Case Report

Dr. Madalina Greere
Prof Assoc. Liana Gheorghe MD. PhD

Center for Digestive Diseases & Liver Transplantation Fundeni Clinical Institute, Bucharest
Clinical history

- 27-years old woman, no smoker, with appendectomy in the past
- Diagnosed in 2000 with indeterminate left colitis
- Treated with sulfasalazine for induction and maintaining remission
- The patient discontinued the prescribed treatment no longer after the remission
Clinical history

- In January 2004 (4 years later) she was admitted to our department for treatment and close examination of her new flare of symptoms.

- Clinical presentation: diarrhea (8-10 stools/day with mucus), rectal bleeding, urgent bowel movements, abdominal cramps and pain, fever, fatigue, and weight loss.

- Laboratory findings: Hb-11.3, Le-8000, PLT-480000, Fgb-523, PCR-25
Clinical history

- Negative coprologic tests

- Colonoscopy done on hospital revealed ulcerative lesions extended over a wide area from the sigmoid colon to the cecum with a discontinued pattern of the lesions
Edematous mucosa with disappearance of the vascular pattern, aphtous ulcers interposed with areas of normal mucosa.
Histological findings

• Irregular glandular architecture - shortened glands, of unequal sizes with diffuse inflammation in the lamina propria, and crypt microabscesses, cryptic eroded superficial epithelium

• basal plasmacytosis

• muscularis mucosae infiltrated by inflammatory cells.
Histological findings

- Cryptic microabcess (eroded gland with exudate in the lumen) and cryptitis (PMN in the glandular epithelium)

Conclusion - colonic lesions of diffuse chronic inflammation, non-granulomatous and transmucosal, without lesions characteristic of CMV infection on fragments examined.
Diagnosis

The endoscopic appearance, clinical and histological findings at this patient are highly suggestive for colonic Crohn disease, inflammatory pattern A2L2B1 (Montreal classification), moderately-severe activity (CDAI 320)
Therapeutic approach

- Systemic corticotherapy without clinical improvement
- Remicade 5mg/kgc (in a clinical trial) - induction doses 5mg/kgc at week 0, 2 and 6 without the possibility to continue the biologic maintenance treatment at that moment
- Spectacular clinical response (clinical remission after 2 weeks)
- Azathioprine 2.5mg/kgc but the patient is noncompliant
Follow-up

Between 2005-2009 the patient presents several moderate disease flares with remission after corticotherapy and maintenance treatment with mesalazine 4g/day
Clinical history (January 2010)

- 6 months after the last relapse the patient was admitted to the hospital because of a painful, tenderness, red swelling of the right foot accompanying muco-bloody diarrhea (3-4 stools/day).

- Laboratory findings: Fgb = 726.5 mg, Le = 13300, Hb = 10.2 g/dl, HCT = 34.1%, PLT = 402000

- CDAI = 260
Clinical and paraclinical findings

- Clinical examination revealed an erythematous area of the lower right leg with draining pustules.
- Radiographs of the left ankle showed soft-tissue edema without evidence of osseous involvement.
- Negative coproculture.
- Cl. difficile toxine A/B negative.
- Colonoscopy showed lesions limited to the colon without involvement of the terminal ileum.
Multiple ulcers with a mucopurulent base, violaceous undermined border and peripheral erythema
Colonoscopy: ulcers, edema, inflammatory pseudopolyps
Diagnosis

The patient has skin lesions mimic those of a pyogenic infection but association with IBD is highly suggestive for a sterile inflammatory process involving neutrophils.

The two most common forms of neutrophilic dermatosis are pyoderma gangrenosum (PG) and Sweet's syndrome, each of which may be idiopathic or related to an underlying systemic disease.
Skin lesions and IBD

- PG may precede or follow the diagnosis of an associated IBD, and may or may not parallel the clinical course of the associated disease.
- PG is one of the most common skin disorders linked to inflammatory bowel disease.
- The proportion of patients with inflammatory bowel disease who develop PG appears to be small.
- In a cohort study of 2402 patients with inflammatory bowel disease, PG was detected in only 0.75 percent of patients.

The differential features of PG and Sweet's syndrome suggests that the most likely diagnosis in this patient is pyoderma gangrenosum.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pyoderma Gangrenosum</th>
<th>Sweet's Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association with inflammatory bowel disease</td>
<td>About 1 in 3 cases</td>
<td>About 1 in 10 cases*</td>
</tr>
<tr>
<td>Predominant location</td>
<td>Legs</td>
<td>Arms, face, and neck</td>
</tr>
<tr>
<td>Appearance of lesion</td>
<td>Pustules</td>
<td>Nonpustular, solid papules or plaques</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Present, with undermined, violaceous borders</td>
<td>Absent</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>About 10 percent</td>
<td>Probably &lt;5 percent</td>
</tr>
</tbody>
</table>

*Data obtained from Daoud et al.
Clinical question: What treatment do you recommend?

