Case Report

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Clinical history

- 27-years old women, no smoker, with appendectomy in the past
- diagnosed in 2000 with indeterminate left colitis
- treated with sulfasalazine for induction and maintaining remission
- the patient discontinue the prescribed treatment no longer after the remission

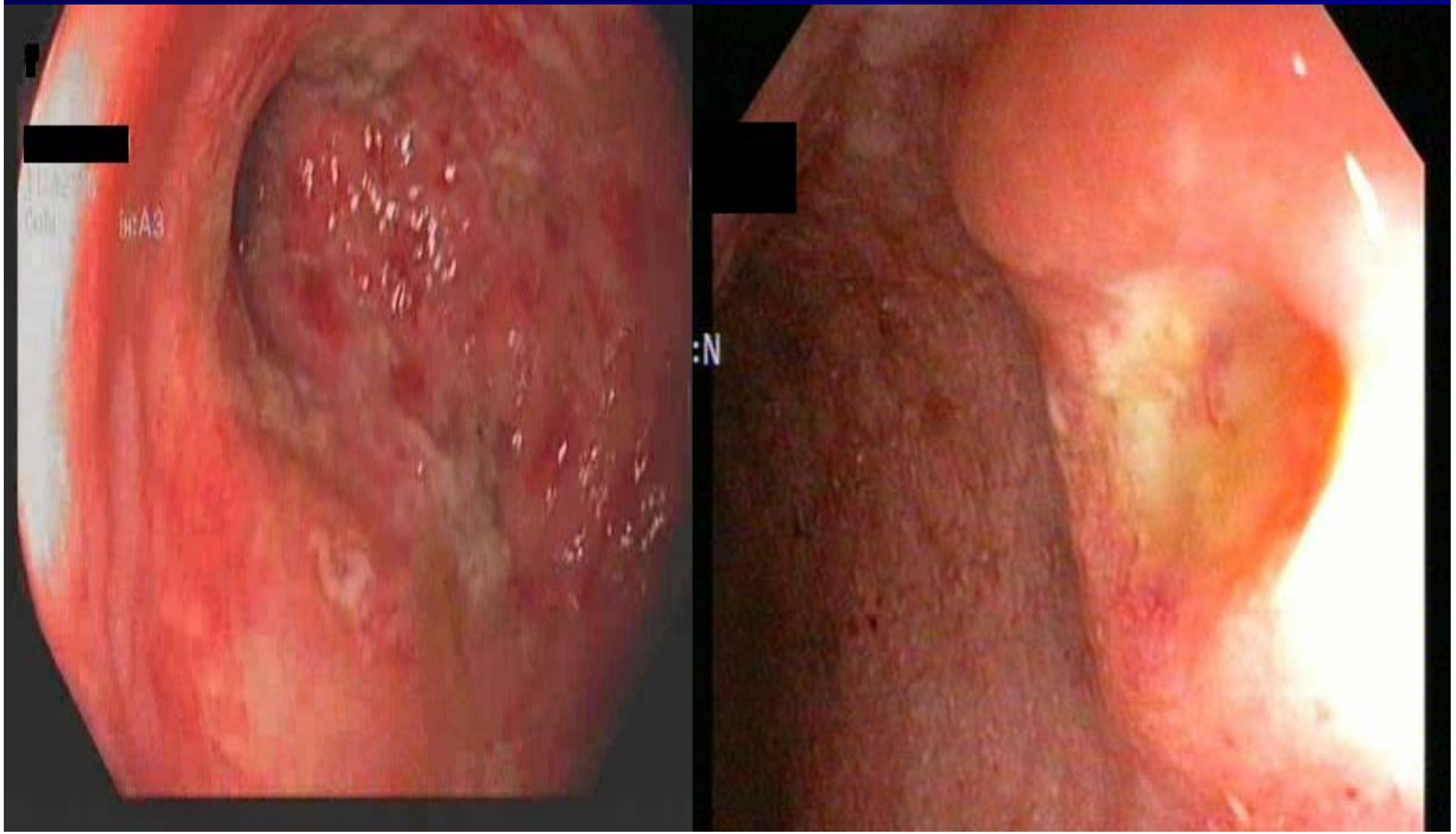
Clinical history

- **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

