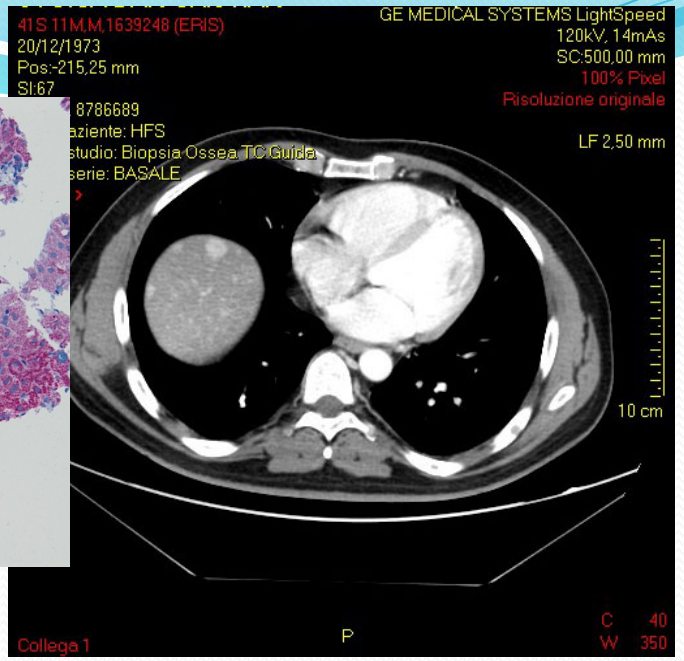




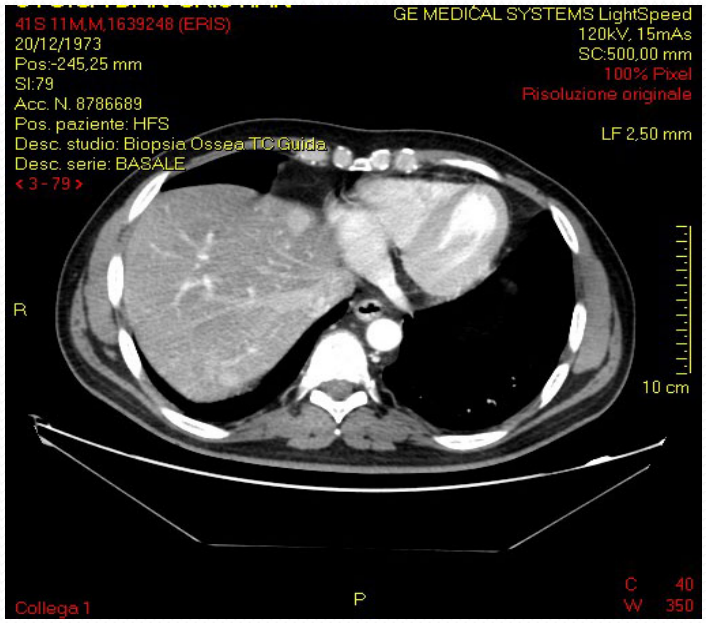




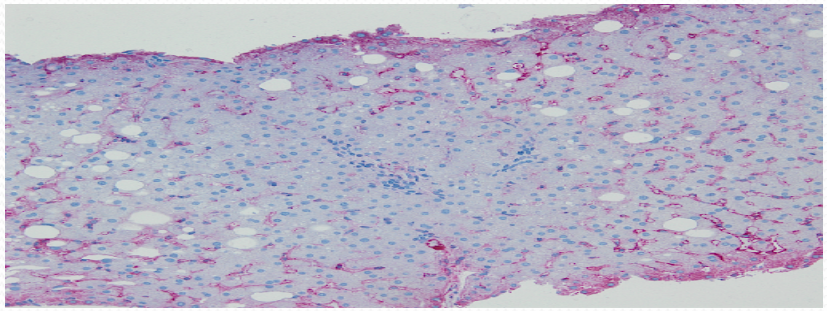




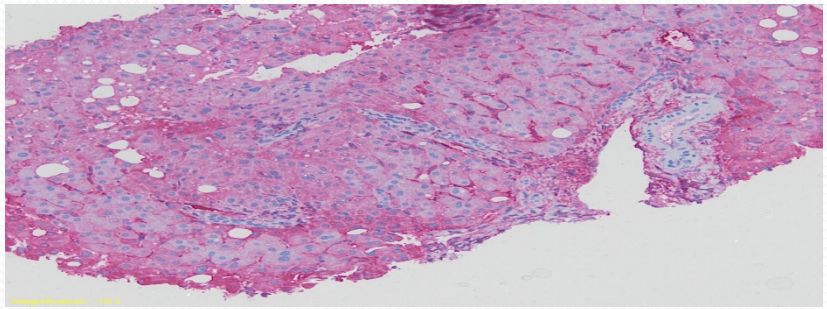
CD38+



Kappa



Lambda



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Time to first progression/survival