- Prednisone 0.75-1mg/kgc
- Mesalazine 4g
- Azathioprine 2.5mg/kgc
- Biological therapy
- MTX 25mg/zi
Therapeutic approach

The regimen that we have chosen was:

**Induction therapy**
- Prednison 40mg/day
- Mesalazine 4g
- IFX induction doses (5mg/kgc at 0,2,6 wk)

**Maintenance therapy**
- AZA 2.5mg/kgc
- Mesalazine 4g

Specific treatment for PG lesions: wound dressing + Diprofos perilesional injections + Dapsone 100mg/day
Pyoderma gangrenosum - Pathogenesis

- PG is characterized by neutrophil-predominant infiltrates in the skin.
- The reason for the development of the inflammatory process that leads to PG remains unclear.
- The primary factors considered to contribute to the pathogenesis of PG:
  - abnormalities in neutrophil function
  - genetic variations
  - dysregulation of the innate immune system

**Pyoderma gangrenosum - Epidemiology**

- 3 to 10 cases per million people per year
- an average age of onset between 40 and 60 years
- women are more frequently affected

Pyoderma gangrenosum –

Clinical Types

- Ulcerative (classic) PG – begins as a tender, inflammatory papule, pustule or vesicle that develops on normal-appearing skin or at a site of trauma; lower extremities and trunk are the most common sites of involvement.

- The initial inflammatory lesion subsequently expands peripherally and degenerates centrally, leading to ulcer formation. The base of the ulcer is purulent and necrotic, and the depth of the ulcer often extends into subcutaneous fat and occasionally reaches the fascia.

Pyoderma gangrenosum – Clinical Types

- **Bullous (atypical) PG** – Bullous PG is a less common, superficial variant of PG that is most commonly seen in patients with PG related to hematologic disease.

- **Pustular PG** – Pustular PG usually occurs in patients with inflammatory bowel disease, and tends to arise during periods of acute exacerbations of bowel disease. Affected patients exhibit the rapid development of painful pustules surrounded by erythema. Concomitant fever and arthralgias are common.

Pyoderma gangrenosum – Clinical Types

Vegetative PG – also known as superficial granulomatous pyoderma is a localized, solitary, superficial form of PG that presents as an indolent, mildly painful nodule, plaque, or ulcer. A verrucous quality is often present. The undermined borders and purulent bases of ulcerative PG are absent. The head and neck are the most common sites for vegetative PG.
Pyoderma gangrenosum - Treatment

Secondary infection, if present, should be treated.

**FIRST-LINE THERAPY** — **Local care** — Wounds should be cleansed gently with tepid sterile saline or a mild antiseptic prior to dressing changes.

Wound dressings that promote a moist wound environment and do not adhere to the wound base are preferred, as they may be beneficial for healing.

Pathergy (exacerbation of lesions at sites of trauma) can occur in PG. Thus, unnecessary traumatic insults to the wound, such as the use of wet to dry dressings and the application of caustic substances should be avoided.

Pyoderma gangrenosum - Treatment

- **Surgery** — Surgical procedures are considered only in select cases, such as those in which accumulation of necrotic tissue presents a risk for infection or where vital tissues such as tendons or ligaments are exposed in the ulcer bed.

- **Local corticosteroids** — are usually applied once or twice daily or/and intralesional corticosteroids injected circumferentially into the ulcer periphery.

- **Local calcineurin inhibitors** — topical tacrolimus in concentrations of 0.03% to 0.3% has demonstrated efficacy for PG in multiple case reports.

- **Systemic glucocorticoids / Systemic cyclosporine**
SECOND-LINE AND ADJUNCTIVE THERAPIES —

Conventional immunosuppressants —
Immunosuppressive agents such as mycophenolate mofetil, methotrexate, and azathioprine have been utilized for the treatment of PG. These agents are generally considered to be most beneficial when used as adjunctive or glucocorticoid-sparing agents, rather than as monotherapy.