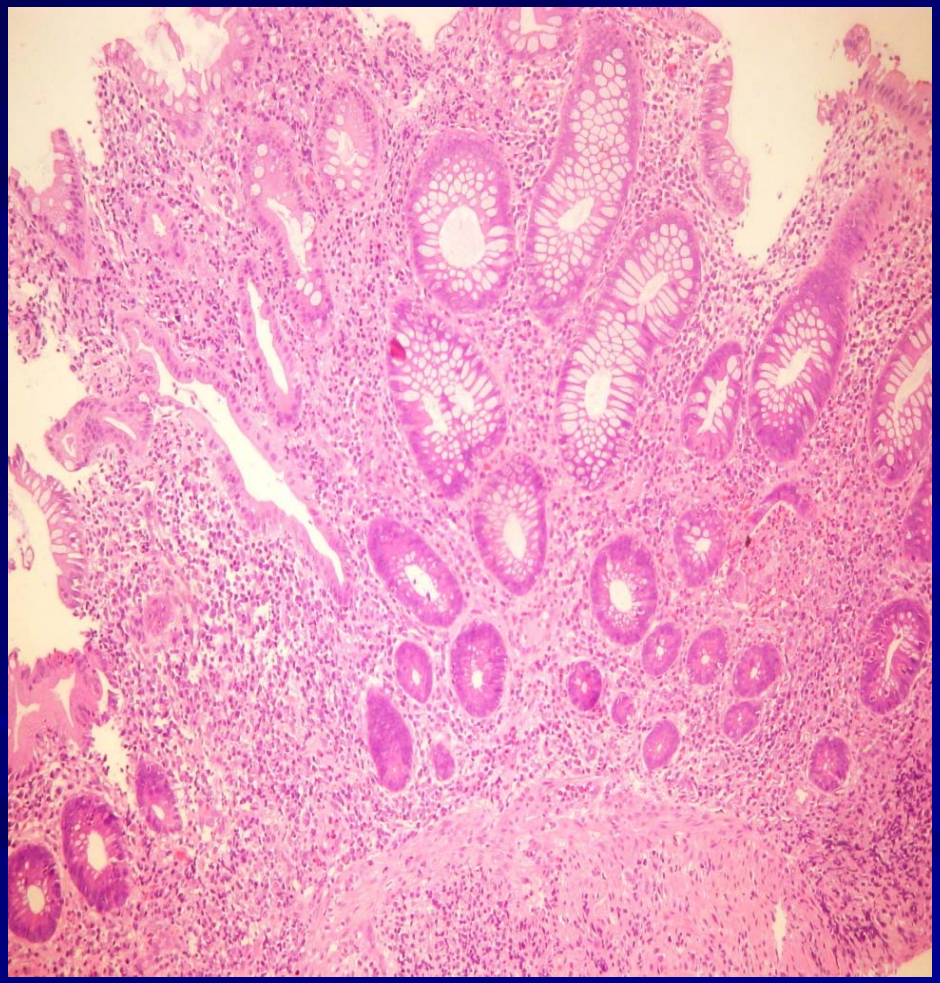
Clinical history

- 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

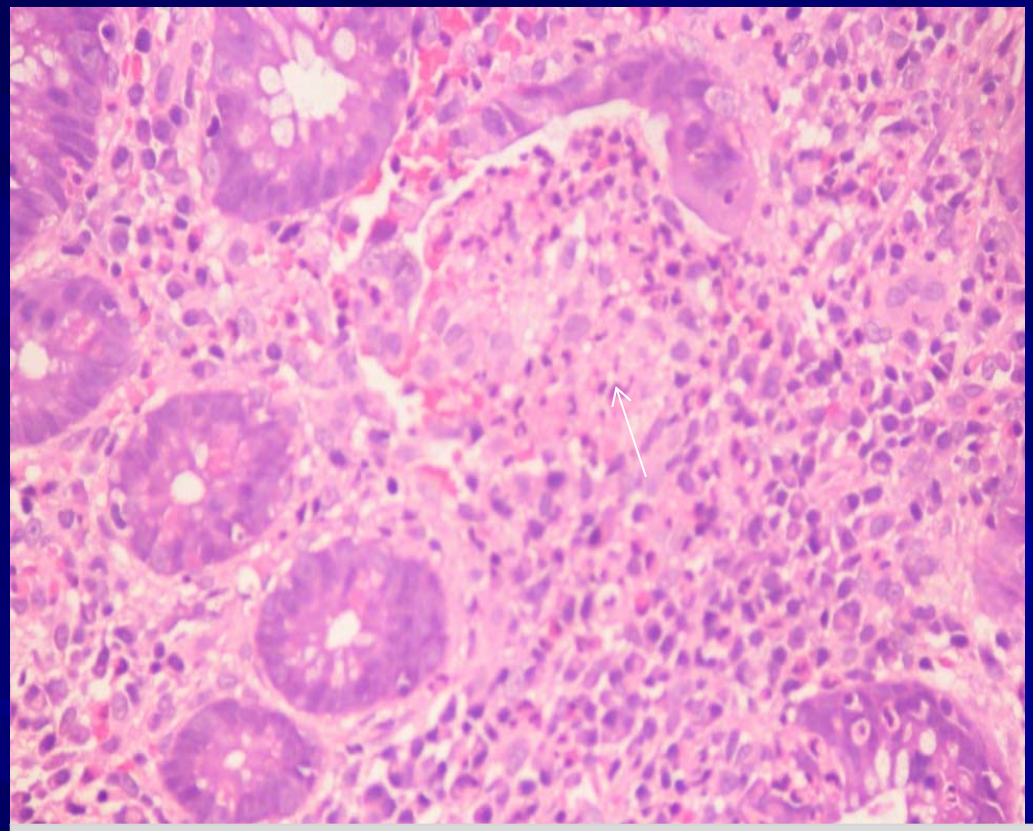


Histological findings



- 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 high 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

6.1.4. Extensive disease

ECCO Statement 6C

For patients with extensive disease, azathioprine is recommended for maintenance of remission [E1b, RG A].