(multivariate analysis - initial patients caracteristics)

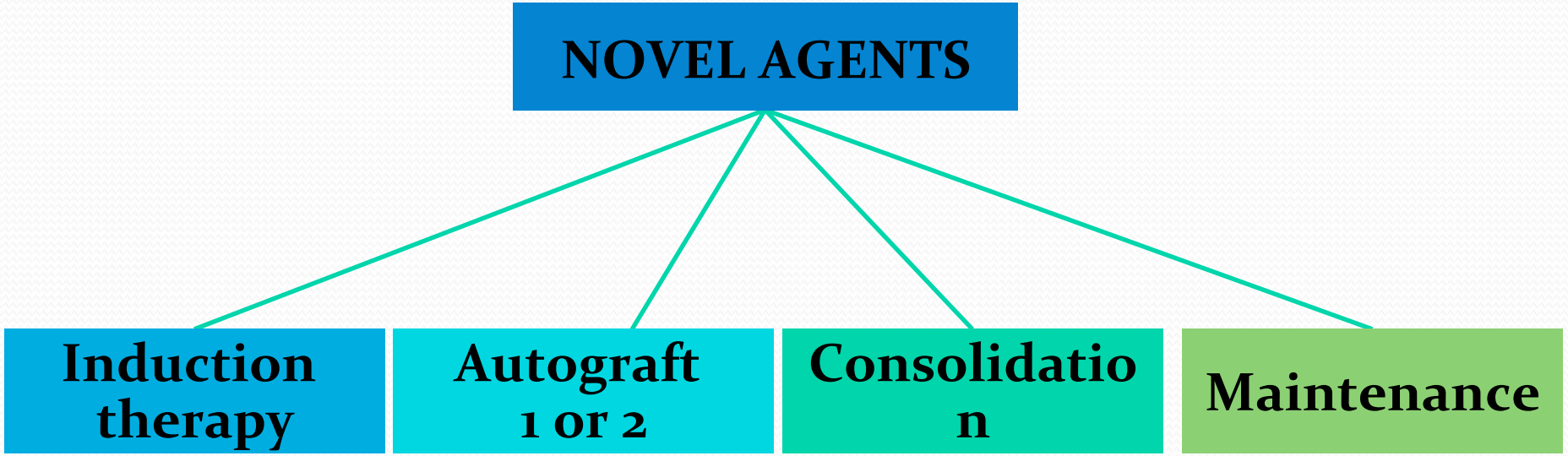
- Platelet count< 150.000/microL
- Albumin< 3g/dl
- Age > 65 years
- Beta-2 microglobulin > 4mg/dl
- Involvement of more than three bones
- Hemoglobin <10g/dl

Poor prognostic features

Rajkumar updated Apr. 2016

Liver involvement ???

New treatment paradigm for patients who are eligible for ASCT



- Maximize the depth of response
- Minimize the burden of residual tumor cells

Cavo M et al. Blood 2011;117(23):6063-73; Cavo et al. Blood 2012;120(1):9-19.

Novel agent–based induction therapies for patients eligible for a transplant

	Bortezomib-based	Thalidomide-based	Lenalidomide-based	PI + IMiD-based
2-drug combinations	VD	TD	Rd RD*	
3-drug combinations	PAD VCD	TAD CTD	RAD CRD	VTD VRD KRD/KTD Ixa-RD
4-drug combinations				VTDC RVCD VTD-Dara VRD-Elo

Regimens in orange: evidence from phase III trials
*Trial was performed in SCT-eligible and –ineligible patients

IMiD, immunomodulatory drug

Adapted from Cavo M et al. Blood. 2011;117:6063;
Rosinol L et al. Expert Rev Hematol. 2014;7:43; Ludwig H et al. Leukemia. 2014;28:981.;
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000539/human_med_001130.jsp&mid=WC0b01ac058001d124

Meta-analysis: Bortezomib-based versus non-bortezomib-based induction prior to ASCT

- Integrated analysis (n=1572) of 3 randomized trials: Bortezomib-based versus non-bortezomib-based induction regimens

Response rate	Bortezomib-based induction (n=775)	Non-bortezomib-based induction (n=772)	OR	95% CI	P
Post-transplant (%)					
CR+nCR	38	24	2.05	1.64–2.56	< 0.001

