Diagnosis and Management of Extraintestinal Manifestations of IBD

Dec. 3, 2016

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Outline

• EIM associated with IBD/ active disease
  – Joints, eyes, liver, skin manifestations
  – Correlations with disease activity
  – Treatments
• EIM associated with therapies
  – Joints, liver, skin manifestations
  – Idiopathic, infectious, malignant
  – Treatment

Focus upon skin manifestations and complications
<table>
<thead>
<tr>
<th>Case 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 37 y o AA female with severe recto-sigmoid CD, with diverting colostomy</td>
</tr>
<tr>
<td>• Currently maintained on anti-TNF and methotrexate</td>
</tr>
<tr>
<td>• Presents with severe rectal pain and pus-like drainage</td>
</tr>
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<table>
<thead>
<tr>
<th>Perianal lesion</th>
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<tbody>
<tr>
<td><img src="image-url" alt="Perianal lesion image" /></td>
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</tbody>
</table>
Clinical Questions: EIM of Disease

- What are the extraintestinal manifestations (EIM) of IBD?
- Which EIM are associated with disease activity?
- Are there shared disease characteristics, genetics among those with EIM?
- What are the treatments of EIM of IBD?

Prevalence of EIM: CD and UC

Extraintestinal Manifestations by Disease Activity in Crohn’s Disease and Ulcerative Colitis


Extraintestinal Manifestations by Disease Location in Crohn’s Disease

Pyoderma gangrenosum

Begins with a sterile pustule or erythematous papule or nodule that rapidly breaks down to form a burrowing, painful ulcer with characteristic erythematous to violaceous, sharply defined, undermined borders, and a necrotic base

Location: typically legs, also peristomal

Marzano et al. Inflamm Bowel Dis. Jan 2014 [epub]

103 Pyoderma Cases in a Tertiary Referral Hospital 2000-2007

Patient characteristics and Pyoderma location

| Age (Mean) Sex | 22-88 (52) years 76% F/24% M |
| Location       | Leg 78%, Trunk 12%, Peristomal 9%, Upper extremity 9%, Head/Neck 8%, 2 or more sites within same time 11% |
| Comorbidities  | 0 comorbidity 25%; 1 comorbidity 29%, 2 comorbidities 36%, 3 or more comorbidities 14% |

Comorbidities: IBD (34%), peripheral vascular disease (29%), Diabetes (28%), hematological disorders (20%), major depression (19%), rheumatological disorders (19%), psoriasis (9%), Hepatitis C (7%)

Therapeutic Options: PG

- High dose oral or intralesional prednisone
- 6-mp/AZA
- Dapsone – caution if G6PD deficiency
- Cyclosporine, tacrolimus (IV, oral, topical)
- Thalidomide
- Hyperbaric oxygen
- IVIG
- Anti-TNF, now the treatment of choice
- Cyclophosphamide
- Proctocolectomy
- Other surgical therapy; ostomy closure

*Level of data: case reports except RCT for infliximab

Infliximab (IFX) in the Treatment of Pyoderma Gangrenosum (PG) (1)

Infliximab (IFX) in the Treatment of Pyoderma Gangrenosum (PG) (2)

IFX (5 mg/kg) (n=13) or Placebo (n=17) week 0  
No IBD 11, CD, 12, UC 6  
Assessment week 2, open label IFX (n=29)  
Assessment week 6 (n=29)

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Remission</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG Duration &lt;12 weeks (n=14)</td>
<td>13 (93%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>PG Duration &gt;12 weeks (n=15)</td>
<td>7 (47%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>


Case 2

- 33 yo female with a history of UC (pancolitis) and PSC maintained on 5-ASA and ursodiol presents with new onset painful lesions on lower extremities
- No change in bowel habits (1-2 BM’s/day without blood)
Erythema nodosum

Acute tender eruption of erythematous plaques and nodules, usually on the extensor surface of the lower limbs


EN Treatment

- Bed rest
- Systemic corticosteroids (prednisone 0.5 mg/kg daily)
- In refractory cases, dapsone and cyclosporine

Clinical and genetic factors of PG and EN

<table>
<thead>
<tr>
<th>Clinical factors PG and EN</th>
<th>Genetic factors (PG)</th>
<th>Genetic factors (EN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>IBD loci IL8RA and PRDM1</td>
<td>IBD susceptibility genes PTGER4, ITGAL</td>
</tr>
<tr>
<td>Colonic disease</td>
<td>USP15, TIMP3</td>
<td>SOCS5, CD207, ITGB3 and rs6828740</td>
</tr>
<tr>
<td>Previous IBD surgery</td>
<td></td>
<td></td>
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<tr>
<td>Non-cutaneous EIMs</td>
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</table>


Case 3

- 27 yo female with a history of colonic CD, presents with new onset scaly, itchy rash behind her ears and in scalp
- No change in bowel movement frequency, 3 BM’s/day
- Currently maintained on adalimumab 40 mg every other week
Psoriasis

Noncontagious, inflammatory systemic disorder with varying manifestations.