Follow-up

- Between 2005-2009 the patient presents several moderate disease flares with remission after corticotherapy and maintenance treatment with mesalazine 4g/day

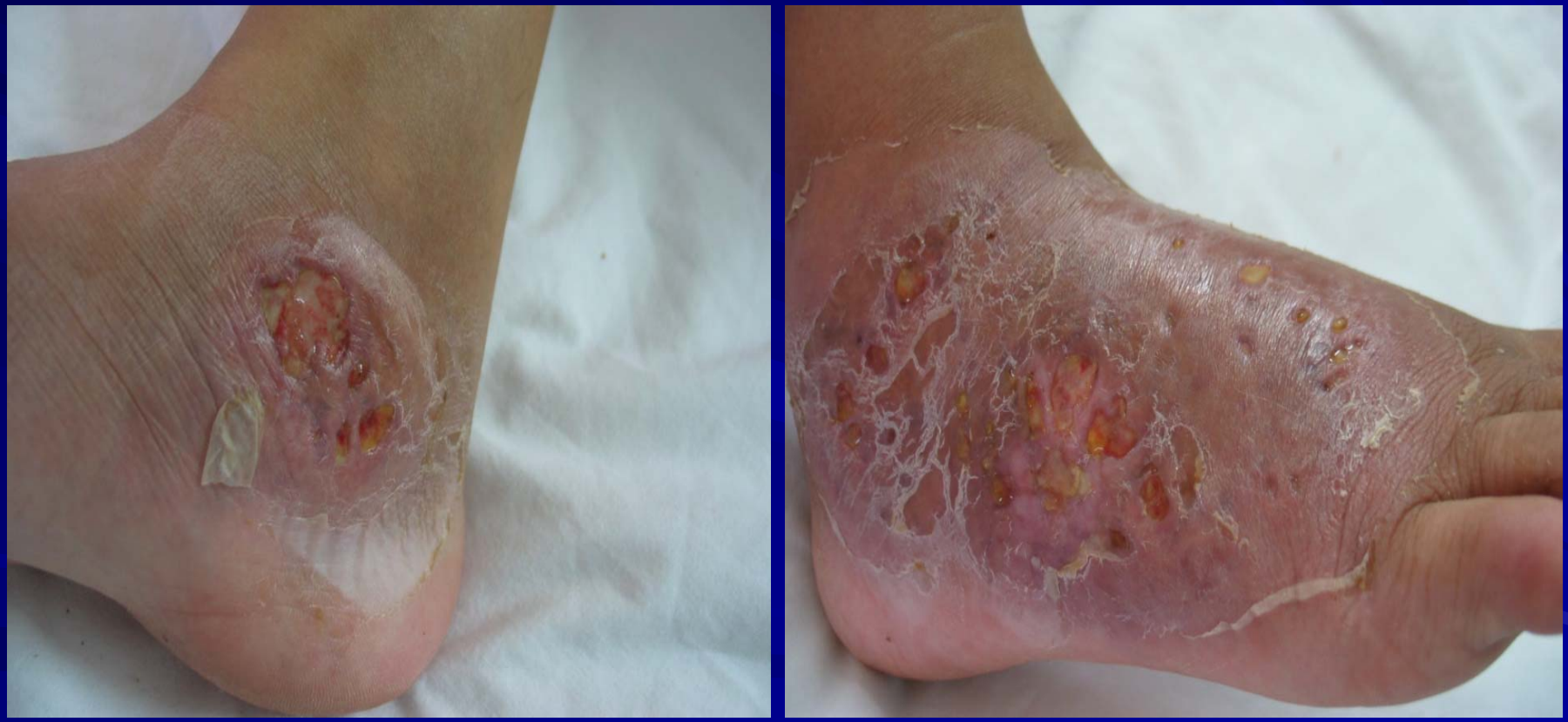
Clinical history (january 2010)