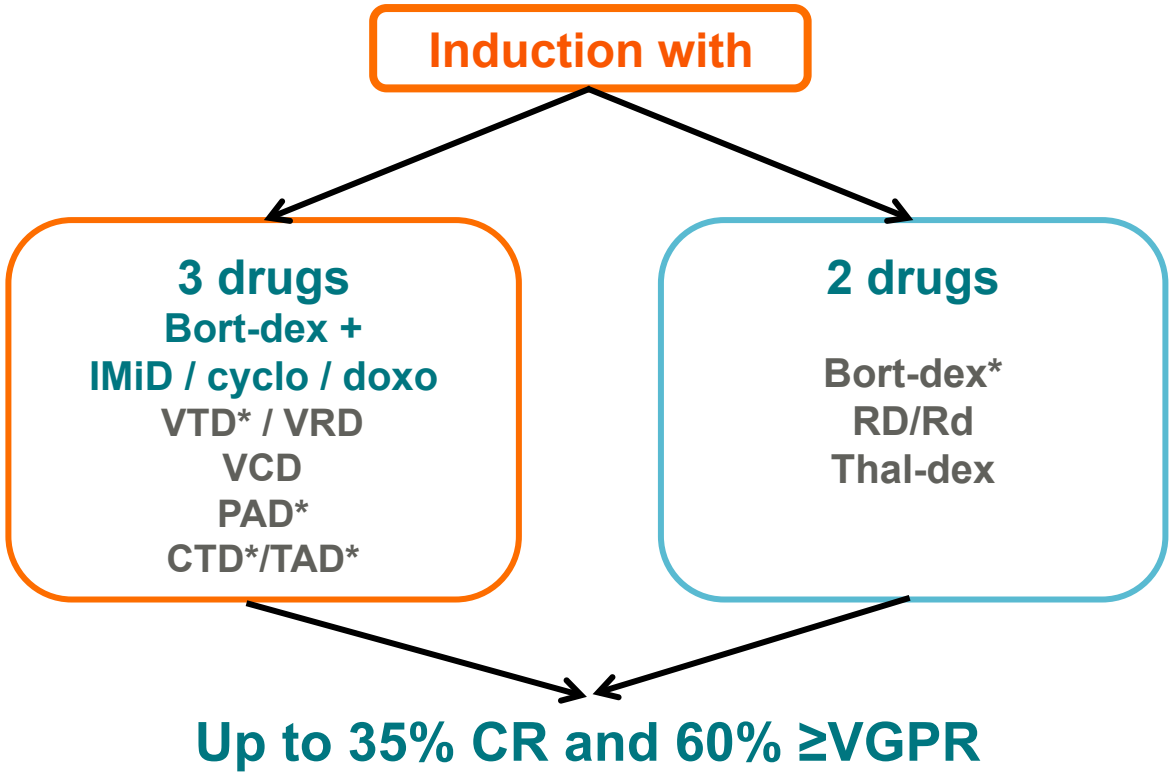
- Median follow-up ~37 months

	Bortezomib-based induction	Non-bortezomib-based induction	HR	95% CI	P
Median PFS, mos	35.9	28.6	0.75	0.65–0.85	< 0.001
3-yr PFS, %	50.0	41.1			

Primary end point: Post transplant CR+nCR and PFS

Sonneveld et al. J Clin Oncol 2013;31(26):3279-87

Novel agent-based induction regimens



Strong preference for 3-drug bortezomib-based regimens

- VTD and VD have been approved by the EMA for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for transplant

Cavo M et al. Blood 2011;117(23):6063-73

Diagnosis MM stage I/IIA (IgG/kappa) Therapy – Vel-Tha-Dex (2-4cycles)+HSCT

- Started therapy at Bucarest on the 11/1/2016 - 1° cycle Vel-CTX-Dex (no Thali in Romania),

VTD vs VCD induction: Response

IFM 2013-04 trial (prospective, intent-to-treat analysis)[1]

	VTD (4-cycles)* N = 169	VCD (4-cycles)† N = 169	p-value
≥ CR	13.0%	8.9%	0.22
≥ VGPR	**66.3%**	**56.2%**	**0.05**

*Bortezomib 1.3 mg/m^2/day SC D1,4,8,11 + Thalidomide 100 mg/day PO D1–21 + Dexamethasone 40 mg/day PO D1–4, D9–12
†Bortezomib 1.3 mg/m^2 /day SC D1,4,8,11 + Cyclophosphamide 500 g/m^2 /day PO D1,8,15 + Dexamethasone 40 mg/day PO D1–4, D9–12

GIMEMA MMY-3006 and EMN-02 studies (retrospective, case-matched analysis)[2]

	VTD (3-cycles)‡ N = 236	VCD (3-cycles)§ N = 236	p-value
≥ CR	19%	6%	< 0.001
≥ VGPR	64%	37%	< 0.001

‡Bortezomib 1.3mg/m^2 twice weekly + Thalidomide 100➔200mg/day + Dexamethasone 320mg/cycle (3 X 21-day cycles)
§Bortezomib 1.3mg/m^2 SC D1,4,8,11 + Cyclophosphamide 500 g/m^2/day IV D1,8 + Dexamethasone 40 mg/day PO D 1, 2, 4, 5,8, 9,11, 12 (3 X 21-day cycles)

