Plasma cell myeloma and other plasma cell neoplasms: Exciting new facts about an old disease
A report from the SH/EAHP Workshop 2009
Cleveland OH

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Plasma Cell Disorders

- Plasma cell is the dominant and proliferating neoplastic population, +/- M-component

- **Multiple myeloma**
  - Smouldering and indolent MM
  - Plasma cell leukemia
  - Osteosclerotic MM (POEMS syndrome)

- MGUS (monoclonal gammopathy of unknown significance)

- Solitary plasmacytoma
  - Osseous
  - Primary extraosseous plasmacytoma (EMP)

- Primary amyloidosis

The Spectrum of Immunoproliferative Disorders and the Border Between B-Cell Lymphoma and Plasma Cell Neoplasms
„Everything with plasma cell differentiation and look-alikes…“

More than 220 cases were submitted

- **Plasma cell myeloma and related neoplasms (53 cases)**
  - Plasmablastic lymphoma and other large cell lymphomas with plasmablastic morphology/differentiation
  - Nodal marginal zone B-cell lymphoma
  - Lymphoplasmacytic lymphoma
  - Non-nodal marginal zone lymphomas
  - Other small B-cell lymphomas with plasma cell differentiation
Plasma cell myeloma
...and its borders and problem zones

- t(11;14)+ PCM (12 cases, plus others)
- PCM and other B-NHL/MBL
- Extramedullary plasmacytoma and extramedullary manifestations of PCM
- Plasmablastic PCM (21 cases)
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- others
  - Amyloidosis
  - Crystal-storing histiocytosis
  - Osteosclerotic PCM
IgH translocation partners in MM

11q13  \textit{CCND1}  (15-20%)

4p16.3  \textit{FGFR3/MMSET}  (10-20%)

8q24  \textit{C-MYC}  (10%, sec. alteration)

6p21  \textit{CCND3}  (<5%)

16q23  \textit{C-MAF}  (2-5%)

20q11  \textit{MAFB}  (2%)

6p25  \textit{MUM1/IRF4}  (rare)

1q21  \textit{IRTA1/IRTA2}  (1-2%)

- Represent 90% of translocation-pos. MM (50-70%)
- Approx. equal frequency in MGUS
Case 54 (D. Visnavantha)

Anemia, no osteolytic Lesions
CD20+, CD19+, Pax5+
CD38+, CD138
sIg and cIg
IgGk paraprot.
t(11;14)

Initially Diagnosed As LPL

CD20  Pax5  CyclinD1
2 groups of t(11;14)+ MM identified by gene expression profiling:

- Lymphoplasmacytic variant with expression of B-cell markers (CD20, Pax 5 etc.)

- conventional form
t(11;14) + MM IgM positive
Usually conventional variant
In LPL: CyD1-, no homogeneous expression of PC markers, mixed morphology, often IgM 
kappa
t(11;14)(q13;q32) in MM

- t(11;14)(q13;q32) due to errors in Ig heavy chain switch recombination results in Cyclin D1 overexpression

- Cyclin D1+ MM usually well differentiated, often lymphoplasmocytoid (40%), frequently CD20+ (50-66%)

- Only strong and homogeneous Cyclin D1 is diagnostic of t(11;14)

- Frequent in IgM, IgE and nonsecretory MM

- Equally common in MGUS

- More commonly leukemic

- **BUT:** otherwise usually classical PCM (CRAB lesions)
**Gene expression patterns in MM**

*Show strong imprint of cytogenetics*

Correlation of Cyclin D1 mRNA and FISH

Specht et al, Blood 2004
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PCM and other B-cell lymphoproliferative disorder or monoconal B-cell lymphocytosis (MBL)

Case 276, M. Salama
69 yo female presented with anemia, renal failure & paraproteinemia
- CBC: WBC 4 K/μL, Hgb 7.1 g/dL, Plts 122K/μL.
- Serum protein studies:
  - TP 9.3 g/dL with 4 g/dL paraprotein
  - IgG 7 g/dL, with suppressed IgA & IgM

