THE MANY FACES OF MONOCLONAL GAMMOPATHIES

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Monoclonal Gammopathies
Objectives.

• 1. Getting acquainted with varied aspects of clinical presentation of the Monoclonal Gammopathies (MG) and their association with different conditions.

• 2. Following the evolution and pathogenesis from MGUS to myelomas or lymphomas.
The immunoglobulin molecule

• The basic structure of immunoglobulins

- Fab. – Antibody binding site regions
- Fc Receptor Region
- Heavy Chain (gamma, miu, alpha Delta)
- Hinge or J region S-S bridges
- Light Chain (kappa, lambda)
The antibody producing and secreting cells

- B-Lymphocytes (CD19,20)

Immunoglobulins in cytosol and surface

Plasma cell
Monoclonal Gammopathies

Medicine involves a life time of learning, not only because treatments change and improve constantly, but because NO TWO PATIENTS ARE IDENTICAL & THE SAME DIAGNOSIS PLAYS ITSELF OUT DIFFERENTLY IN EVERY PATIENT.
Monoclonal Gammopathies, Definition

• A monoclonal expansion of a single NON FUNCTIONAL ANTIBODY, originating in a mutated MONOCLONAL B- LYMPHOCYTE or PLASMA CELL.
• Plasma cells are “terminal” non proliferating cells, secreting gamma globulins = functional antibodies.
• Once they mutated, they can proliferate producing the pathological antibody.
Monoclonal Antibodies
Patient presentations

1. FH, 46 year old female, dental assistant, never exposed to toxic chemicals, fumes or pollutants.
   Experienced fatigue, full physical check up by family MD and investigations revealed an abnormal protein electrophoresis.
   Referred to Hematology. Physical Exam WNL, Past History non contributory, exc. For years of smoking, quit 2 years ago.
Monoclonal Gammopathies, Patient presentations (1. cont.)

- Investigations: CBC, Renal, Hepatic functions N.
- Immune fixation: Monoclonal IgGK of 15 g/L.
- Bone Marrow aspirate and biopsy – perfectly Normal.
- Skeletal survey, chest X ray, abdominal and pelvic US Normal.
- Pt. followed for 3 ½ years with no change.
- Then sudden back pain in the T6-T7 area.
Monoclonal Gammopathies
Patient presentation (1. cont.)

- All tests from before unchanged, exc. IgGK now up to 21 g/l., Skeletal survey showed a collapsed T6 vertebra. Bone marrow aspirate and biopsy Normal.
- MRI of spine showed lytic lesion in T6, nowhere else.
- Vertebral biopsy confirmed Plasmacytoma.
- VAD chemotherapy administered for 6 cycles with monthly Pamidronate, followed by
- Autologous PBSC transplant. Successful.
Monoclonal Gammopathies
Patient presentation 2.

2. 72 year old female from Poland, retired teacher. Suffered for years from Mixed Connective Tissue disorder. Got intermittent steroid therapy.

Ref. to me for monoclonal gammopathy IgGL

Initial investigations, including BM Bx, skeletal survey, CT-s – all Neg.

Two years later, followed regularly – developed significant lymphadenopathy and splenomegaly.
Lymph node and Bone marrow biopsy revealed low grade diffuse lymphocytic lymphoma.

Treated with Cyclophosphamide, Vincristine, Prednisone – 8 cycles.

Improved remarkably for over one year. Even the Mixed Conn. Tissue Dis. Symptoms abated.

18 months later – huge lymph nodes, aggressive large cell lymphoma and

Hypercalcemia.

CHOP chemotherapy, short remission. Died in one year.
Monoclonal Gammopathies,
Lymphocytic lymphoma, diffuse
Monoclonal Gammopathies
Large Cell diffuse Lymphoma
Monoclonal Gammopathies
Patient presentations 3.

- 43 year old African female from Congo, immigrated to Canada to 25 year old daughter.
- Ref. because of extreme weight loss, weakness, diarrheas, peripheral lymphadenopathy and IgGK of 32 g/l.
- Exam: confirmed diffuse lymphadenop., large tonsils, splenomegaly.
- Bone marrow: heavy infiltration with plasma cells with mostly kappa surface immuno globulin.
- No skeletal lesions, HIV positive.
Monoclonal Gammopathies
Patient presentations 3. (cont.)

• Ref. by me to STD Clinic at McMaster.
• Started aggressive HIV therapy, since Myeloma could not be treated until HIV was not under control.
• Dramatic response to Anti-HIV DNA treatment: Clinically gained weight, felt well.
• Lab: PCR – dramatic reduction of viral load and increase of Helper Lymphocytes.
• Reduction and final disappearance of monoclonal gammopathy.
Monoclonal Gammopathies at the Mayo Clinic 1998. 1149 patients

- MGUS: 63%
- Myeloma: 10%
- Amyloid: 3%
- SMM: 3%
- Lymphom: 4%
- SMM: 2%
- Lymphom: 1%
- Other: 3%
Classification of Monoclonal Gammopathies

1. Monoclonal gammopathies of undetermined significance (MGUS):
   - IgG,
   - IgA,
   - IgM,
   - IgD – almost always will evolve into aggressive Myeloma.
   - Idiopathic light chain – Bence Jones proteinuria.
Classification of Monoclonal Gammopathies (2 cont.)

