ARTHRALGIAS in IBD

Liam Martin MB, MRCPI, FRCPC
University of Calgary
Brian Bressler MD, MS, FRCPC
University of British Columbia
Conflicts

- Dr. Bressler and Dr. Martin do not have any conflicts to report
CDDW/CASL Meeting Session: Liam Martin, Brian Bressler

CanMEDS Roles Covered in this Session:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(as <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS framework.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
</tr>
<tr>
<td><strong>Collaborator</strong></td>
<td>(as <em>Collaborators</em>, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
</tr>
<tr>
<td><strong>Manager</strong></td>
<td>(as <em>Managers</em>, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>(as <em>Health Advocates</em>, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>(as <em>Scholars</em>, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
</tr>
<tr>
<td><strong>Professional</strong></td>
<td>(as <em>Professionals</em>, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
</tr>
</tbody>
</table>
OBJECTIVES

In an IBD patient being treated with an anti-TNF therapy:

• 1. Assess and investigate musculoskeletal symptoms

• 2. Differentiate between inflammatory and non-inflammatory causes of musculoskeletal symptoms

• 3. Suggest appropriate management of musculoskeletal symptoms
Case to Consider - 1

• 45 year old female with colonic CD
• Referred by her gastroenterologist - ?DIL
• Complaints
  – Myalgia in arms and legs for 5 months
  – AM stiffness – 45 min
  – Facial rash
  – Dry eyes, dry mouth
  – Mouth ulcers
  – Reflux
Case to Consider - 1

- Symptoms since May 2012
- Slowly increasing
- Can’t work (house painter)
- Can’t comfortably do any ADL
Case to Consider - 1

• **Past Medical History**
  • Crohn disease – diagnosed 4 years ago
  • Treated with Imuran 10/2013
    – D/C secondary to cytopenia
  • Treated with Adalimumab 2014
  • Developed arthralgia with first dose
    – Remained on medication for 4 months
    – MSK Symptoms continued and increased
      • unable to do ADL
    – CD under control
    – Adalimumab discontinued
Case to Consider - 1

• Follow-up colonoscopy showed active left sided colonic inflammation

• How would you manage this patient?
Case to Consider - 2

• A 33 year old female with CD on treatment with infliximab for 2 years
• Referred for assessment of arthralgia
• Complaints
  – joint pain in her hands and shoulders for 9 months
  – Worse at night
  – Symptoms most prominent 3 weeks after her infusions
  – Minimal AM stiffness; ADL not affected
  – Also has psoriatic lesions over her elbows for past 6 months
Case to Consider - 2

• Infliximab dose increased (10mg/kg) over the past 6 months due to an increase in GI symptoms
  – GI symptoms responded
  – no effect on joint symptoms or psoriatic lesions

• Past Medical History
  – Diagnosed with PsA 8 years ago
    • Symptoms in remission for 6 years
  – Umbilical Hernia surgery 10 years ago
Case to Consider - 2

• Systems Review
  – No other complaints

• Medications
  – Infliximab 10mg/kg every 8 weeks

• How would you manage this patient?
MSK symptoms

• How do you approach a patient with MSK symptoms?
What do you ask the patient?

• What elements of the history will help?
  – Pattern of joint involvement
  – Duration/severity of joint symptoms
  – Systemic symptoms
  – Extra-articular manifestations
  – Functional capability
  – Past history
  – Family History
  – Medications
Pattern of Joint involvement

• Which joints are involved?
  – Small joints/large joints
  – Spine

• Are the symptoms intermittent or persistent?

• How many joints are involved?

• Is there swelling in the affected joints?
Pattern of Joint involvement

• Inflammatory arthritis is a persistent problem
  • Rarely intermittent
  • Swelling/Pain are present unless treated
  • Functional problems also persist
    • Making a full fist is not possible when PIP joints are affected
Spine pain

- **Seronegative spondyloarthropathies**
  - A group of inflammatory joint diseases characterized by inflammation of the spine

- **Included in this group are:**
  - Ankylosing spondylitis (prototype)
  - Enteropathic arthritis
    - Crohn’s disease
    - Ulcerative colitis
  - Psoriatic arthritis
  - Reactive arthritis
Seronegative Spondyloarthropathies

• Axial arthritis with involvement of the
  – sacroiliac joints,
  – apophyseal joints
  – spinal ligaments

• Peripheral joints, usually asymmetrical,
  – oligo or polyarticular disease (large joints often)

• Enthesitis
  – inflammation of the insertion point of
tendon/fascia into bone
  – heel spurs, Achilles tendinitis
How does it present in IBD?