Flow cytometry dot plot: Plasma cells (red), Monoclonal B-cells (blue)
PCM and other B-cell lymphoproliferative disorder or monoclonal B-cell lymphocytosis (MBL)

- **Differential diagnosis:**
  - PCM with lymphoplasmacytic morphology
  - B-cell NHL with plasmacytic differentiation
    - LPL, MZL, CLL with clg

- **Clues for diagnosis:**
  - Aberrant immunophenotype of PC (CD56) and lack of B-cell antigens on PC
  - Aberrant immunophenotype of B-cells (CD5)
  - Discordant light chain expression
  - Clinical features
  - Cytogenetics

(Seegmiller et al. *AJCP 2007;127:176-81*)
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Plasma cell leukemia (PCL)

- >20% PC in PB diff. count or >2x10^9/L
- Primary (2-5% of all MM) or secondary during course of the disease
- Broad cytological spectrum
PCL – clinical features

- Sex, age distribution, incidence of osteolysis similar to MM
- More often light chain only, IgD or IgE, non-secretory
- Higher incidence of adverse prognostic features
  - Organomegaly and high tumor mass, more common extramedullary Disease (25-75%)
  - Unfavorable cytogenetics
  - More common t(11;14) (case 151 Tadesse-Heath & Jaffe: both t(11;14) and C-MYC)
    - Higher β2-MG, LDH, PC labelling index, sIL6-R, calcium

Pellat-Deceunynck 1998; Garcia-Sanz 1999; Avet-Loiseau 2001; Saccaro 2005; Dimopoulos 1994
Common absence of CD56
More common CD20+

Poor prognosis similar to high-risk
MM under standard therapy
(8 vs 11 vs 36 mo)

Garcia-Sanz et al, Blood 1999
Pellat-Deceunynck et al, Leukemia 1998
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Primary extramedullary plasmacytoma vs. Extramedullary extension of PCM

- Often a diagnostic problem for pathologist, less so for clinician
  - Extramedullary extension of PCM usually aggressive end-stage disease
  - Evidence of end-organ damage
- No morphological, phenotypical or cytogenetic criteria for distinction in the literature
- Can we derive the clinical behaviour of plasmacytoma from morphology or immunophenotype?
Case 91, J. Frater

80-year-old male with recurrent nasal obstruction
IgG? paraprotein of 1.4g/dl
No bone lesions
Normal PB counts
Discrete polyclonal plasma-cytosis of bone marrow
Case 230 R. Ryan

59 y/o male presented with vomiting, diarrhea, weakness & renal failure.
Endoscopy: prominent gastric folds.
Bx:
PC-rich MALT lymphoma

15 mo later, hip pain. CT multiple bony lesions
• Serum protein studies:
  – Panhypogammaglobulinemia
  – Ig FLC at 21,700 mg/L
• IgH PCR (gastric bx): +
• API2/MALT1 PCR: -
• FISH (fem head) : del(13q)
Primary extramedullary plasmacytoma

- >80% in upper respiratory tract
- Indolent, good prognosis following local therapy
- Local recurrence in 15-30%, transformation to multiple myeloma rare
- No clearcut prognostic features for risk of transformation to MM
- No morphological differentiation from extramedullary MM manifestation (eMM), but usually well differentiated
- MALT lymphoma with plasmacytic differentiation?
Immunophenotype of EMP vs. eMM

- Primary EMP and eMM show similar PC phenotype
- Lack of CD56 and cyclin D1 in EMP
- eMM commonly of higher grade, high MIB1 index and p53 and p21 expression

Kremer et al, J Pathol 2005
FISH in EMP

- Common IgH breaks
- No t(11;14)
- t(4;14) in same frequency as MM
- Common polysomies
- Common deletion/monosomy 13q
- No MALT-type aberrations

- Similar to MM, but differences in translocation partners
- Lack of prognostic significance

Bink et al, Hematologica 2008
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Multistep pathogenesis of PCM

90% of MM patients show M-protein in earlier serum samples (Weiss et al, Blood 2009)

(Bergsagel & Kuehl. J Clin Oncol)
MGUS

**BM stromal cell**

TNFa, TGFß...

