Amyloidosis & the Gut

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2019
Topics to cover

1) Patterns of GI amyloid involvement
2) Symptoms associated with amyloidosis
3) Diagnostic tests at our disposal
4) Treatment options
5) Epidemiology & data regarding variants
Patterns of GI amyloid

- Amyloid can deposit anywhere in the GI tract or nerves that regulate it
- Luminal GI Patterns:
  - Mucosal infiltration
  - Muscle infiltration
  - Neuropathy
  - Vascular
Patterns of GI amyloid

- Mucosal involvement
  - Role: site of absorption
  - Symptoms
    - Diarrhea
    - Malabsorption
  - Diagnosis
    - Endoscopic biopsy
Patterns of GI amyloid

- **Muscular infiltration**
  - Role: site of contraction & motility
  - **Symptoms**
    - Decreased motility/stasis
      - Small intestinal bacterial overgrowth
        » Diarrhea
        » Malabsorption
    - Constipation
    - Pseudo-obstruction
    - Nausea/vomiting/abdominal pain
  - **Diagnosis**
    - Imaging studies
    - Transit studies
    - Manometry
Patterns of GI amyloid

- **Neuropathy**
  - Role: coordination of GI motility & neuroendocrine secretion
  - Symptoms
    - Dysmotility
      - Nausea/vomiting/pain
      - Diarrhea
      - Constipation
    - Increased sensation
  - Diagnosis
    - Manometry
    - Transit studies
Patterns of GI amyloid

• Vascular
  – Role: delivery of blood flow to gut
  – Symptoms
    • GI Bleeding
    • Ischemia (pain/diarrhea)
  – Diagnosis
    • Endoscopy
Non-luminal GI patterns

• Liver involvement
  – Liver enlargement
  – Elevated liver tests (alkaline phosphatase)
  – Clinical manifestations usually mild but a marker of widespread systemic deposition

• Cholangitis
• Pancreas
• Peritonitis
Symptoms

- Symptoms are linked to area of involvement & are often non-specific
  - Esophagus:
    - Reflux
    - Dysphagia
    - Food impaction
  - Stomach
    - Abdominal pain
    - Nausea
    - Vomiting
    - Distention
  - Small intestine
    - Diarrhea
    - Malabsorption
    - Weight loss
    - Pseudo-obstruction
  - Colon
    - Diarrhea
    - Constipation
    - Fecal incontinence
Symptoms Caveat

- When evaluating symptoms in amyloid, it is important to remember that most symptoms are nonspecific and can also be seen outside of amyloid
  - Reflux: 20% adults
  - Dysphagia: 4% adults
  - Functional dyspepsia: 20-30% adults
  - IBS: 13% adults
  - Constipation: 15% adults
  - Fecal incontinence: 6% adults
- Just because someone has amyloid, doesn’t mean they can’t have other GI conditions
  - Inflammatory bowel disease
  - Celiac disease
  - Eosinophilic esophagitis
  - Cancers
- Symptoms can also relate to medication adverse effects
  - GI symptoms most common adverse effects listed for most medications
  - > 80% of people who take 5 or more medications will have at least one adverse effect
Diagnostic tests

- Endoscopy & colonoscopy are usually the first tests performed
  - Allows option to take biopsies for diagnosis
  - Can also allow treatment
    - Bleeding control
    - Dilation
  - Findings can be nonspecific
  - Will only pick up mucosal GI involvement
  - Rectum commonly chosen as yield high (> 75%) and easy to get to
  - Highest yield in GI tract is in duodenum
Diagnostic tests

• Other tests to consider
  – Imaging studies
    • CT
    • MRI
    • Barium
  – Motility studies
    • Scintigraphy
    • Manometry
    • Wireless motility capsule
    • Sitz marker study
  – Breath tests
Treatment options

• Treatment should be tailored to symptoms & GI involvement
Treatment options

• Esophagus
  – Reflux treatment options
    • Dietary modification
    • Antacids
    • Histamine receptor blockers
    • Proton pump inhibitors
    • Endoscopic/surgical options in carefully selected patients
  – Dysphagia treatment options
    • Dietary modification
    • Dilatation
    • Botox
Treatment options

- Stomach
  - Dietary modification
  - Prokinetics
    - Metoclopramide (Reglan)
    - Erythromycin/azithromycin
    - Domperidone (not FDA-approved)
    - Prucalopride
    - Bethanechol
    - Pyridostigmine
  - Agents to help stomach expansion
    - Herbal therapies (peppermint/caraway)
    - Buspirone
  - Neuromodulators
    - Tricyclics (amitriptyline)
    - Mirtazapine (Remeron)
    - Gabapentin (Neurontin)
    - Gabapentin/pregabalin (Lyrica)
  - Anti-emetics
  - Endoscopic options: Botox
Treatment options

- Small bowel
  - Dietary modifications
  - Prokinetics
  - Antibiotics (focused on small intestinal bacterial overgrowth)
  - Octreotide
  - Steroids
  - Bile-salt binding agents
  - Anti-diarrheals
    - Imodium
    - Lomotil
    - Tincture of opium
  - Parenteral nutrition (rare cases)
Treatment options

• Colon
  – Dietary modifications
  – Laxatives
    • Over the counter
      – Miralax
      – Senna
      – Magnesium-based preparations
    • Prescription
      – Lubiprostone (Amitiza)
      – Linaclotide (Linzess)
      – Plecanatide (Trulance)
      – Prucalopride (Motegrity)*
  – Prokinetics
Epidemiology

