LOCALIZED AND SYSTEMIC AL AMYLOIDOSIS

FELLOW: VICTOR CHOW
HEMATOLOGY FELLOWS CONFERENCE
DISCUSSANT: EDWARD LIBBY
CASE #1

• 57M hx of Ehlers-Danlos syndrome, COPD, AVR, severe mitral regurgitation admitted to cardiology for LE swelling, DOE, lethargy thought 2/2 volume overload.
CASE #1 cont...

HEMATOLOGY CONSULT

“He has AL Amyloidosis”
CASE #1 cont…

RECENT HISTORY:

- Jan/Feb 2017 – hypoxemic respiratory failure 2/2 CHF exacerbation, volume overload, MSSA & corynebacteria PNA

- **CT CHEST PE (1/6)** – no PE, bilateral bronchial wall thickening, patchy LUL GGO, LUL and lower lobe peribronchial nodular infiltrates likely inflammatory v. infectious, no pleural or pericardial effusion

- **BRONCHOSCOPY / BAL (1/9)** – small scattered papules, RLL predominance, 5 endobronchial RLL biopsies

- **PATHOLOGY** – tissue sent to the Mayo Clinic for liquid chromatography tandem mass spectrometry, acellular material compatible with amyloid by Congo red stain, no malignancy ID’ed
FINAL DIAGNOSIS:

LOCALIZED
AL (lambda)-TYPE
AMYLOIDOSIS
CLINICAL AMYLOIDOSIS

• Local Amyloidosis

• Acquired Systemic Amyloidosis
  • Light chain (AL) amyloidosis
  • Reactive (AA) amyloidosis – chronic infxn & inflammatory conditions, production of serum amyloid A protein
  • Dialysis-associated amyloidosis
  • Wild-type transthyretin (TTR) in very elderly

• Hereditary Systemic Amyloidosis
  • Very rare, 10,000 patients worldwide
  • Mutation in the gene for transthyretin (TTR)

• Other systemic amyloidoses
  • Apolipoproteins AI and AII, fibrinogen A α-chain, gelsolin, and lysozyme in systemic amyloidosis; cystatin C in the Icelandic form of hereditary cerebral hemorrhage with amyloidosis; and β-protein in the Dutch form of the disease
AL AMYLOIDOSIS

- Extracellular deposition of immunoglobulin (Ig) κ or λ light chain amyloid fibrils from plasma cells
- Self-assembling, β-sheet conformation
- Localized v. Systemic

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<tbody>
<tr>
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<tr>
<td>ORGANS</td>
<td>SKIN</td>
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<td>HEART</td>
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**AL AMYLOIDOSIS**

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PULMONARY AMYLOIDOSIS

- 3 forms of pulmonary disease in localized AL amyloid
- **NOT** associated with systemic deposition
- NODULAR OPACITIES
- DIFFUSE OPACITIES
- TRACHEOBRONCHIAL
  - Uncommon
  - Mayo Clinic Experience\(^1\) 1980-1993, 4 of 55 cases
  - Cordier & colleagues\(^2\) 15 yr period, 5 of 21 cases
  - Armed Forces Institute of Pathology\(^3\), 14 of 48 cases
  - Thompson & Citron\(^4\), 1983 review of literature, 67 of 126 cases
  - Pulmonary Unit of the Hospital of Arezzo\(^5\), 5 yr period, 1 of 298 cases

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CT CHEST

- BRONCH → 2 patterns: NODULAR & DIFFUSE
- AW → 3 patterns: PROXIMAL, MID, & DISTAL

Irregular narrowing
Wall thickening
Calcification/amyloid deposits
CASE #1 cont…

- **RULE OUT** systemic AL Amyloidosis
- Normal renal function and liver function
- Distal neuropathy R > L 2/2 chainsaw accident
- **TTE** – LV severely dilated, mild concentric LVH, LVEF normal at 68%. No regional wall motion abnormalities
- **CARDIAC MR** - No hypertrophy or wall motion abnormality, patchy areas of mid myocardial late gadolinium enhancement, nonspecific but can be seen with an infiltrative cardiomyopathy such as amyloid or sarcoid. However, amyloid is thought to be less likely as the gadolinium enhancement kinetics are normal.
- **24hr URINE IFE** – No monoclonal component
- **SPEP IFE** – IgG κ monoclonal component, not quantified
- **FREE LIGHT CHAINS**
  - κ FLC 2.3mg/dL (H), λ FLC 1.54 (wnl), κ / λ 1.5 (wnl)