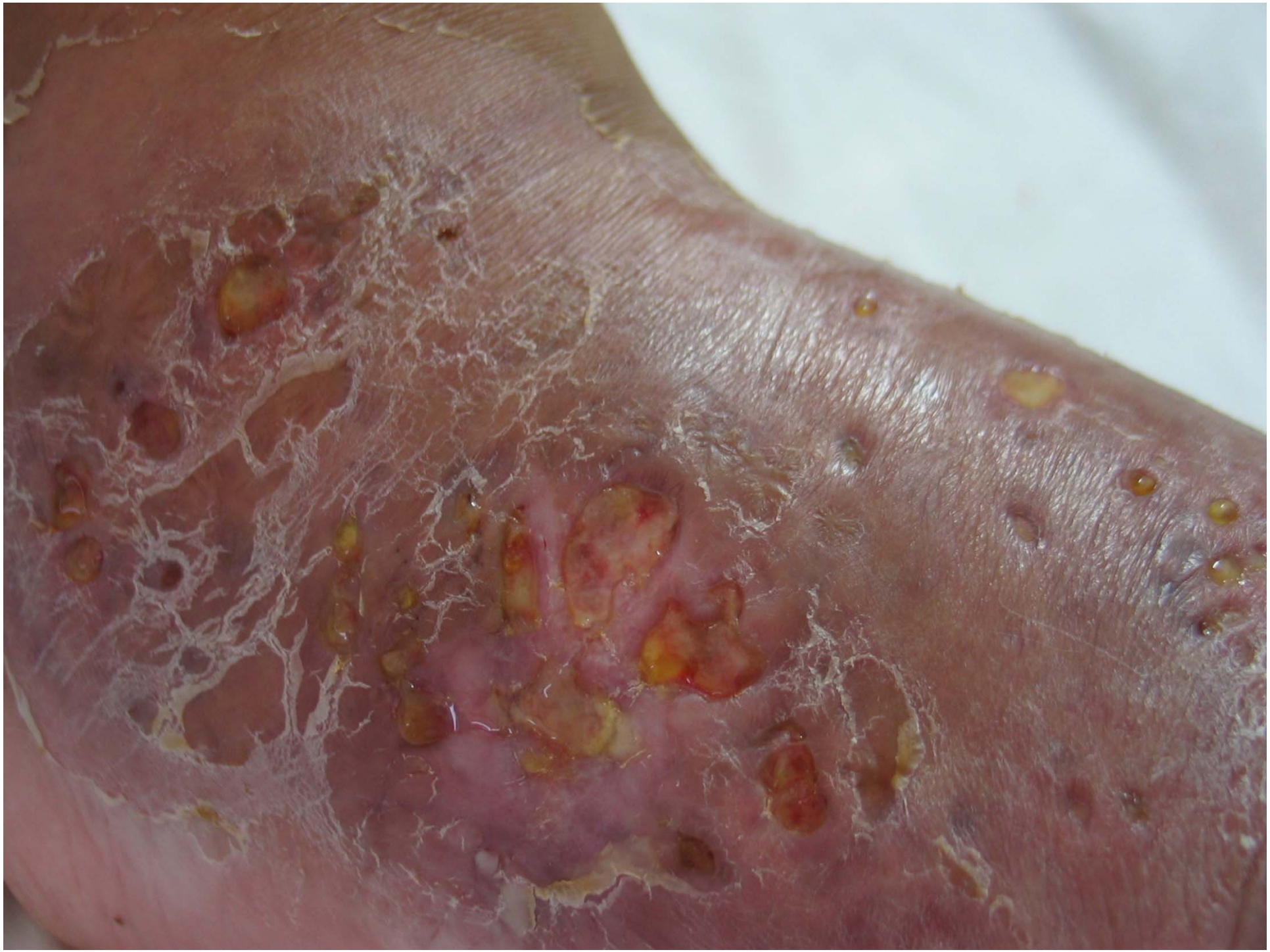
- 6 months after the last relapse the patient was admitted to the hospital because of a painful, tenderness, red swelling of the right foot accompanying muco-bloody diarrhea(3-4 stools/day)
- Laboratory findings :Fgb=726,5mg, Le=13300, Hb=10,2g/dl, HCT=34,1%, PLT=402000
- CDAI-260

Clinical and paraclinical findings

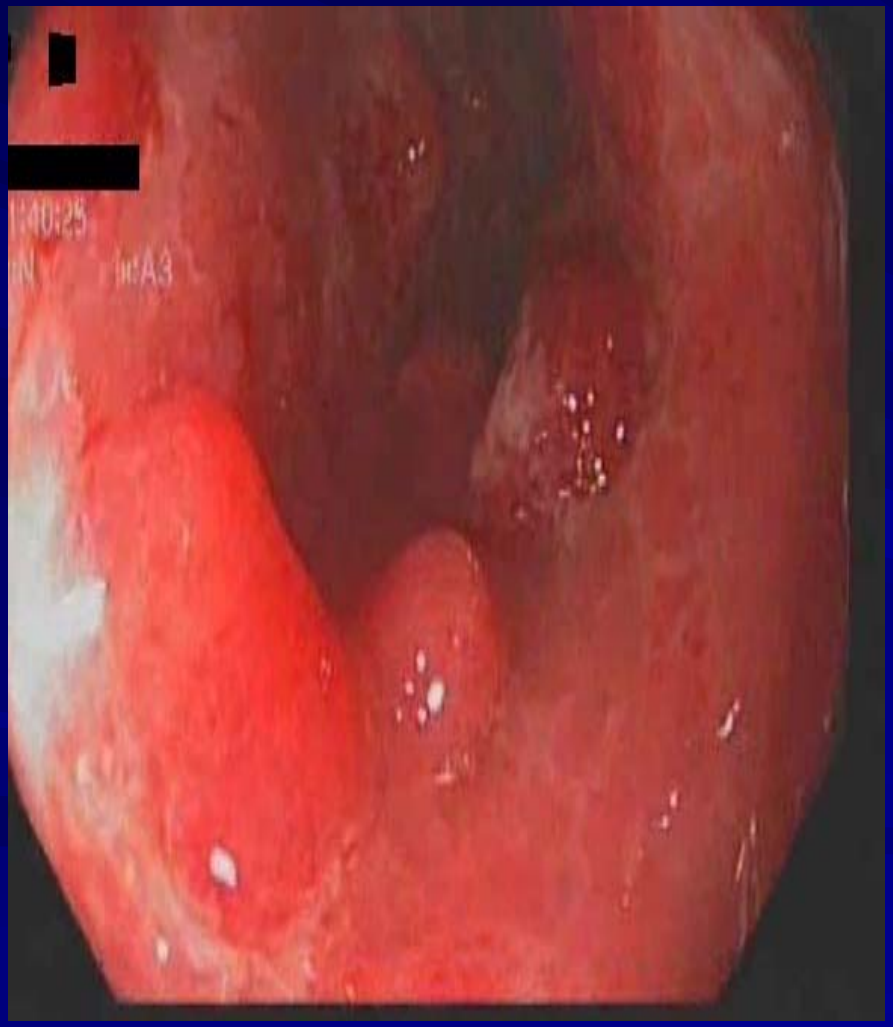
- Clinical examination revealed an erythematous area of the lower right leg with draining pustules
- Radiographs of the left ankle showed soft-tissue edema without evidence of osseous involvement.
- Negative coproculture
- Cl difficie toxine A/B negative
- Colonoscopy showed lesions limited to the colon without involvement of the terminal ileum