1. Moreau, P et al. Blood 2016;127:2569-74;
2. Cavo et al. Leukemia 2015;29(12):2429-31.

Therapy – Vel-Tha-Dex (2-4cycles)+HSCT

- 3 other cycles with VTD
- Liver ➡ Echo progressive nodular disease,

  ➡ repeated needle biopsy: plasma-cells, with prominent nucleoli (G2 – pleomorphic Histotype): CD138+, k light chain+ restriction , Ki67 /MIB (5%), negative for Keratins,CD34, Cyclin D1

- I° ASCT – June 2016: partial remission: bone response, reduction of liver nodular lesions
- II° ASCT – Octobre 2016

The incidence and pattern of **Liver infiltration** in Haematologic malignancies

- 80-100% - in Cronic Myeloproliferative disease
- 60-70% - in Acute Leukemia
- 50-60% in non Hodgkin's Lymphoma, LLC
- 32% in Multiple Myeloma (nodular infiltration is seen only in MM e LNH)

Waltz- Mattmuller at al. Pathol Res Pract 1998

Common sites for EMD

- 5% of pts with MM are diagnosed with EMD plasmacytomas, and less as a primary lesion
- At diagnosis: Skin and soft tissue, upper respiratory
- Less common sites: gastro-intestinal(10%), liver, lymphnodes, testes, CNS(1%).
- Relapse/progression: liver involvement (16% of pts – dg. with endoscopic ultrasound – fine needle aspiration)