**MGUS?**
CONSEQUENCES & TREATMENT

• UPPER AIRWAY OBSTRUCTION, TRACHEOTOMY
• INFILTRATION OF TRACHEAL WALL
• RESPIRATORY FAILURE

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<tr>
<td>EXCISIONAL THERAPY (standard approach)</td>
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<tr>
<td>Nd:YAG (neodymium:yttrium-aluminum-garnet) LASER</td>
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<tr>
<td>BALLOON DILATATION + STENTING</td>
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<tr>
<td>LOW DOSE EXTERNAL BEAM RADIATION</td>
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<td>SUPPORTIVE CARE (abx, steroids, nebs, mucus)</td>
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Berk et al. Seminars in Respiratory & Critical Care Medicine 2002, 23(2):155-165
CASE #1 conclusion

- Received mitral clip
- Discharged home
- Will require follow up with pulmonary medicine and hematology
CASE #2

- 62M hx of CAD s/p PCI (mid + prox LAD), ischemic cardiomyopathy, combined systolic/diastolic HF, OSA, HTN, HLD transferred to the UWMC for advanced heart failure workup after a PEA arrest (profound hypotension - 50/30) unresponsive to IVF. Attained ROSC, started on vasopressin and norepinephrine 2/2 persistently low BPs (60/40), milrinone switched to dobutamine.
CASE #2 cont…

HEMATOLOGY CONSULT

“He has AL Amyloidosis”
CASE #2 cont…

RECENT HISTORY

- **Summer 2016** – progressive DOE
- **Nuclear Stress Test (9/22)** – partially reversible apical-lateral defect 2/2 diaphragm artifact, distal ischemia could not be excluded
- **TTE (9/26)** – LVEF 60%, ↑ filling pressures, bi-atrial enlargement
- **LHC (11/16)** – No obstructive CAD, 45-55% mid RCA narrowing, elevated LVED pressure, probable cardiomyopathy
- **Progressive DOE, PND, 15lb +, NYHA III heart failure, R pleural effusion + thoracentesis 600cc, up-titrations of diuresis…**
- **RHC (2/2)** – PAP 50/33/25, wedge 25, CI 1.47, admitted A on CHF
- **TTE (2/2)** – LVEF 35%, severe global hypokinesis, infiltrative pattern
- **CARDIAC MRI (2/3)** – diffuse enhancement of the entire LV, concerning for amyloidosis, large bilateral pleural effusions
- **RHC / RIJ / ENDOMYOCARDIAL BIOPSY (2/3)**
FINAL DIAGNOSIS:

SYSTEMIC
AL (lambda)-TYPE
AMYLOIDOSIS
# AL Amyloidosis

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<tr>
<td>Source</td>
<td>Bone Marrow</td>
</tr>
<tr>
<td>Surrounding Tissue</td>
<td>Heart</td>
</tr>
<tr>
<td>Skin</td>
<td>Heart</td>
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<td>Gastrointestinal</td>
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Leading cause of morbidity & mortality, biggest impact on outcomes
CARDIAC MRI

TTE: LV wall thickness >15 mm
Interventricular Septal Thickening at Diastole (IVSd) → 19 mm

max wall thickness 2.3 cm
bilateral pleural effusions
biatrial enlargement

2 VIEW

3 VIEW
EKG

LOW limb lead voltage

Poor R-wave progression
Prognostic Models

Mayo Clinic – Revised Staging System for AL Amyloidosis

• 2012 – 758 patients evaluated\(^1\)
• Source of amyloid light chain – clonal plasma cell* 

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<th>STAGE</th>
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<td>cTnT ≥ 0.025 ng/mL</td>
<td>I</td>
<td>0</td>
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<tr>
<td>NT-ProBNP ≥ 1,800 pg/mL</td>
<td>II</td>
<td>1</td>
</tr>
<tr>
<td>FLC-diff ≥ 18 mg/dL</td>
<td>III</td>
<td>2</td>
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<tr>
<td></td>
<td>IV</td>
<td>3</td>
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• cTnT – Cardiac Troponin T, specific/sensitive marker for cardiac injury
• ProBNP – 108 AA propeptide released from myocytes with increased wall stress → cleaved → lead sequence (AA 1-76) **NT-ProBNP** & active (AA 77-108) BNP; 100% diagnostic sensitivity in cardiac AL amyloidosis\(^2\)