**MGUS**

IL-6, IGF-1

**Intramedullary MM**

**Extramedullary MM**

and Plasma cell leukemia

Angiogenesis

Osteolysis

Osteoclasts

Osteolysis

karyotype instability

13q deletion

Mutations in noncanonical NFkB pathway

Chromosome 1p-, 1q+

Gene methylation

c-myc alterations

Ras, p53 mutations

Gene methylation
#312 Sidhu

- 86-year-old female
- 1y history of myeloma
- Renal insufficiency, anemia, IgG/I M-prot.
- Massive retroperitoneal lymphadenopathy
- CD138+, Lambda+, MUM1+, MIB1 80%
- CD20-, CD79a-, EBERs-

- Extramed. Plasma cell myeloma, plasmablastic
Definition:

- ≥ 2% plasmablastic myeloma cells
  - Diffuse chromatin pattern
  - nucleus ≥ 10µm or nucleolus ≥ 2µm
  - High N/C ratio
  - Centrally placed nucleus, no/little perinuclear hof
Bone marrow histology in myeloma (Bartl et al, AJCP 1987)

- Definition of plasmablastic myeloma
  - Predominance of cells
    - Large nuclei with very prominent, central nucleoli
  - High N/C ratio, faint perinuclear hof
Comparison of Grading Systems

- Bartl et al (Munich)
  - Predominantly histology-based
  - Based on predominant cell type

- Greipp et al (Mayo Cl.)
  - Exclusively cytology-based
  - 2% cut-off for „plasmablasts“

- Mostly based on old series, relatively limited data under new therapy regimens

Plasmablastic Morphology — An Independent Prognostic Factor With Clinical and Laboratory Correlates: Eastern Cooperative Oncology Group (ECOG) Myeloma Trial E9486 Report by the ECOG Myeloma Laboratory Group

Plasma cell myeloma plasmablastic

Morphological diagnosis, however, two different definitions in use

- Cytology-based, 2% threshold (Greipp et al)
- Histology-based, pred. cell-type (Bartl et al)

Do diagnose „plasmablastic“ PCM (but use the correct classification with respect to material!) – probably identifies high risk disease (high risk genetics)

- Other high grade morphology may be identified
- High MI B1 index does not define „plasmablastic“
C-myc breaks and p53 loss in plasmablastic PCM

- 18 workshop cases examined (break-apart probe)
  - 8/16 (50%) cases positive for c-myc
  - 3 cases with deletion of p53
- Frequency in PCM in general 15%
  - Prognostic significance uncertain, but hints to more aggressive behaviour
- Thought to be secondary event, often very complex, with varying breakpoints
- >90% human myeloma cell lines show c-myc (or N/L-MYC) rearrangements, 40% with non Ig partners

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51-year-old male, multiple bone lesions, no M-protein


Negativ: CD10, CD20, CD30, CD43, CD45, CD79a, CD99, LMP1, cyclin D1, PAX5, HHV8, IgA, IgD, IgG, or IgM.
11-year-old (!) female, multiple osteolytic lesions

Courtesy of Carlos Ortiz, Hosp. ABC, Mexico City
MUM1

CD138

Cyclin D1

No breaks in C-MYC, CCND1

CD56

EBERs
EBV+ plasma cell neoplasms

- **Chang et al** (AJCP 2007):
  - 1/4 extramedullary plasmacytomas (ENT region)
  - 3/54 multiple myelomas (2 plasmablastic)

- **Colomo et al** (AJSP 2004)
  - 2/8 plasmablastic myelomas / plasmacytomas

- **Aguilera et al** (Mod Pathol 95)
  - 3/23 EMP of head and neck

- **Dong et al**, (AJSP 2005)
  - 14 cases of EBV+ lymphomas in HIV+ patients with plasmablastic features
    - 4/14 with overlap features with plasma cell myeloma
    - 4/4 with bone and soft tissue lesions, 2/4 with BM involvement
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Robert Lorsbach & Eric Hsi
the other members of the
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SH Workshop Cleveland

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