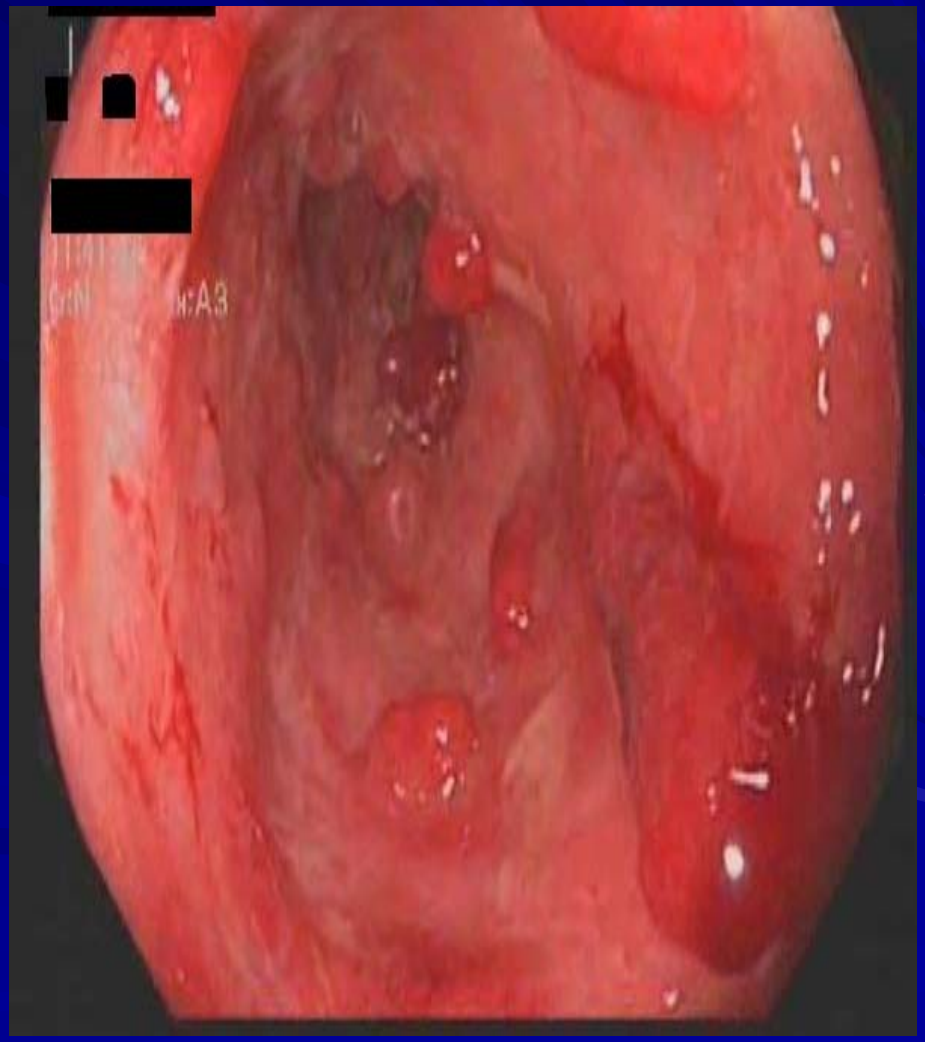
Multiple ulcers with a mucopurulent base, violaceous undermined border and peripheral erythema

