Plasma cell neoplasms

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Definition

Epidemiology

Pathogenesis

Diagnostic considerations
Definition

Malignant expansion of terminally differentiated, rearranged, somatically hypermutated and heavy chain class-switched B cells that usually secrete a monoclonal immunoglobulin.
History

1844
First documented case

1845
Abnormal serum proteins

Steel and quinine (T. Watson)

Rhubarb and orange peel (S. Solly)

1939
Serum identified

NORMAL

\( \alpha_1 \alpha_2 \beta \gamma \)

\( \text{alb} \)

MYELOMA

\( \alpha_1 \alpha_2 \beta \)

\( \text{alb} \)

1962
Autologous transplantation
(T. J. McElwain and R. L. Powles)

1983
Thalidomide (S. Singhal and B. Barlogie)

1999
Bortezomib (R. Z. Orlowski)

2002
Lenalidomide (P. G. Richardson and K. C. Anderson)


Treatment
Definition

Epidemiology

Pathogenesis

Diagnostic considerations
3rd most common lymphoid neoplasm

- B-CLL/SLL: 23%
- DLBCL: 20%
- MM: 18%
- FL: 10%
- Hodgkin lymphoma: 8%
- other mature B-cell lymphomas: 10%
- ALL, B- and T-cell: 6%
- mature T-cell lymphomas: 5%
Incidence and risk factors

• 0.4-5/100,000/y
• M:F=1.4:1
• Median age 70y
• Risk factors
  – MGUS (25x)
  – age >65 (13x)
  – AIDS (8x)
  – family history (3.5x)
  – black race (2.5x)
  – Herpes zoster (1.8x)

http://safetyca.info/diseases/myeloma-incidence-statistics-cancer-research-uk
Definition

Epidemiology

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Diagnostic considerations
Pathogenesis

• Activation of mitotic cycle entering
  – constitutional expression of a cyclin D gene
    • cyclin D/IGH switch region gene translocations
    • early and unifying oncogenic event
  – disruption of other Rb-pathway components
    • methylation of $p15$ and $p16$
    • $p18$ bi-allelic deletions
  – NF-$\kappa$B-/JAK/STAT3- and/or PI3K-pathway activation
    • microenvironment (IL-6, IGF-I, VEGF)

• Microenvironmental independence
  – 8q24 rearrangements ($MYC$), del17p13 ($p53$)
Cyclin D expression in myeloma

CD38/cyclin D1
Critical role of cyclin D type activity
Stepwise molecular events in plasma cell neoplasm progression

Hideshima et al. Blood 2004
The Achilles heel

Morgan et al. Nat Rev Cancer 2012
Definition

Epidemiology

Pathogenesis

Diagnostic considerations
**Plasma cell myeloma**

**Variants:**
- Non-secretory myeloma
- Indolent myeloma
- Smoldering myeloma
- Plasma cell leukaemia

**Plasmacytoma**
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma

**Immunoglobulin deposition diseases:**
- Primary amyloidosis
- Systemic light and heavy chain deposition diseases

**Osteosclerotic Myeloma (POEMS syndrome)**

**Heavy chain diseases (HCD):**
- Gamma HCD
- Mu HCD
- Alpha HCD

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**WHO 2001**

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**WHO 2008**

**Monoclonal gammopathy of undetermined significance (MGUS)**

**Plasma cell myeloma**
- Variants:
  - Asymptomatic (smoldering) myeloma
  - Non-secretory myeloma
  - Plasma cell leukaemia

**Plasmacytoma**
- Solitary plasmacytoma of bone
- Extraosseous (extramedullary) plasmacytoma

**Immunoglobulin deposition diseases**
- Primary amyloidosis
- Systemic light and heavy chain deposition diseases

**Osteosclerotic myeloma (POEMS syndrome)**
MGUS

• Definition
  – M-protein <30g/L
  – <10% clonal bone marrow plasma cells
  – no end organ damage
  – no B-cell lymphoma

• Only IgG and IgA MGUS progress to myeloma

• Risk of progression
  – 1%/y
  – M-gradient height
  – IgA>IgM>IgG
Plasma cell myeloma

• Definition
  – end organ damage, related to plasma cell neoplasia
    • hypercalcemia, renal failure, anemia, bone lesions (CRAB)
    • recurrent (bacterial) infections (?)
  – M-protein, usually >30g/L
  – clonal bone marrow plasma cells, usually >10%
Plasma cell myeloma