- Bi- & triclonal Gammopathies,

A. Malignant Monoclonal Gammopathies:

1. Myeloma,
2. Smoldering myeloma,
3. Plasma cell leukemia,
5. Osteosclerotic myeloma (POEMS)
Classification of Monoclonal Gammopathies (cont.3)

B. Plasmacytoma:
1. Solitary Plasmacytoma of bone
2. Extramedullary plasmacytoma.

C. Lymphoproliferative disorders:
1. Waldenstrom’s Macroglobulinemia,
2. Heavy chain diseases (HCD):
   - gamma, alpha, miu (u)
3. Primary Amyloidosis.
4. CLL and other B-cell Lymphomas, PTLD
IgG Myeloma in bone marrow
Classification of Monoclonal Gammopathies (cont. 4)

- D. Connective Tissue disorders:
  - SLE,
  - Rheumatoid Arthritis,
  - Sjogren syndrome and Mixed conn. Tissue Disorders,
  - Scleroderma,
  - Psoriatic Arthritis,
  - Polymyalgia rheumatica,
  - Cryoglobulinemia.
Cryoglobulinemia – rash on legs
Classification of Monoclonal Gammopathies (cont. 5)

• E. Associated with infections:
  • Hepatitis C virus,
  • HIV/AIDS

• F. Dermatologic disorders:
  • Scleredema, Lichen myxoedematous,
  • Diffuse plane xanthomatosis,
  • Urticaria and IgM (Schnitzler’s syndrome)
  • Subcorneal pustular dermatosis,
  • Necrobiotic xanthogranuloma.
  • Pyoderma gangrenosum
Classification of Monoclonal Gammopathies, (cont. 6)

- **G. Miscellaneous:**
  - Acquired von Willebrand’s syndrome with Anti – Factor VIII Ag. Activity.
  - Acquired C 1 esterase deficiency (angioedema)
  - Eosinophilic Fasciitis,
  - Myelodysplasia,
  - Chronic Neutrophilic Leukemia,
  - CIDP with MGUS,
  - Capillary Leak syndrome,
  - T-cell large granular lymphocyte leukemia.
Monoclonal antibody – Anti-F.X
# Course of 241 pts. With MGUS from Kyle, RA: JAMA 251:1849, 1984

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>F/U 24-38 yrs</th>
<th>No. of pts.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No substantial increase of serum or urine monoclonal protein</td>
<td></td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Monoclonal protein =&gt;3.0g/dl, but no myeloma or related disease</td>
<td></td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Died of unrelated causes</td>
<td></td>
<td>127</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>Development of Myeloma, macroglob. Amyloidosis or related disease</td>
<td></td>
<td>63</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>241</td>
<td>100</td>
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Monoclonal Gammopathies of undetermined significance (MGUS)

- Diagnostic Criteria:
  - 1. Presence of a Monoclonal antibody: IgG, A, or M at a concentration of < 3.0 g/dl.
  - 2. Less than 10% plasma cells in bone marrow.
  - 3. Absence of:
    - Anemia,
    - Lytic bone lesions,
    - Renal impairment,
    - Hypercalcemia

Predilection of developing myeloma or related malignancy at a rate of 1% per year.
No evidence of underlying plasma or lymphoproliferative disorder.
Monoclonal Gammopathies
Serum Protein Electrophoresis.
Monoclonal Gammopathies, Incidence and Clinical Characteristics

• MGUS is found in 1-2% of adults in studies from Sweden, US, France and Japan.
• It becomes higher after the age of 70 yrs and 3-4 X higher in African Americans than Caucasians.
• Prevalence of MGUS in Olmsted county, Minnesota: Immunofixation in 21,463/ 28,038 residents (77%) of persons > 50 yrs. Jan.1.1995:
Prevalence of MGUS in Olmsted county Minnesota

- => 50 years 3.2%
- => 70 years 5.3%
- => 85 years 7.5%
- Men : Women ratio = 4.0 : 2.7%
- MGUS concentration:
  - < 1.0 g/dl in 63%  IgG - 69%  IgA - 11%
  - => 2.0 g/dl in 4.5%  IgM 17%  Biclonal – 3%
    kappa -62 and lambda 38%
Monoclonal Gammopathies
Clinical course by Mayo Clinic

• Derived from long term F/U of 1,384 patients with MGUS 11,009 person-years during which 70% pts. Died.

• 115 - 8.3% developed Myeloma, Macroglob., Amyloidosis or Lymphoma.