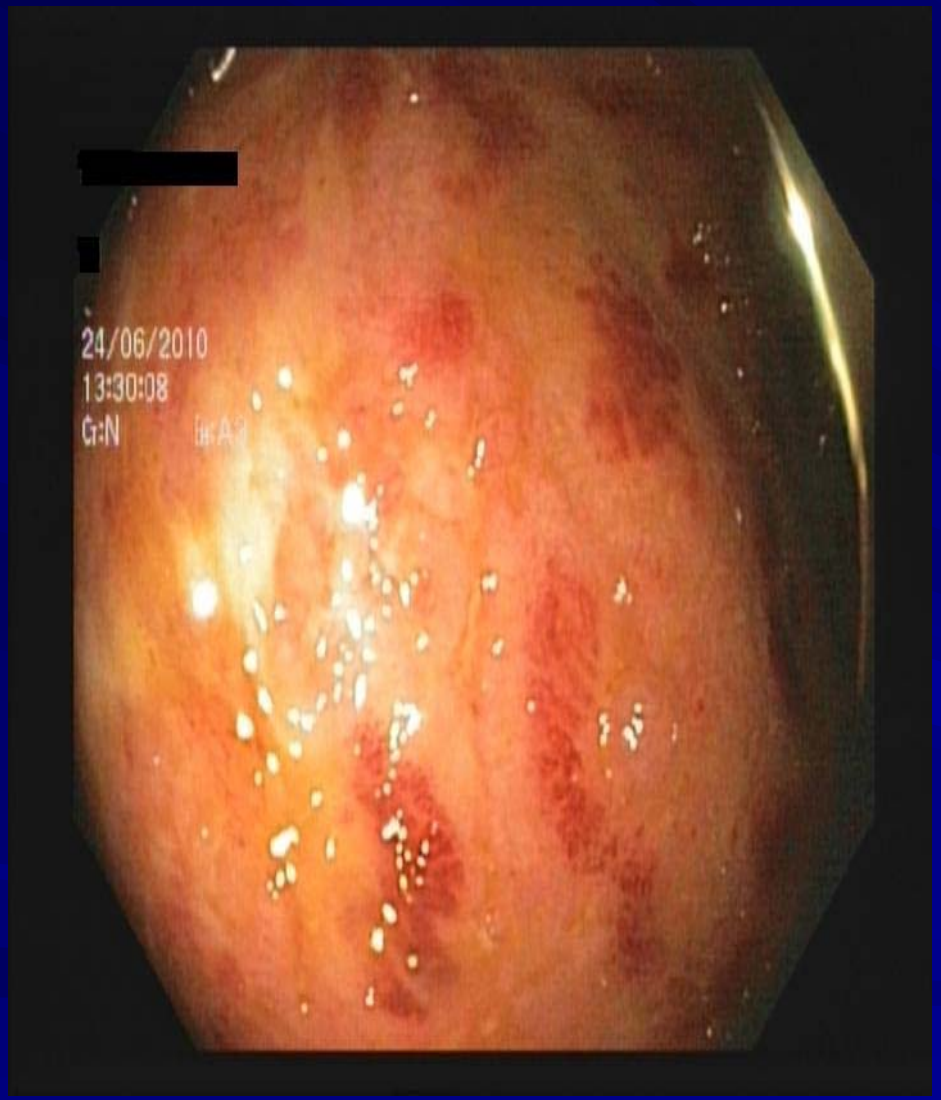




Colonoscopy: ulcers, edema, inflammatory pseudopolyps



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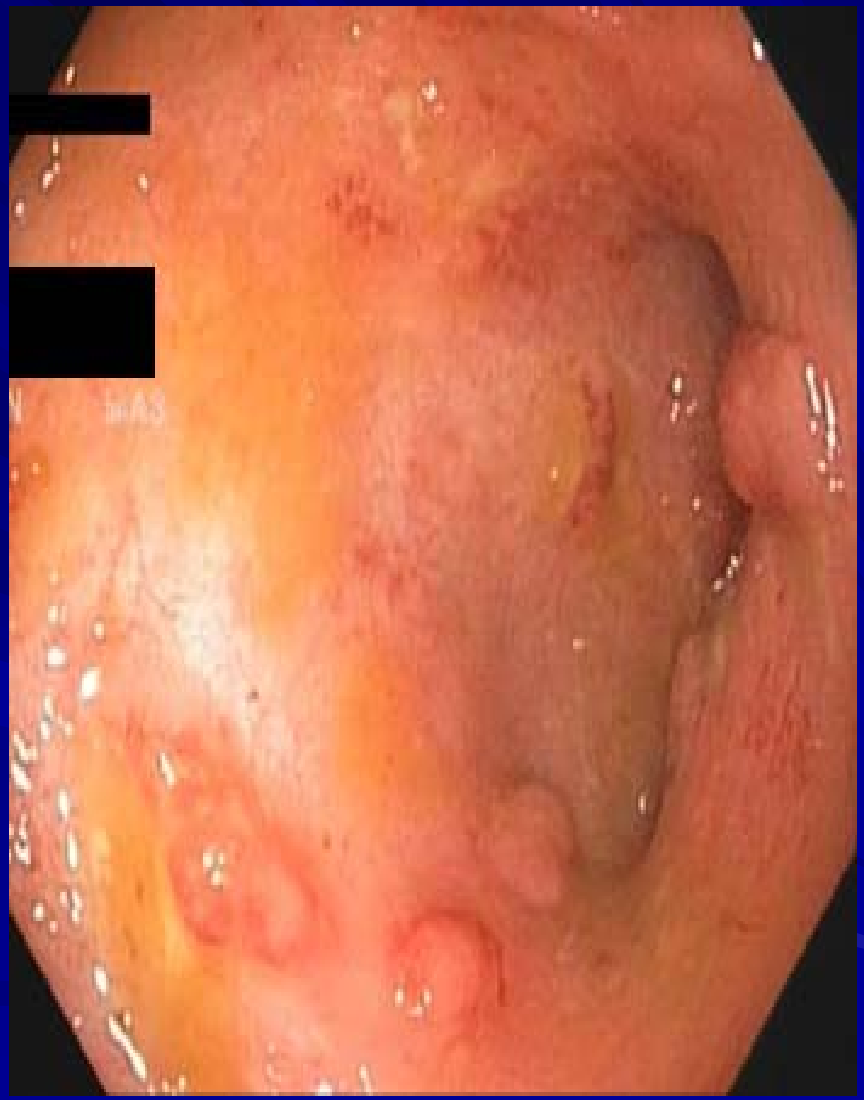


Diagnosis

- 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

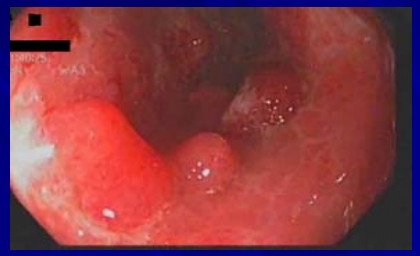
Farhi D, Cosnes J, Zizi N, et al. A cohort study of 2402 patients. Medicine (Baltimore) 2008; 87:281.