In up to 10% of cases, it is associated with inflammatory conditions.


Clinical Questions: EIM of Therapy

- Which EIM are associated with specific IBD therapies?
- How do these drug-induced EIMs commonly present?
- What are the treatments of drug induced EIM?
  - Do medications need to be stopped?
### EIM of specific IBD therapies

<table>
<thead>
<tr>
<th>Class</th>
<th>Reaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>Hypersensitivity</td>
<td>12% of cases, prompt discontinuation with complete resolution</td>
</tr>
<tr>
<td></td>
<td>Sweet's syndrome</td>
<td>Prompt discontinuation</td>
</tr>
<tr>
<td></td>
<td>Infectious: zoster</td>
<td>Treat with anti-viral, withdraw therapy based on severity</td>
</tr>
<tr>
<td></td>
<td>Non-melanoma skin cancer</td>
<td>Treatment/excision. Patient education, skin protection, examination</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Common reactions</td>
<td>Maculopapular rash (15%), alopecia (8%), photosensitivity (5%), urticaria (4%). Drug withdrawal not routine.</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Class</th>
<th>Reaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF</td>
<td>Drug hypersensitivity</td>
<td>Incidence of 1%. Prompt drug withdrawal and an in-class switch to another agent suggested</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>Incidence of up to 0.5%. Temporary cessation of drug suggested until improvement observed</td>
</tr>
<tr>
<td></td>
<td>Drug induced lupus</td>
<td>Incidence of ~1%. 94% of the cases respond to drug cessation. Re-challenging with another drug is a potential option with a low recurrence observed</td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
<td>Occurs in 3% of treated cases, commonly in women. Prompt drug withdrawal is not recommended. Use topical, systemic or phototherapy, only if ineffective should agent be withdrawn. Drug re-challenge is a possible option, although associated with a high recurrence (up to ~50%)</td>
</tr>
</tbody>
</table>

Skin Paradoxical Reactions

- Prevalence of anti-TNF induced skin lesions has ranged from 2-29%
- Incidence 5/100 person-years
- Not limited to IBD, occurs with other autoimmune mediated conditions
- Can occur as early as 1 month into treatment, more commonly during maintenance therapy
- Retrospective cohort studies


Skin Paradoxical Reactions: Characteristics

- Retrospective cohort of 917 patients with IBD initiating anti-TNF therapy
- Median follow up 3.5 years after initiation of infliximab
- Characterization/distribution
  - Psoriasiform eczema 30.6%
  - Eczema 23.5%
  - Xerosis cutis 10.6%
  - Palmoplantar pustulosis 5.3%
  - Psoriasis 3.8%
  - Other 26.1% (infections, tumor, alopecia, etc)
- Lesions typically flexural regions, genitalia, scalp

Skin Paradoxical Reactions: Risk factors

- Similar prevalence men (26%) and women (31%), smokers and non smokers (32% for both)
- 33% of patients without skin lesions developed +ANA; vs. 47% of those with skin lesions
- Median cumulative doses and trough levels in patients with and without skin lesions on infliximab were similar (trough 4.2 um/mL (IQR 2.6 to 5.8) vs. 4.0 (IQR 1.6-5.9))
- 31% of those with 1-4 risk variants for identified SNPs developed skin lesions; 48% for those with >4 risk variants


Skin Paradoxical Reactions: Risk factors

<table>
<thead>
<tr>
<th>Increased Risk of Skin Lesions</th>
<th>Reduced Risk of Skin Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Immunomodulator</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Ulcerative Colitis</td>
</tr>
<tr>
<td>Higher doses anti-TNF (?)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
</tr>
</tbody>
</table>

Skin Paradoxical Reactions: Treatment

Outcome of 30 patients with TNF-induced psoriasis

- Response to topical therapy: 21
  - Psoriasis on anti-TNF: 30
  - Cont anti-TNF: 14
  - No response to topical therapy: 9
    - Stop anti-TNF: 6
      - Cont 2nd anti-TNF w/o recurrence: 2
      - Recurrence on 2nd anti-TNF: 1
    - Switch to 2nd anti-TNF: 3
      - Cont 2nd anti-TNF w/o recurrence: 4
      - Recurrence on 2nd anti-TNF: 1
    - Switch 2nd anti-TNF non-derm reasons: 5
      - Cont anti-TNF non-derm reason: 2

Of those switched to alternate anti-TNF, 2/8 (25%) had recurrence with 2nd anti-TNF.


Skin Paradoxical Reactions: Treatment

- Majority managed with conservative treatment (topical emollients, steroids +/- systemic treatment –antibiotics or antihistamines) with improvement and continuation of anti-TNF agent
  - 62% -89% improvement in separate cohorts
- Main indications for discontinuation
  - Could not tolerate due to location
  - Itching or pain
  - Recurring symptoms
  - Associated arthralgias
- After stopping anti-TNF; 17/28 with resolution of symptoms over a median of 3 months in one cohort
- In severe cases, ustekinumab (IL 12/23 inhibitor) with efficacy (up to 100%)

Treatment Algorithm: Paradoxical Psoriasis

1. Confirm diagnosis; communicate with dermatologist.
2. Smoking cessation.
3. Conventional treatments: topical steroids, emollients, keratolytic therapy, vitamin D analogs, phototherapy, and occlusive therapy.
4. Addition of immunomodulator (MTX or AZA).

