Expanding Spectrum of Diseases Associated with Plasma Cell Dyscrasias

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Plasma cell dyscrasias

- Plasma cell dyscrasias represent a clonal expansion of abnormal plasma cells which produce a monoclonal protein that could be either the whole immunoglobulin (Ig) or a fragment of Ig (monoclonal free light or heavy chain in a variable quantity).

- LCs are removed from circulation by the kidneys, renal damage is a common complication and can be very heterogeneous.
Plasma cell function

- Normally plasma cells, and in lesser extent some type of B-cells, produce one of five heavy chain types (G, A, M, E, D), together with κ or λ molecules and create immunoglobulins.

After binding of the antigen, a naive B cell is changed to a plasma cell.
Signal to the nucleus 2-3 days

After 10 days there will occur IgM
Switch to produce IgG (2-3 weeks) and change to a memory cell
Second contact with antigen: IgG almost immediately
Plasma cell dyscrasias

- Antibody molecules are composed of two identical heavy and light chains, each containing variable and constant domains.
- The variable domains form an antigen-binding site,
- Light chains are of two types, κ and λ, and in any given antibody molecule only one type occurs.
Discovery of Bence-Jones protein: who is behind it?

• more than 150 years ago, the presence of Bence Jones protein was discovered
• the first in vitro cancer test

- In 1845, Dr William MacIntyre, a physician in London, was called to see a 45 year-old patient,
- general practitioner, Dr Thomas Watson
- Edema- possibility of nephrosis, he tested the urine for albumin
- Both Dr MacIntyre and Dr Watson then sent urine samples to the Dr. Henry Bence Jones
- The patient died, Dr MacIntyre subsequently published the post-mortem examination in 1850.
- Henry Bence Jones had already described the patient’s urinary findings in two, single-author articles (one in The Lancet, in 1847).
- Bence Jones’s reputation was assured, while the contributions of his colleagues – a footnote in the history of medicine.
Discovery of Bence-Jones protein

- Waldayer first identified - the protein originate in bone marrow plasma cells (1875).
- In 1922, Bayne-Jones and Wilson characterized two types of BJ protein (using antisera). The proteins were classified as group I and group II types.
- In 1956 Korngold and Lipari showed that antisera against the different groups also reacted with myeloma proteins. As a tribute to their observations the 2 types of BJ protein were designated: kappa and lambda.
- Edelman and Gally, in 1962, subsequently showed that FLCs prepared from IgG monoclonal proteins were the same as BJ protein.

It had taken more than 100 years from the original observation than the features of Bence Jones protein were finally determined.
Classification of monoclonal gammopathies, multiple myeloma (MM) and related disorders include following groups:

1. Monoclonal gammopathy of undetermined significance (MGUS)
2. Smouldering (asymptomatic) multiple myeloma
3. Symptomatic multiple myeloma
4. Nonsecretory multiple myeloma
5. Solitary plasmacytoma of bone
6. Extramedullary plasmacytoma
7. Multiple solitary plasmacytoma
8. Plasma cell leukaemia
Hematology classification & nephropathology

- Several problems in daily practice
- The clonal expansion of cluster of plasma cells is not only benign or malignant
- Production of Igs or FLCs and these light chains can be deposited
- Important facts were not incorporated in the classification schema
- MGUS and AL amyloidosis
- The term MG of renal significance
- The prevalence of plasma cell dyscrasias increases with advancing age
- Disorders associated with plasma cell dyscrasias often have NS or severe PU
The most frequent categories of renal diseases associated with MGUS and MM

FLCs are nephrotoxic and can damage all kidney compartments: gli, tubuli and vessels.