• GI involvement in amyloid as a whole is (to me at least) reported to be surprisingly low:
  – 2013: In retrospective study of 2334 patients with amyloidosis, only 76 (3%) had amyloid on GI biopsies
  – 2015: In Korean study, only 24 of 155 symptomatic; all with amyloid on biopsy (15%)
  – 2017: In retrospective study of 583 amyloid patients, only 96 reported GI symptoms; 82 underwent endoscopy with biopsies; only 45% had amyloid on biopsies (16% symptomatic; 6% amyloid on biopsies)
Data regarding variants

• Extremely limited, but report from THAOS suggests GI manifestations are common
• Survey data from 1579 hereditary TTR amyloidosis (75% V30M) & 160 wild type analyzed
  – Hereditary: 63% GI symptoms
  – Wild type: 15% GI symptoms
• Most common symptoms:
  – Unintentional weight loss
  – Early satiety
  – Alternating diarrhea/constipation
• GI symptoms:
  – More common with V30M mutation versus other mutations
  – More common in younger onset patients (< 50)
• For patients with predominantly cardiac complications & wild type, the authors estimated that “the prevalence of gastrointestinal manifestations was not evidently higher than that expected in the general population”

Wixner J. Orphanet J Rare Dis 2014
Data regarding variants

Wixner J. Orphanet J Rare Dis 2014

Figure 2 GI symptoms in relation to duration of disease in patients with TTR mutations. Prevalence of gastrointestinal (GI) symptoms in patients with a disease duration of <5 years, 5-10 years and >10 years, respectively. A majority of the patients suffered from GI symptoms even at early stages of the disease whereas the reported prevalence of GI symptoms in the general population usually ranges from 10 to 25%. Unintentional weight loss, early safety and alternating diarrhea/constipation were the most common symptoms in all disease stages. The symptom prevalence increased significantly with disease duration for all symptoms (p < 0.002, for all), except for early safety (p = 0.14).
Data regarding variants

Table 1 Most abundant TTR mutations and their clinical manifestations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Sensory neuropathy</th>
<th>Motor neuropathy</th>
<th>Gastrointestinal symptoms</th>
<th>Cardiac complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>V30M</td>
<td>707 (89.5%)</td>
<td>305 (38.6%)</td>
<td>547 (69.3%)</td>
<td>212 (26.9%)</td>
</tr>
<tr>
<td>V122I</td>
<td>35 (60.3%)</td>
<td>11 (19.0%)</td>
<td>16 (27.1%)</td>
<td>57 (96.6%)</td>
</tr>
<tr>
<td>S50R</td>
<td>26 (89.7%)</td>
<td>16 (55.2%)</td>
<td>19 (65.5%)</td>
<td>13 (44.8%)</td>
</tr>
<tr>
<td>E89Q</td>
<td>21 (95.5%)</td>
<td>10 (45.5%)</td>
<td>13 (68.4%)</td>
<td>13 (65.0%)</td>
</tr>
<tr>
<td>T60A</td>
<td>16 (80.0%)</td>
<td>5 (25.0%)</td>
<td>8 (40.0%)</td>
<td>19 (90.5%)</td>
</tr>
<tr>
<td>F64L</td>
<td>18 (90.0%)</td>
<td>11 (55.0%)</td>
<td>10 (50.0%)</td>
<td>7 (35.0%)</td>
</tr>
<tr>
<td>S77Y</td>
<td>16 (94.1%)</td>
<td>8 (47.1%)</td>
<td>12 (70.6%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>I68L</td>
<td>7 (46.7%)</td>
<td>6 (40.0%)</td>
<td>2 (13.3%)</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>I107V</td>
<td>10 (83.3%)</td>
<td>9 (75.0%)</td>
<td>7 (58.3%)</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>G47A</td>
<td>8 (72.7%)</td>
<td>2 (18.2%)</td>
<td>2 (18.2%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>L111M</td>
<td>1 (10.0%)</td>
<td>0 (0.0%)</td>
<td>1 (10.0%)</td>
<td>7 (70.0%)</td>
</tr>
</tbody>
</table>

Mutations carried by ten individuals or more listed in a descending order.

Table 2 Distribution of GI symptoms in patients with ATTR amyloidosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Wild-type n = 140</th>
<th>TTR mutation n = 1114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GI symptom</td>
<td>21 (15.3%)</td>
<td>696 (63.0%)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>5 (3.6%)</td>
<td>291 (26.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (2.2%)</td>
<td>189 (17.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0%)</td>
<td>147 (13.4%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (3.6%)</td>
<td>230 (20.9%)</td>
</tr>
<tr>
<td>Diarrhea/constipation</td>
<td>2 (1.5%)</td>
<td>267 (24.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (3.6%)</td>
<td>218 (19.8%)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>0 (0.0%)</td>
<td>68 (62%)</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>4 (2.9%)</td>
<td>346 (31.5%)</td>
</tr>
</tbody>
</table>

Number of patients, n (%), reporting gastrointestinal (GI) symptoms at enrollment.

Wixner J. Orphanet J Rare Dis 2014
Conclusions

• Amyloid can cause symptoms by either direct deposition or nerve involvement
• Only the mucosa can be evaluated by endoscopy so the absence of amyloid on endoscopic biopsy does not exclude amyloid involvement
• Involvement appears to be common (60%) in familial amyloidesis, particularly in neuropathic variants
• Diagnostic options & treatment options exist and can be customized to specific symptoms
Thank you

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