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Diagnosis and Management of Common Dermatologic Problems in Our IBD Patients

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University of North Carolina
Inflammatory Bowel Diseases Center
Outline: Skin complications and IBD

• Extraintestinal manifestations
  – Pyoderma gangrenosum
  – Erythema nodosum

• Cutaneous manifestations of paradoxical inflammation
  – Psoriasiform skin eruptions

• Skin cancer
  – Non-melanoma skin cancer
  – Melanoma
Outline: Skin complications and IBD

- Extraintestinal manifestations
  - Pyoderma gangrenosum
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- Cutaneous manifestations of paradoxical inflammation
  - Psoriasiform skin eruptions
- Skin cancer
  - Non-melanoma skin cancer
  - Melanoma

Illustrated by a series of cases
Case 1

• 37 y o AA female with severe inflammatory colonic CD
• Maintained on methotrexate
• Presents with severe rectal pain and pus-like drainage
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]
Pyoderma Gangrenosum in IBD

- Prevalence in tertiary care center population 1.9%
- Most common location: leg, followed by peristomal
- Risk factors:
  - Active bowel inflammation
  - Colonic or ileocolonic inflammation in CD
  - Extensive colitis in UC
  - Female gender

Therapeutic Options: PG

- High dose oral or intralesional prednisone
- 6mp/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)

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)

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

**Improvement**

- IFX: 6/13 (46%)
- Placebo: 1/17 (6%)

**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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 weeks</td>
<td>13 (93%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>7 (47%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>

Case 2

- 33 yo female with a history of UC (pancolitis) maintained on 5-ASA 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

Clinical and genetic factors of EN

**Clinical factors EN**
- Female gender
- Colonic disease
- Previous IBD surgery
- Non-cutaneous EIMs

**Genetic factors (EN)**
- IBD susceptibility genes
- PTGER4, ITGAL, SOCS5, CD207, ITGB3
- and rs6828740

EN Treatment

- Bed rest
- Systemic corticosteroids
- Dapsone
- Cyclosporine
- Disease-specific therapy

# Systematic review of anti-TNF in EIM

<table>
<thead>
<tr>
<th>Extraintestinal manifestation</th>
<th>Response in interventional studies</th>
<th>Response in non-interventional studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyoderma*</td>
<td>21-25%</td>
<td>92-100%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Reduction from 47.1% to 26.8%</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Reduction from 8.7% to 2.1%</td>
<td>Reduction from 58% to 12.5%</td>
</tr>
</tbody>
</table>

*Erythema nodosum or aphthous stomatitis, similar rates to pyoderma
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

Psoriasis as “Paradoxical” Inflammation

- Biologic use has increased dramatically over the past 2 decades
- Delay in literature on reports of autoimmune pathologies occurring in tandem with biologics (not reported initially in clinical trials)
  - Suggests low incidence or that reactions are associated with prolonged or cumulative doses of biologics
- “Paradoxical” as they occur in patients on biologics initiated with the intent to treat an inflammatory condition such as RA or IBD

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

Increased Risk of Skin Lesions

- Smoking
- Crohn’s disease
- Higher doses anti-TNF (?)
- BMI
- Female gender

Reduced Risk of Skin Lesions

- Immunomodulator
- Ulcerative Colitis

References:

Skin Paradoxical Reactions: Treatment

• Majority managed with conservative treatment (topical emollients, steroids +/- systemic treatment) 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 (reported up to 100% in some series)

Treatment Algorithm: Paradoxical Psoriasis

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

   - No Improvement
     - Is the TNF effective for bowel inflammation?
       - Yes: Consider dose reduction of anti-TNF based on levels
       - No: Consider alternate anti-TNF (up to 50% recurrence)

   - Improvement
     - Continue current anti-TNF therapy +/- immunomodulator

   - Lack of response or recurrence
     - Initiate Ustekinumab
Case 4

• 42 y o Caucasian male with ileal stricturing CD of 10 years duration
  – Prior ileocecal resection
  – In clinical and endoscopic remission on azathioprine monotherapy

• Presents with scaly, red, non-painful rash on his nose
Non melanoma skin cancer

- 1 in 5 Americans develops skin cancer, which accounts for 1/3 of all cancers in the US
  - Categorized into squamous and basal cell carcinoma
- Environmental risk factors for NMSC
  - Ultraviolet light
  - Chemical exposures
- Host risk factors
  - Human papilloma virus
  - Genetic susceptibilities
  - Immunosuppression

Incidence of Skin Cancer in IBD

## NMSC: Risks of Immunosuppression

<table>
<thead>
<tr>
<th>Medication Class*</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>OR 4.25 (2.81-6.42)</td>
<td>OR 4.34 (2.53-7.43)</td>
</tr>
<tr>
<td>Biologic Anti-TNF</td>
<td>OR 2.18 (1.07-4.46)</td>
<td>N/A</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>OR 2.69 (0.63-11.56)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Persistent medication use, > 1 year

### 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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Mechanism of thiopurines in NMSC

- Azathioprine has been shown to selectively increase photosensitization of human skin to UVA light
  - 6-Thioguanine DNA photoproduts
- Sunlight induces chronic oxidative stress and increases the levels of oxidative DNA skin lesions

Photosensitivity testing

Melanoma

- 20.8/100,000 p-y incidence
- Rate tripled in Caucasians over the past 20 yrs
- Risk factors
  - Environmental
  - Intermittent high intensity exposure
  - Genetic
  - Immunosuppression
    - Transplant patients with 3.4 fold increased risk

Incidence of Melanoma in IBD

# Melanoma: Risks of Immunosuppression

## Crohn’s disease

<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

Summary: Skin cancer in IBD

• NMSC risk driven by thiopurine use
• Melanoma risk driven by anti-TNF
• Innate differences in underlying IBD immune dysfunction may contribute to these risks
• Mechanisms likely differ, as do absolute risks

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
  – Reaplication 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
    • Consider 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

- Case 1: Perianal pyoderma -> Add anti-TNF, intralesional steroid injections, may require diversion
- Case 2: Erythema nodosum -> Assess disease activity; corticosteroid taper
- Case 3: Anti-TNF induced psoriasis of scalp -> topical steroid, pine tar shampoo, UV light, continue anti-TNF; if not tolerable/responsive consider immunomodulator and/or change to ustekinumab
- Case 4: NMSC -> local resection via Moh’s surgery, sunscreen use, screening skin examinations, continue azathioprine with intensified skin surveillance and sunscreen/sun protective clothing