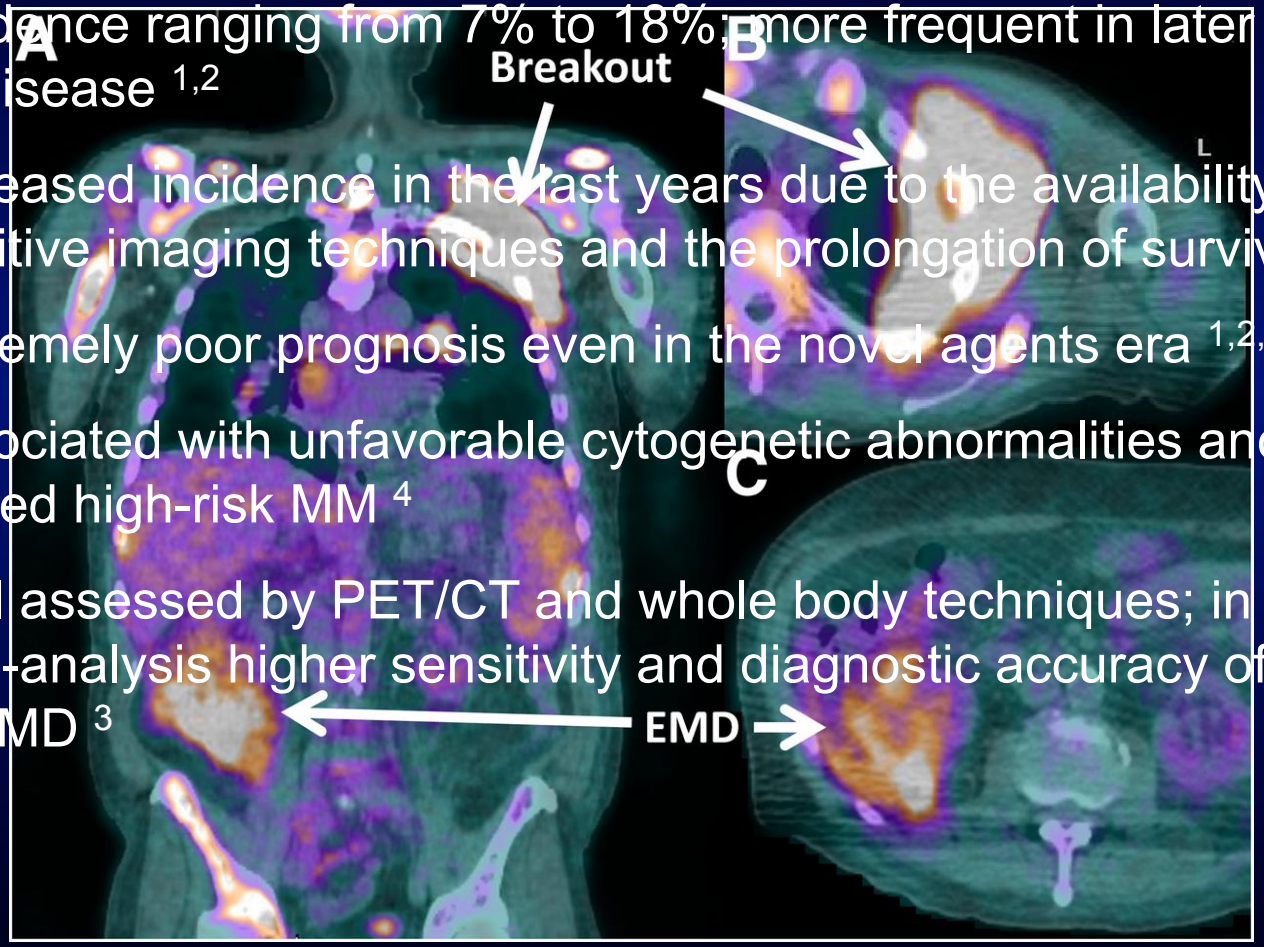
Husney J. Endoscop Ultrasound 2016

Sites of extramedullary disease (Usmani Ematologica 2012)

Anatomic site	EMD-1 (n=66) % of affected patients	EMD-2 (n=35) % of affected patients
Head & neck		
Central nervous system	3%	3%
Oral Cavity	1,50%	-
Lymph Nodes	6%	6%
Chest		
Chest wall	14%	-
Breast	9%	3%
Lung	3%	3%
Pleura	3%	6%
Abdomen & pelvis		
Liver	21%	34%
Spleen	9%	11.5%
Pancreas	-	3%
Gastrointestinal tract	-	6%
Kidney	6%	6%
Testes	4.5%	3%
Lymph nodes	10.5%	12%
Skin/soft tissue	30%	14%
Skeletal muscle	4.5%	-
Paraspinal area	25%	23%
Lymphadenopathy(>2sites)	21%	11%

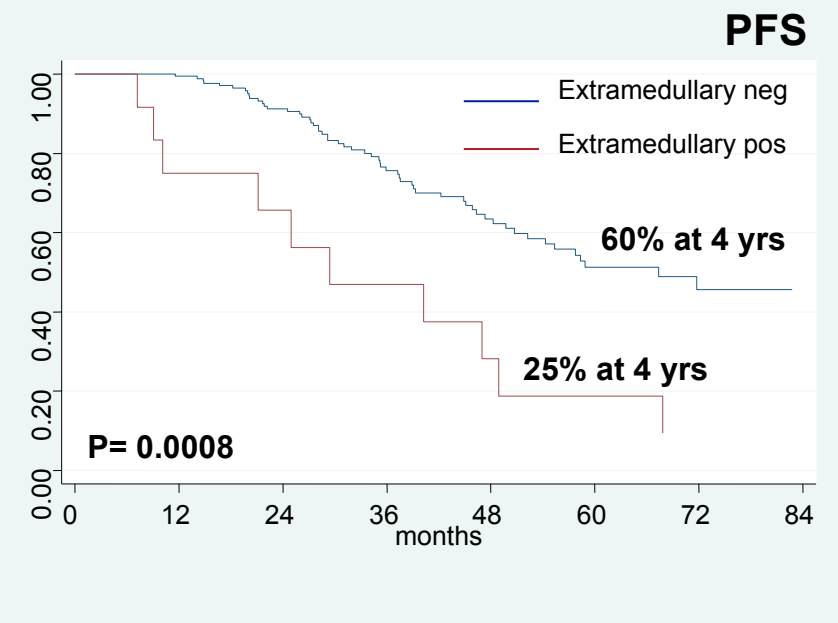
EXTRAMEDULLARY DISEASE (EMD)

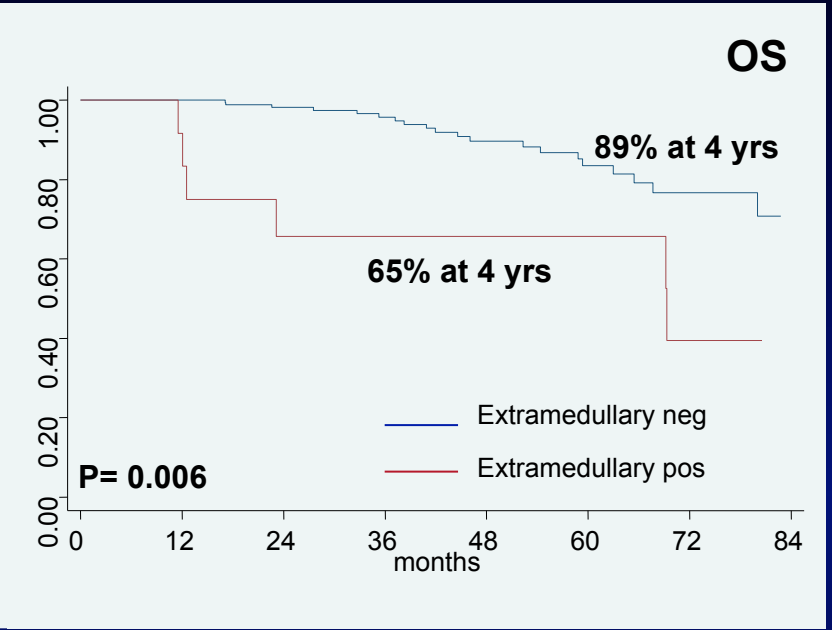
- Need to identify true EMD from para-medullary/breakout lesions
- Incidence ranging from 7% to 18%; more frequent in later phases of the disease [1,2]
- Increased incidence in the last years due to the availability of more sensitive imaging techniques and the prolongation of survival [1,2]
- Extremely poor prognosis even in the novel agents era [1,2,3,4]
- Associated with unfavorable cytogenetic abnormalities and GEP defined high-risk MM [4]
- Well assessed by PET/CT and whole body techniques; in a recent meta-analysis higher sensitivity and diagnostic accuracy of PET/CT for EMD [3]