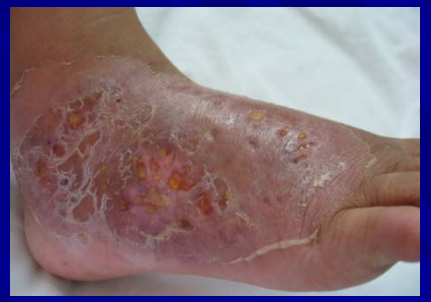
Differential Diagnosis

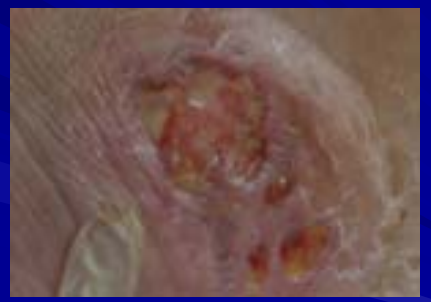
TABLE 4. DIFFERENTIAL FEATURES OF SWEET'S SYNDROME AND PYODERMA GANGRENOSUM.

FEATURE	PYODERMA GANGRENOSUM	SWEET'S SYNDROME
Association with inflammatory bowel disease	About 1 in 3 cases	About 1 in 10 cases*
Predominant location	Legs	Arms, face, and neck
Appearance of lesion	Pustules	Nonpustular, solid papules or plaques
Ulcers	Present, with undermined, violaceous borders	Absent
Monoclonal gammopathy	About 10 percent	Probably <5 percent

*Data obtained from Daoud et al.[6]







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

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

Ahronowitz I, Harp J, Shinkai.Am J Clin Dermatol 2012; 13:191.

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

Ruocco E, Sangiuliano S, Gravina AG, et al. Pyoderma gangrenosum: an updated review. J Eur Acad Dermatol Venereol 2009; 23:1008.

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

Ruocco E, Sangiuliano S, Gravina AG, et al. Pyoderma gangrenosum: an updated review. J Eur Acad Dermatol Venereol 2009; 23:1008.

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**

Powell FC, Hackett BC, Wallach D. in: Fitzpatrick's Dermatology in General Medicine, 8th ed, Goldsmith LA, Katz SI, Gilchrest BA, et al. (Eds), McGraw-Hill Companies, Inc., 2012. Vol 1, p.371.

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

Miller J, Yentzer BA, Clark A, et al. A review and update on new therapies. J Am Acad Dermatol 2010; 62:646.

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

Pyoderma gangrenosum-
Treatment

- **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**

Ahronowitz I, Harp J, Shinkai.Am J Clin Dermatol 2012; 13:191.

Pyoderma gangrenosum-

Treatment

Table 2: Treatment options for Pyoderma Gangrenosum (PG) versus Crohn's Disease/Inflammatory Bowel Disease (IBD) [14, 15]

	Treatment of PG	Treatment of Crohn's Disease/ IBD
Topical Agents	Corticosteroids Tacrolimus (0.5%) Benzoyl peroxide Nitrogen mustard	Budesonide (limited for disease affecting ileum and ascending colon)
Systemic Agents Immunosuppressive	Oral Corticosteroids in pulse therapy Tacrolimus 6-Mercaptopurine Azathioprine Cyclophosphamide Cyclosporine Methotrexate Cytosine arabinoside Daunorubicin Melphalan	Chronic low dose steroids (non-responsive IBD) Tacrolimus (refractory CD) 6-Mercaptopurine Azathiopurine Cyclophosphamide Cyclosporine Methotrexate
Systemic Agents Antimicrobial	Sulfasalazine Dapsone Rifampicin Clofazimine Vancomycin Mexlocillin Minocycline	Aminosalicylates: sulfasalazine, mesalamine, olsalazine, balsalazide Ciprofloxacin Metronidazole(used to treat infectious complications CD, or mild active CD)

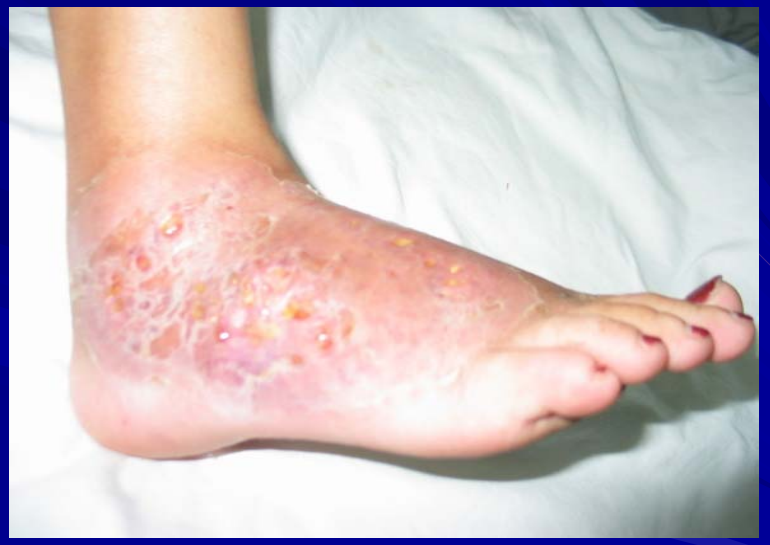
Table 2: Treatment options for Pyoderma Gangrenosum (PG) versus Crohn's Disease/Inflammatory Bowel Disease (IBD) [14, 15]