Dapsone — administered as monotherapy or as a glucocorticoid-sparing age

<table>
<thead>
<tr>
<th>Topical Agents</th>
<th>Treatment of PG</th>
<th>Treatment of Crohn’s Disease/IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Tacrolimus (0.5%)</td>
<td>Budesonide (limited for disease affecting ileum and ascending colon)</td>
</tr>
<tr>
<td></td>
<td>Benzoyl peroxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitrogen mustard</td>
<td></td>
</tr>
<tr>
<td>Systemic Agents Immunosuppressive</td>
<td>Oral Corticosteroids in pulse therapy</td>
<td>Chronic low dose steroids (non-responsive IBD)</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-Mercaptopurine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Agents Antimicrobial</th>
<th>Sulfasalazine</th>
<th>Aminosalicylates: sulfasalazine, mesalamine, olsalazine, balsalazide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dapsone</td>
<td>Ciprofloxacin Metronidazole (used to treat infectious complications CD, or mild active CD)</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mexlocillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-diarrheal Meds</strong></td>
<td><strong>Biologic Agents</strong></td>
<td><strong>Immune Modulators</strong></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Anti-TNF therapy: Infliximab, Alefacept, Adalimumab, Efalizumab, Etanercept</td>
<td>Combination therapy (infliximab in combination with 6-MP, azathioprine or methotrexate)</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Anti-TNF therapy: Infliximab (used in individuals with disease resistant to steroids and 6-MP), Adalimumab (disease resistant to infliximab), Certolizumab</td>
<td>Natalizumab (effective induction agent for CD)</td>
</tr>
</tbody>
</table>
Follow-up

1 month after appropriate therapy:
- improvement of skin lesions
- clinical remission
6 months later…

- Reactivation of skin lesions
- Clinical remission without mucosal healing at colonoscopy
A wound culture yielded colonies of meticilino resistant *Staphylococcus aures*

The patient followed the same treatment for skin lesions with: Diprofos perilesional injections and Dapsone 100mg/day + AB (Vancomycin and FQ iv)

Good outcome through healing skin lesions
January 2012 (2 years later)

Another flare occurs two weeks before the next application of IFX

- Clinical presentation: 4-5 stools / day (diurnal and nocturnal) with pathological products, without active skin lesions

- Laboratory findings: no anemia, leukocytosis (secondary to corticosteroid therapy), PCR-9.13.

- Colonoscopy: longitudinal ulcers in the rectum, no other injuries 30cm explored.

- IFX level<3
How should we treat at this point?

- Shortening the interval between administration of IFX to 4 weeks
- Dose escalation of IFX to 10mg/kgc at 8 wk
- MTX 25mg/week
- Prednisone 0.75-1mg/kgc
What guidelines recommend?

ECCO Statement 5J (new)
Loss of response to anti-TNF therapy should lead to re-evaluation of disease activity, exclusion of complications and discussion of surgical options with the patient [EL5, RG D]. For active disease, reduction in interval between doses, or dose escalation are appropriate strategies before switching to another agent [EL5 RG D]. Switching is an effective strategy [EL1b, RG A], but reduces future therapeutic options. For intolerance, especially if severe, switching to an alternative anti-TNF agent is appropriate. Response to a third anti-TNF therapy occurs in some patients and may be an appropriate option [EL3 RG C], although surgical options should also be considered and discussed. Primary lack of response may be determined within 12 weeks and an alternative anti-TNF agent tried for active disease [EL3, RG C].

Our therapeutic choice was: IFX 5mg/kgc at 4 weeks
Follow-up

- Favorable outcome after shortening the interval between administration of IFX to 4 week
- Clinical and endoscopic remission

- Restart the initial IFX regimen (5mg/kg every 8 weeks)
January 2013 (one year after the last flare)

Moderate flare, 2 weeks after the last application of IFX:

- **Clinical presentation**: 6-7 stools/day sometimes with mucus and blood
- **Laboratory findings**: PCR-7, Fgb-500 no anemia, no leukocytosis
- **Negative coproculture**, negative Cl. Difficile toxin A/B
- **IFX level < 3**
- Colonoscopy shows lesions localized only in the rectum (superificiale ulcers, edematous mucosa and friable mucosa)
Colonoscopy: ulcers, swelling, redness, friable mucosa with spontaneous bleeding
What treatment suggestion do you have in this situation?

- A new course of prednisone 0.75-1mg/kg
- Budenofalk foam 6 mg 1/day
- Increasing the dose of IFX to 10mg/kg
- Shortening the interval between administration of IFX to 4 wk
- Salofalk 4g/day
The chosen regimen was:

- IFX 10mg/kgc at 8 wk
- Budenofalk foam 6mg/day
- AZA 2.5mg/kgc
- Salofalk 4 g/day
Follow-up
March 2013 (after 3 months of IFX dose escalation)

- Favorable outcome under IFX 10 mg/kg+c+rectal foam Budenofalk
- Clinical and endoscopic remission which allows dose reduction of IFX to 5mg/kgc
We are facing a young patient with Crohn's disease that associates multiple relapses and extraintestinal manifestations (severe lesions of PG) which requires biological therapy. Effective treatment of the bowel disease in this case results in resolution of the PG. Over time, the patient loses the response to biological therapy requiring for IFX dose optimization. A therapeutic goal is to adopt a personalized approach to therapy considering the particular disease severity and its heterogeneity.
Thank you!