Diagnostic approach to cardiac amyloidosis: A case report

Georgia Vogiatzi, MD, MSc, PhD
1st Cardiology Department, Hippokration Hospital, Athens Medical School
Disclosures

• I have no relevant relationships to disclose.
Case description

- 77-years-old, man
- Ix: HTN (Irbesartan 300mg), anemia, gastritis
- Dyspnea on minimal exertion
- Echo: pericardial effusion
Physical examination

- Ill appearing
- BP: 160/80mmHg
- HR: 62 bpm
- RR: 17/min
- Dyspnea NYHA III
- Myoclonic seizures

- S1, S2
- Systolic murmur 2/6 at cardiac apex
- Diastolic murmur 1-2/6 at right 2nd IC
- No pericardial friction rub
- ↓ sound at left lung base
ECG
Rö Thorax
Laboratory findings

- WBC: 8,900/μL
- Hb: 10,1g/dL Hct: 33,1%
- PLT: 240x10³/μL

- Glu: 84mg/dL
- U: 91mg/dL
- Cr: 1,6mg/dL eGFR: 43mL/min/1,73m²
- K: 4,2meq/L Na: 137meq/L

- CA125: 60,20U/mL
- BNP: 463pg/ml
- TnI: 0,03ng/ml
- CRP: 6,45mg/l
- C3, C4
- Ra test (-)
- HIV (-), HBV (-), HCV (-)

pH: 7.47  
pO₂: 65.8mmHg  
pCO₂: 29.9mmHg  
HCO₃: 23.5mmol/L  
SaO₂: 95.5%  
FiO₂: 21%
Pleural paracentesis

- Transudate
- (-) mycobacterial culture
- ADA normal value
- Both aerobic and anaerobic cultures (-)
- Cytologic examination (-)
Echo
**Immunoelectroforesis**

**Immunofixation**

<table>
<thead>
<tr>
<th>Test</th>
<th>Significance</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>1761 H</td>
<td>700.00 - 1600.00 mg/dL</td>
</tr>
<tr>
<td>IgA</td>
<td>151</td>
<td>70.00 - 400.00 mg/dL</td>
</tr>
<tr>
<td>IgM</td>
<td>49</td>
<td>40.00 - 230.00 mg/dL</td>
</tr>
<tr>
<td>IgG kappa</td>
<td>470 H</td>
<td>200.00 - 440.00 mg/dL</td>
</tr>
<tr>
<td>IgG lambda</td>
<td>123</td>
<td>110.00 - 240.00 mg/dL</td>
</tr>
<tr>
<td>B2-Microglobulin</td>
<td>4.47 H</td>
<td>1.1 - 2.0 mg/L</td>
</tr>
</tbody>
</table>

**Comment:**

- Micro gamma monoclonal protein of IgG type.
Biopsies

- Fat biopsy negative for amyloid

- Plasma cell increase (~ 30%) with a set of findings that characterize the diagnosis of multiple myeloma
Final diagnosis - outcome

- Primary AL amyloidosis (AL amyloidosis)
- Insoluble amyloid fibrils composed of immunoglobulin light chains $\kappa$
- Multiple myeloma

The patient died suddenly a few days after the completion of the first chemotherapy regimen.
Discussion
• Systemic disease

• **Extracellular** deposition of insoluble fibrils of LMW proteins

• >30 different proteins
  – Structure heterogeneity
  – Function heterogeneity

• The most common forms are
  – light-chain amyloidosis (AL)
  – amyloid A amyloidosis (AA)
  – transthyretin-related amyloidosis (ATTR)

• Amyloid deposition in various organs, locally or systemically

• Multiple organ dysfunction

• Cardiac involvement is found in around 50% of patients with AL amyloidosis, but is rare in AA amyloidosis

• Usually diagnosed late
  – symptoms nonspecific
  – disregarded or confused with other conditions
Classification of restrictive cardiomyopathies

Restrictive Cardiomyopathy

- Inflammatory
  - Endomyocardial
  - Loeffler cardiomyopathy
  - Postirradiation therapy