[1] Varettoni M. et al, Annals of Oncology 2010
[2] Bladè J. et al, JCO 2011
[3] Lu Y.Y. et al, Clinical Nuclear Med 2012
[4] Usmani S.Z. et al, Haematologica 2012

PROGNOSTIC RELEVANCE OF PET/CT AT DIAGNOSIS IN PATIENTS WITH EXTRAMEDULLARY DISEASE [1,2]





VARIABLES	HAZARD RATIO (95% CI)	P VALUE
PFS		
Extramedullary disease	5. 93 (2.27-15.51)	0.000
del (17p) ± t(4;14)	1.90 (1.09-3.32)	0.023
Not complete FDG PET suppression	1.89 (1.06-3.35)	0.030

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[1] Zamagni E. et al, Blood 2011

[2] Bartel T.B. et al, Blood 2009

Histological Liver Involvement in MM

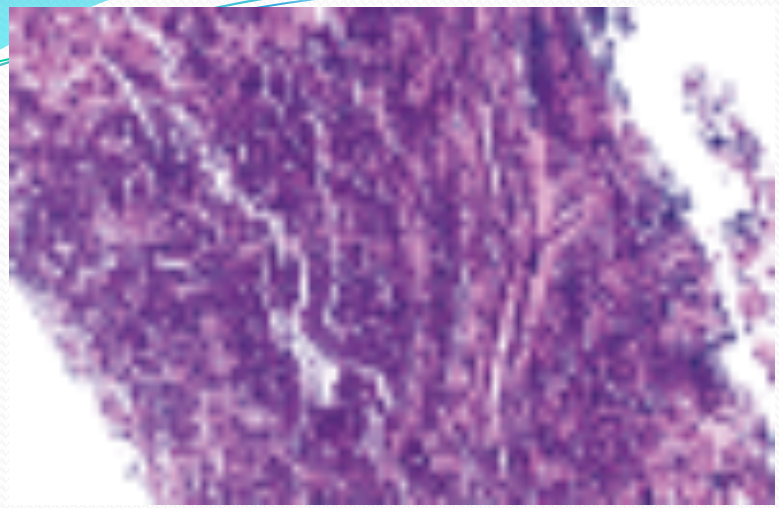
- Light chain deposition disease (usually K type)- membrane of biliary ducts and sinusoid without parenchimal lesions (1, 2)
- Extramedullary plasmacytoma
- AL Amiloydosis (15% of MM)
- Nodular or Diffuse infiltrative pattern (sinusoidal, diffuse, mixed types)