- Most common presentation is with back pain or stiffness
- Worse in morning or after periods of inactivity
- May improve with exercise
- Some patients present with peripheral joint symptoms
  - usually large joints, commonly asymmetrically
- **IBD and arthritis symptoms may behave independently**
- Condition is often missed
Inspect/Examine the Hands
Inspect/Examine the Feet
What test do you order?

• In most clinical scenarios the following tests are helpful
  – CBC – Hgb, WBC, Platelet count
  – ESR, CRP
    – *(Especially helpful if you do not find any swollen joints on exam)*
  – Baseline blood chemistry, urinalysis
  – RF and anti-CCP (ACPA) antibodies,
  – ?ENA profile, ?Anti-DNA antibodies
  – ?HLA B27
  – X-rays of joints (affected plus contralateral joints) and pelvis
Laboratory Tests

• Autoantibody tests are helpful in assessing patients with systemic rheumatic diseases
• However a positive test is not diagnostic of a disease
• For example anti-DNA antibodies are found in SLE patients
  But
• Occur in 30% of patients on anti-TNF therapies
Ankylosing spondylitis: early sacroiliitis
Anti-TNF Induced Lupus

- New subset of lupus related diseases
- First described with the introduction of anti-TNF therapies in 2000’s
- Women are affected 5 times more often than men
- ANA and anti-dsDNA antibodies may be induced by anti-TNF therapy
- Incidence of DIL is very low but data is scarce
- Prevalence: infliximab 0.19%; adalimumab 0.41%; and etanercept 0.18%
Classic Drug Induced Lupus

• DIL is a subset of lupus related diseases
• First described in 1945 secondary to sulfadiazine
• Other drugs were added to the list of potential causes
• This form of the disease may be referred to as ‘Classic’ DIL
• Occurs more commonly in women than men
• Incidence is up to 20% per year for Procainamide, 5-8% for hydralazine and <1% for other drugs
Classic DIL associated drugs

- **Drugs definitely capable of inducing DIL**
  Hydralazine, Procainamide, Isoniazid, Metyldopa, Chlorpromazine, Quinidine, Minocycline

- **Drugs possibly causing DIL**
  - Sulfasalazine
  - **Anticonvulsants**: carbamazepine, etosuximide, phenytoin, diphenylhydantoin, pirimidine, trimethadione, valproate, and zonisamide.
  - **Antithyroid drugs**: propylthiouracil, methimazole, and thiamazole.

- **Drugs suggested to induce DIL**
  - Gold salts, penicillin, streptomycin, tetracycline, phenylbutazone, estrogens and oral contraceptives, reserpine, lithium, para-aminosalicylic acid, captopril, griseofulvin, calcium channel blockers, ciprofloxacin, rifampin, clonidine, hydroxyurea, interferon, and gemfibrotil

- **Drugs recently reported to induce DIL**
  - Interleukin-2, clobazam, clozapine, tocainide, lisinopril, zafirlukast, etanercept, adalimumab, and infliximab
Classic DIL presentation

Symptoms
• Usually occur with chronic use of the offending medications (>1 month)
• The most common symptoms are
  – Arthralgia;
  – Myalgia;
  – Serositis;
  – Fevers;
  – Skin rash – not photosensitive, not malar
  – Oral ulcers are unusual
Classic DIL Clinical presentation

Common
• Tender but infrequently swollen joints
• Tender muscles – mild
• Skin rash

Occasional
• Serositis

Rare
• Neurological deficits
Anti-TNF DIL presentation

Symptoms

• Usually occur with chronic use of the offending medications (>1 month)
• The most common symptoms are
  – Arthralgia;
  – Myalgia;
  – Serositis;
  – Fevers;
  – Skin rash – may have a malar distribution
Anti-TNF DIL Clinical presentation

Common
• Tender and swollen joints
• Skin rash

Occasional
• Serositis

Rare
• Neurological deficits
• Vasculitic lesions
Anti-TNF DIL skin rash - 1
Anti-TNF DIL skin rash - 1
Anti-TNF DIL skin rash - 2
Classic DIL presentation - Laboratory