- Noninfiltrative
  - Hypertrophic

- Infiltrative
  - Amyloidosis
  - Familial
  - Diabetic
  - Scleroderma

- Storage
  - Hemochromatosis
  - Glycogen storage disease
  - Fabry disease

- Idiopathic
## Characteristics of different types of amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Precursor protein</th>
<th>Main organs affected</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Specific characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AL, primary</strong></td>
<td>Light-chain amyloid</td>
<td>Kidney, heart, CNS, GIT, liver, skin</td>
<td>Serum and urine protein immunofixation Myelogram (5-10% plasma cells) Abdominal fat pad biopsy Bone marrow biopsy</td>
<td>Chemotherapy Stem cell transplantation</td>
<td>M/F ratio 3:2 10–15% associated with multiple myeloma</td>
</tr>
<tr>
<td><strong>AA, secondary</strong></td>
<td>Amyloid A</td>
<td>Kidney</td>
<td>Treat underlying disease Liver transplant Tafamidis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ATTR, hereditary</strong> (autosomal dominant)</td>
<td>Transthyretin, mutant</td>
<td>Heart, liver, CNS and PNS</td>
<td>$^{99m}$Tc-DPD scintigraphy Genetic study of transthyretin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSA</strong></td>
<td>Transthyretin, wild-type</td>
<td>Heart, carpal tunnel syndrome, heart</td>
<td>$^{99m}$Tc-DPD scintigraphy Genetic study of transthyretin</td>
<td></td>
<td>M/F ratio 20:1</td>
</tr>
</tbody>
</table>

### Notes
- Isolated atrial amyloidosis
  - Atrial natriuretic peptide
  - Increased incidence with age and in women

**Abbreviations:**
- AA: amyloid A amyloidosis
- AL: light-chain amyloidosis
- ATTR: transthyretin-related amyloidosis
- CNS: central nervous system
- GIT: gastrointestinal tract
- M/F: male/female
- PNS: peripheral nervous system
- SSA: senile systemic amyloidosis
Cardiac Manifestations

- Progressive dyspnea
- Findings of right-sided HF
  - lower extremity edema
  - Hepatomegaly
  - Ascites
  - Elevated JVP
- Fatigue
- Weight loss

- AF
- Syncope (precursor of SCD)
- Angina
- Heart murmur (valvular insufficiency)
- Pericardial effusion
In other organs...

- Renal involvement
  - Proteinuria
  - Nephrotic syndrome

- Dermatological manifestations
  - easy bruising
  - periorbital purpura

- Macroglossia

- Neurologic symptoms
  - Carpal tunnel syndrome
  - Peripheral and autonomic neuropathy
Diagnostic algorithm of cardiac amyloidosis
ECG characteristics

- Low ECG voltage (dd obesity, emphysema, hypothyroidism, pericardial effusion)
- Pseudoinfarction pattern (QS waves in consecutive leads)
- Conduction delays
- AF, AFL, VT, AVB
- Positive SA-ECG (predictive of all-cause cardiac death and SCD)
- ↓ HR variability on 24-hour ECG monitoring
- Prolonged QT interval
Diastolic dysfunction, with a restrictive pattern in 21-88% of pts

‘Granular sparkling’ refractile myocardium *pathognomonic* for cardiac amyloidosis

Thickening of the LV wall in the absence of HTN

Severe CHF may occur despite a normal or mildly reduced LVEF

RV dilatation

Reduced LV GLS at an early stage of the disease (even with pEF)
CMR characteristics

- Ventricular wall thickening
- Global subendocardial LGE, localized or diffuse
  - Sensitivity 80%
  - Specificity 94%
- Increased LV mass
- Interatrial septal thickness
- Diastolic function
In diagnostic approach...

- **Cardiac catheterization**
  - Endomyocardial biopsy (safe, simple, sensitive)
  - Hemodynamics (right-sided heart catheterization)
  - Evaluation of coronary anatomy

- **Tissue Diagnosis**
  - Sample stained with Red Congo → green birefringence is observed under polarized light (sensitivity 57-85% and specificity 92-100%)

- **Fine-needle aspiration of the abdominal fat**
  - Simple procedure that is positive for amyloid deposits in 70% of patients with AL amyloidosis
In diagnostic approach...

- Serum and urine immunofixation more sensitive than serum and urine electrophoresis

- Bone marrow biopsy mandatory
  - to assess the % of plasma cells
  - to exclude MM and other less common disorders

- (NT-pro-) BNP for prognosis and treatment response
Management

- **Medical Therapy**
  - Diuretics
  - Vasodilators
  - B-Blockers
  - **No Digoxin**

- **Devices**
  - PCM
  - ICD

- **Management of Underlying Amyloid Disease Process**
  - Chemotherapy
  - ASCT

- **Heart Transplantation** (controversial option, poor prognosis)

- **Management of Secondary Systemic Amyloidosis**
Conclusions

- Rare disease
- Late diagnosis
- High level of suspicion
- Definitive diagnosis with histological study
- Treatment of the underlying causes
- Poor prognosis


Fernandes et al. Rev Port Cardiol. 2016;35(5):305.e1-305.e7
Falk et al. Circulation. 2005;112:2047-60
Current Diagnosis and Treatment Cardiology Chapter 24. Restrictive Cardiomyopathy
Thank you for your attention!