• **glomerulopathic FLCs**
  1. AL amyloidosis
  2. LCDD
  3. GN with monoclonal deposits

• **tubulopathic FLCs**
  1. cast nephropathy
  2. proximal tubulopathy
  3. TIN associated with M protein

+ Combinations of the above diagnoses
+ Combinations with other diseases (hypertension, vascular nephrosclerosis, DM)

Kidney involvement may represent the first manifestation of hematological disease.
AL amyloidosis
The kidney is the most common organ involved in several types of systemic amyloidosis
Amyloidosis: detection of amyloid
Amyloidosis: diagnosis
IF is the best method for typing amyloid. It allows to classify more than 90% of amyloid in kidney biopsy samples.
Fascinating story of amyloidosis

- Only a small number of patients with „preconditions“ suffer from amyloidosis
- Per Westermark
- Comparison with prion diseases: change in the protein structure, conformational diseases
- Prion diseases are transmissible by food
- Amyloid enhancing factor (amyloid fibrils)

- Is amyloidosis transmissible? Yes, very probably
  - AA amyloidosis is transmissible in several animal experimental models
  - AA amyloid can occur in human food (ducks, geese: pate de foie gras; cattle)
  - AA amyloidosis is transmissible by blood monocytes
Experimental works showed that LCs can transform the phenotype of mesangial cells. In cases of AL amyloidosis the phenotype evolves toward macrophages with development of lysosomes within which degradation and remodeling of LCs into amyloid occur. Amyloid deposition in the extracellular matrix results in activation of metalloproteinases followed by destruction of the native mesangial matrix. The normal mesangium is replaced by amyloid and mesangial cells disappear.

In cases of LCDD, mesangial cells evolve into a myofibroblast phenotype, and mesangial cells proliferate under the influence of overproduction of TGF-β, resulting in the formation of mesangial nodules.
LCDD

kappa
LCDD

DM!!!

GBM

TBM
Proliferative GN with monoclonal deposits
(IgG3 kappa)

- Mimics immune-complex GN (MPGN, MGN).
- Restriction of LC: IF positive is only kappa or less frequently only lambda.
- IgG3 or IgG1
- Proteinurie or NS, 50% have monoclonal protein in serum

More frequent than LCDD
(20 AL amyloidosis, 8 GN with monoclonal dep., 5 LCDD)
Proliferative GN with monoclonal deposits (IgG3 kappa)

The key to the diagnosis: recognition of single light chain restriction
Proliferative GN with monoclonal deposits

- **IgG3**: greatest complement fixing ability
- Most **positively charged** subtype of IgG (can interact with negatively charged GBM)
- **Highest MW** (size restricted by glom. filter)
- Ability to **self-aggregate** spontaneously through Fc-Fc fragment interactions

**Monoclonal gamapathies can lead to proliferative GN via 2 mechanisms:**

1. **deposition of monoclonal Igs** in the mesangium and along capillary walls – activation of complement – proliferative GN

2. **monoclonal Igs** cause the activation of alternative complement pathway by **acting as autoantibodies** (to complement-regulating proteins) – deposition of C3 (**C3 GN**) *without Igs*
Group II, tubulopathic light chains

1. cast nephropathy
2. proximal tubulopathy
3. TIN associated with M protein

**cast nephropathy**
(historically called myeloma kidney)
wanted the first renal complication to be recognized in patients with myeloma
Higher concentration of sodium changes the consistency of T-H protein from a fluid to the gel
The development of the casts involves binding of T-H protein to the CDR3 region of Ig free LCs
Cast nephropathy (myeloma kidney)

no guidelines for how many cast must be present in a biopsy sample
Proximal tubulopathy

Two morphological patterns
Kappa light chains
IF remains the most sensitive method for the detection of LCs restriction
...and many others: cryoglobulins, Waldenstrom GN, Lc crystal storage disease, ect.
Combined patterns

Combined patterns of glomerulopathic and tubulopathic LCs injury (such as LCDD and LC cast nephropathy, amyloidosis and LC cast nephropathy)

Because especially older patients suffer from plasma cell dyscrasias, differential diagnosis can be also more complicated by vascular diseases, DM and other glomerulopathies.
The diagnoses do not jump from the microscope