- Clinical variants
  - smoldering myeloma
    - M-protein >30g/L and/or >10% clonal bone marrow plasma cells
    - AND
    - no end organ damage
  - non-secretory (often IgD+) and non-producer myeloma
    - >10% clonal bone marrow plasma cells, no M-gradient
    - 75% of patients have abnormal free light chain ratios
  - plasma cell leukemia
    - >2x10⁹/L or >20% clonal plasma cells in the peripheral blood
    - often IgD or IgE+, CD56-
Plasma cell myeloma, additive multimodal diagnostic approach
Plasma cell myeloma, bone marrow biopsy

- Non-perisinusoidal clonal plasma cell clusters
  - >10% of hematopoiesis or
  - <10% with organ damage

- Clonal restriction
  - immunohistochemistry or CISH
    $\kappa/\lambda > 1:15$ or $15:1$ - diagnostic
    $\kappa/\lambda > 5.5:1$ and $< 0.45 : 1$ – suspicious

- Other morphologic features
  - prominent osteoclast activity, new bone formation
  - tunneling fibro-osteoclasia
  - amyloidosis
Plasma cell myeloma, morphology
Plasma cell myeloma, morphologic variants

- Marshalko type
- Small cell (CD20, cyclin D1)
- Convoluted/cleaved
- Polymorphous
- Asynchronous
- Plasmablastic

Plasma cell myeloma, inclusions

- Flame cells (IgA)
- Dutcher or Russell bodies
- Mott cells
- Crystal storing cells
- Gaucher-like cells

www.healthsystem.virginia.edu/internet/hematology/hessidb/
Plasma cell myeloma, phenotype

- **Uniform expression**
  - CD38, CD138, vs38c, CD79a, MUM1, BLIMP1
  - heavy and/or light chains
    - 1% true non-producers

- **Aberrant expression**
  - CD56 (70%)
  - cyclin D1 (40%)
  - CD117>CD20>CD52

- **Phenotypic loss**
  - CD19, CD45RA
Plasma cell myeloma, differential diagnosis

• Lymphomas
  – lymphoplasmacytic lymphoma
    • clinical setting, bone marrow infiltration pattern
    • CD19+, PAX5+/-, CD20+/-, CD56-, cyclin D1-, IgM+, MYD88mut
  – marginal zone lymphoma
    • clinical setting, bone marrow infiltration pattern
    • CD19+, PAX5+/-, CD20+/-, CD56-, cyclin D1-, CD43+/-
  – plasmablastic lymphoma
    • clinical setting
    • EBER+, cyclin D1-, PAX5-/+,(CD56-, CD4+, CD30+)

• Carcinomas
  – cave, myeloma can express CK and carcinoma CD138
    • MUM1, light/heavy chains (CISH), clonality (PCR)
Lymphoplasmacytic lymphoma

CD20
Plasmablastic tumors

Vega et al. Mod Pathol 2005
Collisions

CD138

CCND1

PAX5
Plasma cell myeloma, prognosis

- Clinical parameters
  - Durie and Salmon/ISS stage
  - $\beta_2$ microglobulin
  - light chain restriction type

- Histopathology
  - morphological variants
  - infiltration pattern
  - cyclin D1 expression

Souverini et al. Blood 2003
Plasma cell myeloma, molecular genetics

- Prognostic and therapeutic implications
  - hyperdiploid>non-hyperdiploid
  - t(11;14) (*cyclin D1*), benefit form high dose therapy
  - t(4;14) (*MMSET*), overcome by bortezomib
  - t(14;16) (*C-MAF*)
  - del17p13 (*p53*)
  - del13q14
  - 8q24 rearrangements (*MYC*)

Dewald et al. Blood 2005
Plasmacytoma

• Definition
  – localized plasma cell neoplasm
    • osseous or extraosseous
      – upper respiratory tract, usually IgA
    • no end organ damage

• Differential diagnosis to (EN) marginal zone lymphoma
  – phenotypic markers
    • PAX5, CD19, CD20, CD43 in MZL
    • CD56, cyclin D1, (IgA) in plasma cell neoplasia
  – genotypic markers
    • t(11;18), t(14;18), t(3;14), +3, +18 in MZL
    • t(11;14), t(14;16), t(4;14), t(6;14) in plasma cell neoplasia
Plasmacytoid extramedullar neoplasms
Take home messages

• *plasma cell dyscrasia, indolent myeloma* - obsolete

• no major/minor criteria for diagnosis of plasma cell neoplasms

• % of plasma cells - not required for myeloma diagnosis

• % of plasma cells - important for differential diagnosis of MGUS and smoldering myeloma

• morphological differential diagnoses to be considered LPL, MZL, PBL, carcinomas