Diagnosis of Amyloidosis
Why fat pad is not always the way

Maria M. Picken MD, PhD
Loyola University Medical Center
Chicago
mpicken@luc.edu
Outline
Congo red dye
Generic diagnosis of amyloidosis
Fat pad
Other options
Amyloidosis

$\alpha$ helix

Amyloid formation

Conformational shift to $\beta$-pleated sheet $2^0$ structure

$\beta$-pleated sheet conformation confers affinity to Congo red

*common to ALL types of amyloid*

*Diagnosis of amyloid requires biopsy*
Congo red binding sites
Congo red = bright red color:
- first synthesized in 1883 by Paul Bottiger (Friedrich Bayer Company, Germany)
- textile dye
- the company was not interested, filed the patent under his name and sold it to the AGFA company of Berlin
- AGFA marketed the dye under the name "Congo red"
1884 Berlin West Africa Conference, colonization of Africa
The **Congo River** (aka the **Zaire River**) = a river in Africa
- deepest river in the world, with measured depths >230 m (750 ft)
- 2nd largest river in the world by volume of water discharged (after Amazon)
Current gold standard
FAT STORY

Schilder (1909): amyloid frequently present in subcutaneous fat tissue in patients with amyloid A (AA) amyloidosis

P. Westermark and Stenkvist B (1971): diagnosis of secondary (AA) generalized amyloidosis by fine needle biopsy of the skin

Libbey, Skinner, Cohen, 1983, high yield of detection (88%) in AL, ATTR
Congo red stained fat smears: semi-quantitative assessment

1+ (< 1%)
2+ (1-10%)
3+ (10-60%)
4+ (> 60%)

Bright field
Polarised light

CR Score

Congo red - a great stain in experienced hands but too many pitfalls for general pathologists! scoring, quantification…. Hazenberg et al,
Amyloid detection in fat – AA, AL, ATTR:

Sensitivity highly variable 54-93%
Specificity: 93-100%

Affected organ – best yield
Other options?
Fat aspiration was the most commonly performed followed by bone marrow biopsy
Other: rectum, kidney, carpal ligament, liver, small intestine, sural nerve

<table>
<thead>
<tr>
<th>biopsy</th>
<th>all</th>
<th>Familial ATTR</th>
<th>Wild type Senile ATTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat aspirate</td>
<td>225/106+47%</td>
<td>141/94+67%</td>
<td>84/12+14%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>164/60+37%</td>
<td>100/41+41%</td>
<td>64/19+30%</td>
</tr>
<tr>
<td>heart</td>
<td>131/131+100%</td>
<td>42/42+100%</td>
<td>89/89+100%</td>
</tr>
<tr>
<td>Sural nerve</td>
<td>54/45+83%</td>
<td>54/45+83%</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 1. Prevalence of amyloid protein deposition among patients with ATTR cardiac amyloidosis for the study population and for patients with FAC and SSA for (A) any type of noncardiac tissue sampling including noncardiac biopsy or abdominal subcutaneous fat aspiration and (B) only abdominal subcutaneous fat aspiration. Positive = positive for amyloid protein deposition, Negative = negative or equivocal for amyloid protein deposition.

Nowell M. Fine, Adelaide M. Arruda-Olson, Angela Dispenzieri, Steven R. Zeldenrust, Morie A. Gertz, Robert A. Kyle, Paul L. Swiecicki, Christopher G. Scott, Martha Grogan

**Yield of Noncardiac Biopsy for the Diagnosis of Transthyretin Cardiac Amyloidosis**


http://dx.doi.org/10.1016/j.amjcard.2014.02.030
Coelho et al in FAP:
Labial salivary gland: 89%
Abdominal fat: sensitivity 50-70%
Nerve biopsy: 75-90%
Fat aspirate in wild-type (senile) ATTR amyloid cardiomyopathy

Fine et al 2014, 84 patients, sensitivity of 14%

Ikeda et al 2011, sensitivity increased to 73% (8 of 11 patients), deep layer of surgical fat biopsy, patchy distribution

Takashio et al 2012: amyloid in blood vessels of fat
AL > ATTR cardiomyopathy (14 patients)
Amyloid in fat in non-AA, non-AL, non-ATTR systemic amyloidosis:

AApoAI (apolipoprotein AI), Aβ₂M (β₂-microglobulin) - frequently absent
AFib (fibrinogen α-chain)

ALys (lysozyme) amyloidosis

AGel: amyloid was easily detected in fat tissue in 3/3 patients
(Hazenberg et al, unpublished observation)

No published data for:
AApoAII (apolipoprotein AII),
AH (immunoglobulin heavy chain),
ALect2 (leukocyte chemotactic factor 2) amyloidosis
AIns (insulin) amyloidosis:

- rare localized type of nodular amyloidosis,
- site of repeated insulin injections

Potential pitfall
long-term diabetics can have hypertrophic cardiomyopathy, proteinuria, peripheral polyneuropathy, and autonomic neuropathy, symptoms and signs can be mistaken for systemic amyloidosis.

Presence of monoclonal gammopathy may even confound the situation
Pathology of Familial amyloidoses:

1. Detection of amyloid in the index patient
   - lack of a family history
   - new mutation

2. Examination of family members/known carriers
   - experience from domino transplants

3. Staging, definition of organ involvement
Familial Amyloidoses
Mutation in the amyloid fibril protein

Variants of serum proteins

- Transthyretin
- Gelsolin
- Apolipoprotein I
- Apolipoprotein II
- Fibrinogen A α-chain
- Lysozyme
- Lect2
- Cystatin C

Phenotypes

heart
peripheral nerve

kidney
gastrointestinal tract
Domino liver transplantation – the Concept

Metabolic liver disorder → Deceased or live donor

Domino recipient → Pathology
Screening?

↑ awareness

Suspicion $\rightarrow$ 2\textsuperscript{nd} opinion
amyloid

pre-amyloid phase toxicity
Amyloid and Related Disorders
Surgical Pathology and Clinical Correlations
Humana Press