**Haematology**
- May have cytopenia
- Elevated ESR and/or CRP levels

**Chemistry**
- Normal renal function
- Normal complement levels

**Serology**
- Positive ANA
  - Anti-histone antibodies (not specific)
- Anti-nucleosome (chromatiin) antibodies
- Antiphospholipid or Lupus anticoagulant
  - No reports of thromoembolism

**Anti-dsDNA and Anti-Sm antibodies are rare**
Anti-TNF DIL presentation - Laboratory

**Haematology**
- May have cytopenia
- Elevated ESR and/or CRP levels

**Chemistry**
- Renal function may be affected
- Occasionally low complement levels

**Serology**
- Positive ANA
- Infrequent anti-histone antibodies
- Anti-nucleosome (chromatin) antibodies
- Anti-dsDNA antibodies are relatively common
## TNF versus Classic DIL

<table>
<thead>
<tr>
<th>Feature</th>
<th>Anti-TNF-Related Lupus (%)</th>
<th>Procaainamide-Related Lupus (%)</th>
<th>Idiopathic SLE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>79</td>
<td>&gt;95</td>
<td>99</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>72</td>
<td>&lt;5</td>
<td>90</td>
</tr>
<tr>
<td>Rash/cutaneous involvement</td>
<td>67</td>
<td>&lt;5</td>
<td>54-70</td>
</tr>
<tr>
<td>Arthritis</td>
<td>31</td>
<td>20</td>
<td>83</td>
</tr>
<tr>
<td>Fever/general symptoms</td>
<td>23</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Hypocomplementemia</td>
<td>17</td>
<td>&lt;5</td>
<td>48</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14</td>
<td>15</td>
<td>66</td>
</tr>
<tr>
<td>Serositis</td>
<td>12</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>aCL</td>
<td>11</td>
<td>5-20</td>
<td>15</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7</td>
<td>&lt;5</td>
<td>34</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>&lt;5</td>
<td>31</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>3</td>
<td>&lt;5</td>
<td>12</td>
</tr>
<tr>
<td>Anti-histone antibodies</td>
<td>ND</td>
<td>&gt;95</td>
<td>50-60</td>
</tr>
</tbody>
</table>

*Abbreviations: aCL = anticardiolipin antibodies; ND = no data.*

(Medicine 2007;86:242–251)
Management of DIL

- Discontinue the suspected agent
- Some patients require therapy
  - Course of prednisone to treat symptoms
  - Some patients require other immunosuppressive therapies for disease control
Management of DIL

• What about using another anti-TNF therapy?
• Can they be safely used?
Management of DIL

• What about using another anti-TNF therapy?
• Can be safely used?

**Answer:**

• Number of studies have reported no adverse effects from switching
• Effectiveness of the new anti-TNF therapy not adversely affected
Back to the patients
Case 1

- More History
- Joint pain is associated with swelling
- Swelling present in the am when she wakes
- Clears within minutes
- She can make a full fist but it hurts
- Skin rash present on her face for years
- Fair skin
- Poor sleep for number of years
Case 1

Examination revealed:
• No swollen joints
• Full ROM in all sore joints
• Skin rash – acne rosacea
• Tender points all over

• Clinical diagnosis most likely Fibromyalgia
Case 1

- Haematology test results are normal
- Serology shows marginally elevated anti-dsDNA - 4.5 kIU/L (0-4kIU/L)
- Histone antibodies – negative
- Complement levels are normal
- ESR 2mm/hr

- Advise patient that she does not have IBD or anti-TNF DIL
- Refer for advice on Exercise to manage MSK symptoms
- Continue anti-TNF therapy
Case 2

• More History
• Joint pain associated with swelling in fingers
• States she is unable to make a full fist
• No history of eye symptoms
• Examination revealed
• Psoriatic lesions along her hair line and over her elbows
• Swelling and tenderness in the 2\textsuperscript{nd} MCP joints
Case 2

- **Diagnosis**
- Psoriatic arthritis and IBD
- **Management:**
- ?
Case 2

• **Diagnosis**
  - Psoriatic arthritis and IBD
  - Not anti-TNF DIL

• **Management:**
  - Increase frequency of infliximab to every 6 weeks
  - Add MTX 15mg P.O. weekly for psoriasis
Summary

- Arthralgias occur relatively frequently in IBD patients
- It can be difficult to assess patients with multiple complaints
- Careful clinical exam is important
- Appropriate laboratory tests may help in diagnosing the condition
- Ask your rheumatology colleagues for advice when possible