1.Sammanez C Eur. J. Haematology 2006
2. Michopoulos S Dig Dis Sci 2002

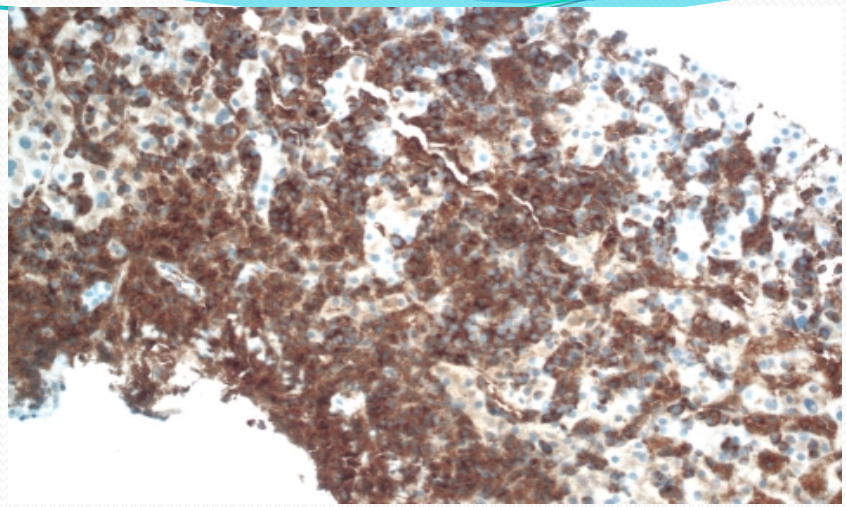
Liver EMD in MM

- Is rarely clinically evident pre-mortem. Pattern:
  - diffuse infiltration with hepatomegaly
  - rarely as nodules (unifocal o multifocal)
- On autopsy: myeloma cells proliferated not only in the nodular lesions, but also in the sinusoides (from nodular to nodular and diffuse pattern at the end-stage)
- Immuno-histochemistry: myeloma cells were negative for p53 at diagnosis, but positive at relapse.
- Several case reports described that nodular hepatic EMD is associated with end-stage disease and a very poor prognosis

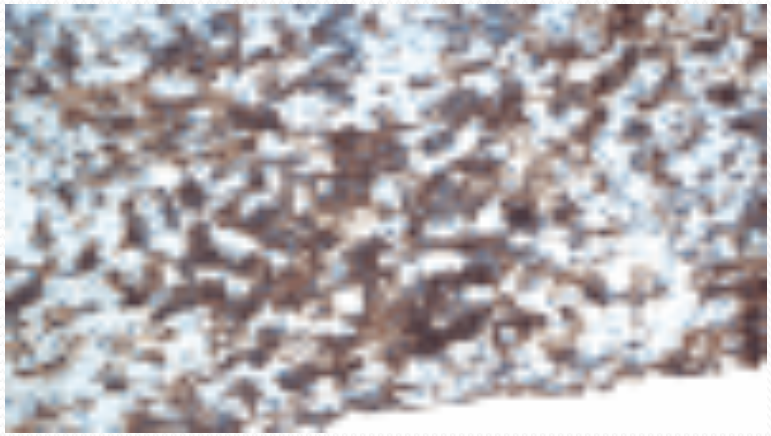
Histology



HE liver biopsy showing massive plasma cell infiltration (HE)