\(^1\) Kumar et al. J Clin Oncol 2012, 30(9):989-995
Prognostic Models

N = 758

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<tr>
<th>Stage</th>
<th>%</th>
<th>OS</th>
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<tbody>
<tr>
<td>I</td>
<td>25</td>
<td>94.1</td>
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<tr>
<td>IV</td>
<td>23</td>
<td>5.8</td>
<td>14</td>
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Kumar et al. *J Clin Oncol* 2012, 30(9):989-995
Additional Validated Staging Systems

- Palladini & Colleagues – Renal Involvement (2014)
  - Proteinuria > 5 gm/24 hr, eGFR < 50 mL/min
  - Both not meeting threshold – 0 to 3% risk for HD at 2 yr
  - Either meeting threshold – 11 to 25% risk for HD at 2 yr
  - Both meeting threshold – 60 to 75% risk for HD at 2 yr

Case #2 cont…

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- $\kappa$ FLC: 1.14 mg/dL
- $\lambda$ FLC: 86 mg/dL
- $\kappa/\lambda$: 0.01
- 24 hr urine w/ IFE: 0.09 gm/24 hr, $\lambda$ Bence Jones protein
- SPEP w/ IFE: IgA $\lambda$ component to small to quantify

STAGE IV – OS 5.8 months
CASE #2 cont…

SKELETAL SURVEY (2/14) – No lytic lesions

BONE MARROW (2/17)

• FLOW: plasma cell neoplasm 10.4% of total WBC

• ASPIRATE DIFF COUNT: 18% plasma cells

• CD138 IHC: 30% positive cells

• CONGO RED STAIN: focal amyloid deposition

• CYTOGENETICS: 46XY
BONE MARROW

ASPIRATE

Bi-nucleated plasma cell

Dutcher body

CORE
Risk-adapted treatment possibly in the framework of clinical trials
Frequent assessment of response based on FLC and biomarkers of organ function

Low-risk, transplant-eligible
(NT-proBNP < 5000 ng/L, cTnT < 0.06 ng/mL, age < 65 years, PS 0–2, eGFR > 50 mL/min per 1.73 m² unless on dialysis, NYHA class < III, EF > 45%, sBP > 90 mm Hg (standing), DLCO > 50%)
- ASCT with MEL 200 mg/m²
- Consider induction with CyBorD if BMPC > 10% or if patient refuses upfront transplant
- Consider BDex if < CR after ASCT

Intermediate-risk (ineligible for ASCT, stages I-IIla)
- MDex, preferred in case of neuropathy or refractory disease with t(11;14)
- CyBorD, stem cell sparing, preferred in renal failure and in patients with gain 1q21
- BMDex, preferred if dFLC > 180 mg/L

High-risk
(stage IIIb, NYHA class ≥ III)
- Low-dose combination regimens
- Bortezomib can be preferred because of the rapidity of action

TREATMENT

Treatment of relapsed/refractory patients
- Repeat frontline therapy in relapsing patients if possible
- Bortezomib-naïve: Bortezomib, ixazomib
- Alkylators-naïve: MDex, ASCT if eligible
- Bortezomib-refractory: Lenalidomide, pomalidomide, bendamustine
**CASE #2 conclusion**

- Weaned off bumex gtt
- Attempting to wean off dobutamine gtt
- Hypotensive to 60/40 → PEA arrest → CPR → ROSC
- CyBorD → received subq Bortezomib 1mg/m2
- Unresponsive during routine turning → PEA arrest → CPR → intubated → significant bloody output from ETT → unable to achieve ROSC → death pronounced
SUMMARY

- AL Amyloidosis – localized v. systemic

- Suspect **localized** disease – TISSUE + rule out systemic
  - Treatment based on organ involvement

- Suspect **systemic** disease – TISSUE + biomarkers
  - Cardiac involvement significantly impacts outcomes
  - Staging systems
  - Treatment based on staging
THANK YOU

EDWARD LIBBY    BARBARA KONKLE    SIOBAN KEEL