• Cumulative probability of progression to one of those dis. was:
  • 10 yrs – 10%,
  • 20 yrs. - 21%
  • 25 yrs – 26%

This is where the average of 1% per year was calculated.
Monoclonal Gammopathies
Clinical Course continued

- Number of pts. With MGUS progressing to plasma cell or lymphoid neoplasia was 7.3 X that expected in the general population.
- Median interval from Dg. Of MGUS to one of its complications was 10.4 years.
- 32 pts. (2.3%) had a serum M-protein of =>3.0g/dl and >10% plasma cell in the bone marrow without developing Myeloma.
- Only 6 pts. (0.4%) had MGUS, that spontaneously disappeared.
Monoclonal Gammopathies
Predictors of progression

• A. Low risk:
  1. M-protein < 1.5 g/dl
  2. Marrow plasma cells < 5.0%
  3. No reduction in polyclonal immunoglobulins.
  4. No light chain proteinuria.
  5. ESR < 40 mm/hr
  6. High IgA and IgM monoclonal protein – have a significant risk for progression.
  7. K or L light chains don’t seem to impact on progression.
Monoclonal Gammopathies
Risk stratification model.

• B. Free Light Chain (FLC) proteinuria or in serum carries a high risk of progression to MM, or Amyloidosis, confirmed in a cohort of 1,148 pts.
  • Hazard ratio: 3.5; 95% CI – 2.3 – 5.5
  • Indep. Of size and type of serum M protein.
  • 3 adverse risk factors:
    1. Serum M – protein > 1.5 g/l
    2. Abnormal FLC ratio
    3. Non-IgG MGUS
Monoclonal Gammopathies
Risk stratification model (cont.)

- 3 risk factors (high risk MGUS) - 58%
- 2 risk factors (high-interm. MGUS) - 37%
- 1 risk factor (low-interm. MGUS) - 21%
- No risk factor (low risk MGUS) - 5%

- The higher the M-protein concentration, the higher the risk of progression to plasma cell or lymphoid neoplasias.
Immuno fixation of MGUS on Agarose Gel

- Serum prot. Eph.
- Ig G
- Kappa
- IgA
- Lambda

- Alb.
- Alpha 1, +2 beta, M-prot
- gamma
Monoclonal Gammopathies
Evaluation of Asymptomatic MGUS

- CBC
- Urea, Creatinine, Calcium, Phosphorus and Uric Acid
- Serum protein Electrophoresis and immunofixation
- Quantitative Immunoglobulins
- 24 hour urine for total protein and light chains.
- Bone marrow biopsy and aspiration if MGUS is => 1.5 g/dl
- Metastatic skeletal survey.
- Monitoring every 6 months with careful history and physical exam, lab. Testing for the rest of the pts. Life.
Monoclonal Gammopathies
Speculation on their pathogenesis.

1. Chronic Antigenic stimulation as in HIV Hepatitis or other longstanding chronic infections and skin diseases.

2. Environmental Factors: Osserman had an inbred mouse highly susceptible to develop Plasmacytomomas. If these mice were kept in a strictly sterile environment from birth, they did not develop the plasmacytoma.
Monoclonal Gammopathies
Speculation on their pathogenesis.2

• 3. Evolution from auto-antibodies in autoimmune diseases or from hyper-polyclonal gamma globulinemia to MGUS.
• 4. As age progresses immune surveillance diminishes.
• 1 in 1.0 X 10^6 cells is usually mutated, but gets eliminated by our cytotoxic lymphocytes and mono-macrophages.
• These defenses start failing with age and neoplasia is more frequent in elderly.
IgA Myeloma in bone marrow
Current Therapies for Myeloma

1. Induction therapy with Vincristine, Adriamycine and Dexamethasone,
2. Harvesting of peripheral blood stem cells (PBSC) through apheresis,
3. High dose chemotherapy with Melphalan +/- TBI only if necessary.
4. After relapse – Thalidomide and Prednisone, followed by
5. Bortezomib (Velcade) have been very successful.
Monoclonal Gammopathies
Summary 1.

1. The prevalence of MG is high and increases with age after the 6-th decade.

2. Its potential and susceptibility to evolve at 1.0 to 1.5 % per year into a plasmacytoid or lymphoid neoplasmia is high: 7.3 X from the base line in an unaffected population of the same age group.
3. MG is often associated with underlying non-lympho-plasmacytoid disorders, which when treated successfully, lead also to the disappearance of the MG.

4. Diff. Dg. Of MGUS from Myeloma:
   - MG < 30 g/l
   - Plasma cells in bone marrow < 10%
   - NO Anemia,
   - NO Hypogammaglobulinemia,
   - NO renal failure and urine light chain proteinuria.
   - NO hypercalcemia, NO lytic bone lesions.
   - NO CD 56 markers on plasma cells.
Monoclonal Gammopathies
Summary 3.

Life long periodic monitoring of MG, as well as searching for an underlying or associated disorder is extremely important, since when they evolve into lymphomas or myelomas these diseases can be very successfully treated.