- No Improvement
  - Is the TNF effective for bowel inflammation?
  - Yes: Continue current anti-TNF therapy +/- immunomodulator.
  - No: Consider dose reduction of anti-TNF based on levels.
- Improvement
  - Consider alternate anti-TNF (up to 50% recurrence).
  - Initiate Ustekinumab.

Case 4

- 42 y.o. Caucasian male with history of prior ileocecal resection in remission on azathioprine monotherapy presents with scaly, red, non-painful rash on his nose.

Non-melanoma skin cancer
### NMSC: Risks of Immunosuppression

**Medication Class**  | **Crohn’s disease** | **Ulcerative colitis** |
--- | --- | --- |
Thiopurines | OR 4.25 (2.81-6.42) | OR 4.34 (2.53-7.43) |
Biologic Anti-TNF | OR 2.18 (1.07-4.46) | N/A |
Methotrexate | OR 2.69 (0.63-11.56) | N/A |

*Persistent medication use, >1 year*

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**NMSC: Risks of Immunosuppression**

#### Crohn’s disease

<table>
<thead>
<tr>
<th>Medication Class*</th>
<th>Cases n=228</th>
<th>Controls n=913</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>154 (68%)</td>
<td>817 (89%)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>56 (25%)</td>
<td>73 (8%)</td>
<td>4.45 (2.94-6.75)</td>
</tr>
<tr>
<td>Biologic Anti-TNF</td>
<td>7 (3%)</td>
<td>13 (1%)</td>
<td>3.23 (1.24-8.45)</td>
</tr>
<tr>
<td>Combined thiopurine and biologic</td>
<td>11 (5%)</td>
<td>10 (1%)</td>
<td>6.75 (2.74-16.65)</td>
</tr>
</tbody>
</table>

*Persistent medication use, >1 year*

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Melanoma: Risks of Immunosuppression

<table>
<thead>
<tr>
<th>Medication Class*</th>
<th>IBD overall</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ASA</td>
<td>1.06 (0.77-1.45)</td>
<td>0.98 (0.63-1.53)</td>
<td>1.22 (0.76-1.96)</td>
</tr>
<tr>
<td>Biologic Anti-TNF</td>
<td>1.88 (1.08-3.29)</td>
<td>1.94 (1.03-3.68)</td>
<td>1.73 (0.53-5.63)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>1.10 (0.72-1.67)</td>
<td>0.92 (0.53-1.59)</td>
<td>1.31 (0.66-2.60)</td>
</tr>
</tbody>
</table>

*Any use, adjusted OR controlled for other medication use, comorbidities, health care utilization


Mechanisms of skin cancer risk

- Azathioprine has been shown to selectively increase photosensitization of human skin to UVA light
  - 6-Thioguanine DNA photoproducts
- Sunlight induces chronic oxidative stress and increases the levels of oxidative DNA skin lesions
- Mechanism of anti-TNF agents is not known

### Skin Cancer Prevention

- **Primary prevention**
  - Sun protective clothing with a UPF of 30
  - Broad-spectrum sunscreens (UVA and UVB) with a SPF of 30 or greater
  - Reapplication of sunscreen every 2 hours


### Skin Cancer Prevention in IBD

- **Secondary prevention**
  - No current recommendation for annual skin examination in IBD (or in the general population), but this should be considered
    - Annual skin examinations are recommended in post-transplant patients on immunosuppression
    - Consideration of routine skin examinations in IBD patients on immunosuppression
  - Any skin lesion suspicious for malignancy in a patient with IBD on immunosuppression should be evaluated by a trained dermatologist

### Summary of cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>perianal pyoderma -&gt; Optimize anti-TNF/mtx, intralesional steroid injections</td>
</tr>
<tr>
<td>2</td>
<td>erythema nodosum -&gt; Corticosteroid taper</td>
</tr>
<tr>
<td>3</td>
<td>Anti-TNF induced psoriasis of scalp-&gt; topical steroid, pine tar shampoo, UV light, continue anti-TNF; if not tolerable/responsive consider immunomodulator and/or change to ustekinumab</td>
</tr>
<tr>
<td>4</td>
<td>NMSC -&gt; local resection via Moh’s surgery, sunscreen use, screening skin examinations, continue azathioprine with intensified skin surveillance and sunscreen/sun protective clothing</td>
</tr>
</tbody>
</table>

### Take home points

- **EIM of IBD are common**
  - Risk factors: women, colonic disease, severity
  - Management includes immunosuppressive therapies used in the treatment of IBD
- **EIM can also occur as a result of therapies**
  - Recognition of important complications: psoriasis/psoriasiform eruptions, drug induced lupus, skin cancers
  - Often treated locally/topically
  - Cessation of therapy may be required, depending on type and severity of EIM