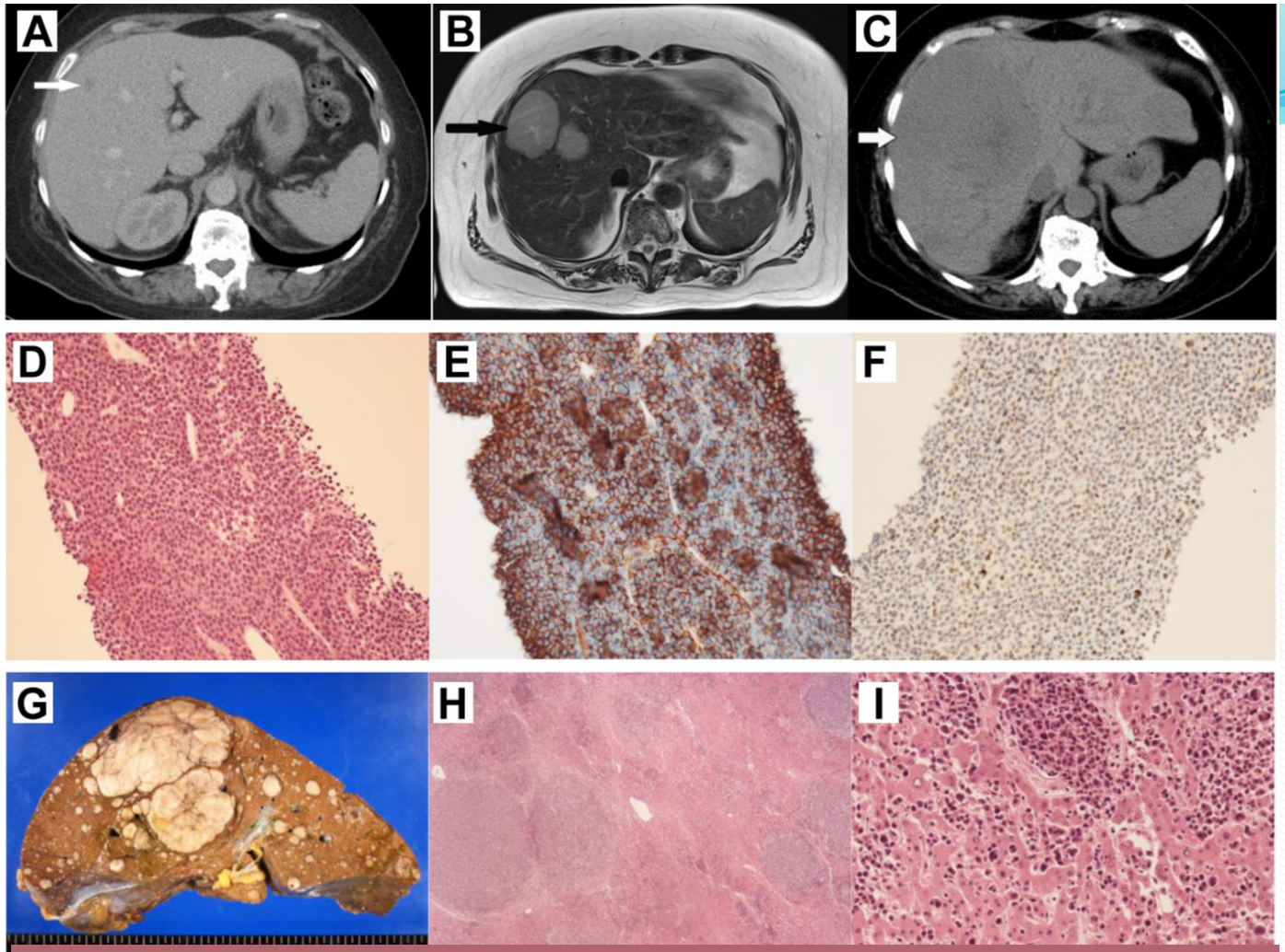


Positive kappa light chain stain on liver biopsy.



Positive CD138 (syndecan-1), a plasma cell marker. CD138 is expressed on plasma cells, including the malignant plasma cells of MM and some lymphomas

Fadi E Rahhal World J Gastroent 2009



Hepatic Extramedullary Disease (Arrows). (A) CT Scan in April 2011 Showing a Small Solid Lesion Measuring 9 mm in the Liver S8 (Right Anterior Superior Segment). (B) Abdominal MRI in July 2011 Showing Multiple Lesions in The Liver Without Hepatomegaly, Which Were Hyperintense on T2-Weighd Images. (C) CT Scan in October 2011 Showing That the Hepatic Lesion Had Increased In Size to 117 mm. (D-F) Histological and Immunohistochemical Studies of a Hepatic Nodular Lesion Showing Sheets of Plasma Cells (D; H&E Stain) That Were Positive for CD138 (E). Myeloma Cells Were Also Positive for p53 (DO-7, A Mouse Monoclonal Antibody Which Recognized the Wild-Type and Mutant-Type of the p53 Protein; F). (G-I) Autopsy Specimen of the Enlarged Liver in October 2011 Showing Numerous Nodular Lesions (G and H). Myeloma Cells Also Proliferated in the Sinusoids (I)

Mikiko Clinical Lymph, Myeloma & Leukemia, 2014

- Mayo clinic: 869 case of MM – 21% liver was palpable (5% of pt. >5cm). Other symtomes: jaundice, portal hypertension, enzyme level, abnormal liver function. (Kyle RA, 1975)

- Little Rock: Talamo 2584 pts with MM: liver mass of nodules : found in 9 pts

- Thomas et al: Reviewed 64 cases of MM (including autopsy)

- Hepatomegaly > 4cm right costal margin : 58% of pts
- Splenomegaly: 25% of pts
- Jaundice (serum bilirubine 3,2-17,3mg/dl): 14%
- Some pts: only elevations of alkaline phosphatase from PC liver infiltration
- Only 9% - normal liver in pathological exam
- 40% - PC involvement of the liver from plasmacytomas to diffuse sinusoidal infiltration

Conclusions

- Liver infiltration is not a classical manifestation of MM
- The initial presentation con be subtle, but rapidly progressive
- Nodular hepatic lesions enlarged rapidly despite novel agents' therapy, resulting in nodular and diffuse infiltration
- The cytogenetic and immunohistochemical have been related with 17p deletion (p53 locus) -10% of pts at dg. and increases in disease progression: -agressive such EMD, -lack of treatment response, - shorter survival even in novel agent era.
- Additional studies for GEP in patients who develop EMD for understanding the distinctive biology of the patients' subset with EMD
- Necessary to study if /when /where/ why the neoangiogenesis and loss of adhesion molecules such as CD56 could play a part in the extramedullary progression of the disease

- The number of clinically liver's involvement reports is small, difficult to ascetain the prognosis or it's response to therapy
- Some reports demonstrated successful managment of EMD with novel agents: it's not our case!!!
- SCT is effective in inducing remission but relapse is common
- Short at al. : EMD pomalidomide's response rate - approximately 30%
- Improved therapeutic strategies are required for this subgroup of pts with EMD

Ringraziamenti

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- Dr.ssa Zamagni Elena
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- Dr.ssa Pantani Lucia
- Dr.ssa Mancuso Katia

Istolinfopatologia – Dr.ssa Sabattini

- Dr.ssa Sabattini Elena
- Dr. Sagramoso Carlo
- Dr. Bacci Francesco

PET - Prof. Fanti

- Dr.ssa Nanni Cristina