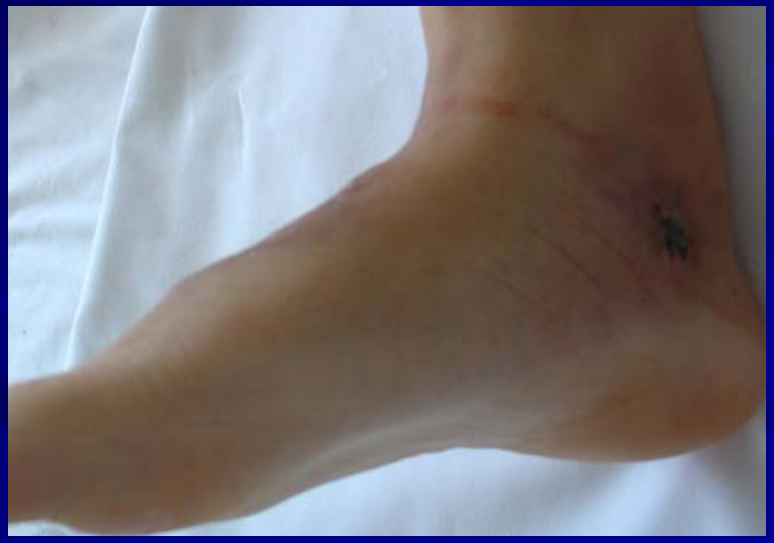
Anti-diarrheal Meds		Loperamide Cholestyramine
Biologic Agents	Anti-TNF therapy: Infliximab Alefacept Adalimumab Efalizumab Etanercept	Anti-TNF therapy: Infliximab (used in individuals with disease resistant to steroids and 6-MP) Adalimumab (disease resistant to infliximab) Certolizumab
		Combination therapy (infliximab in combination with 6-MP, azathioprine or methotrexate)
		Natalizumab (effective induction agent for CD)
Immune Modulators	IVIG Interferon Granulocyte apheresis	
Anti-inflammatory	Thalidomide Mesalazine Colchicine Heparin Potassium Iodide Isotretinoin	Thalidomide (refractory IBD)
Last resort	NO surgery - can make PG worse and progressive	Surgery (used in unresponsive disease or patients who develop abscess, fistula or strictures or with limited regional involvement)

Follow-up

1 month after appropriate therapy:

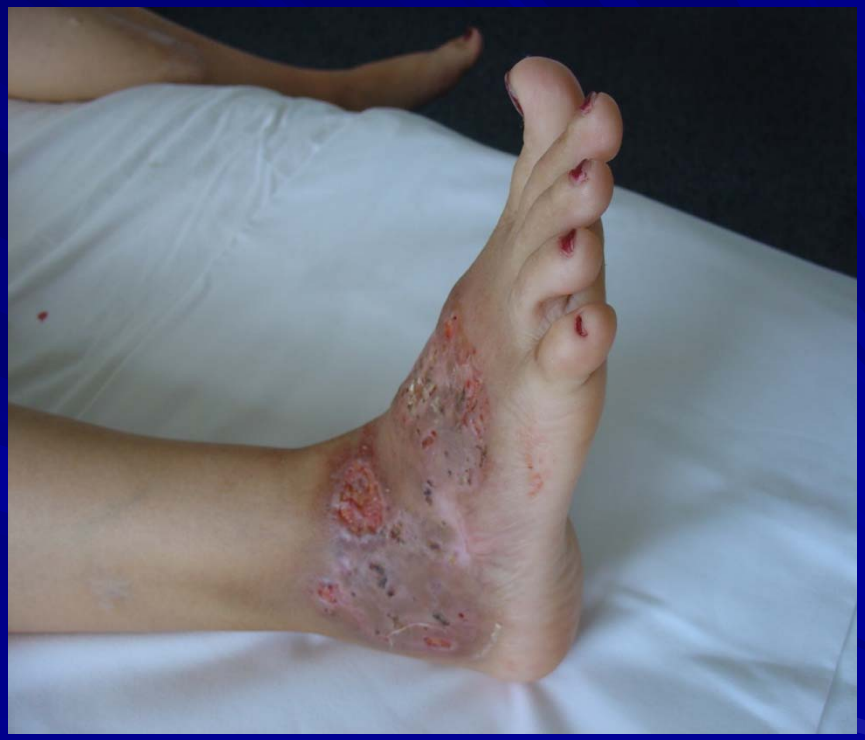
- **improvement of skin lesions**
- **clinical remission**

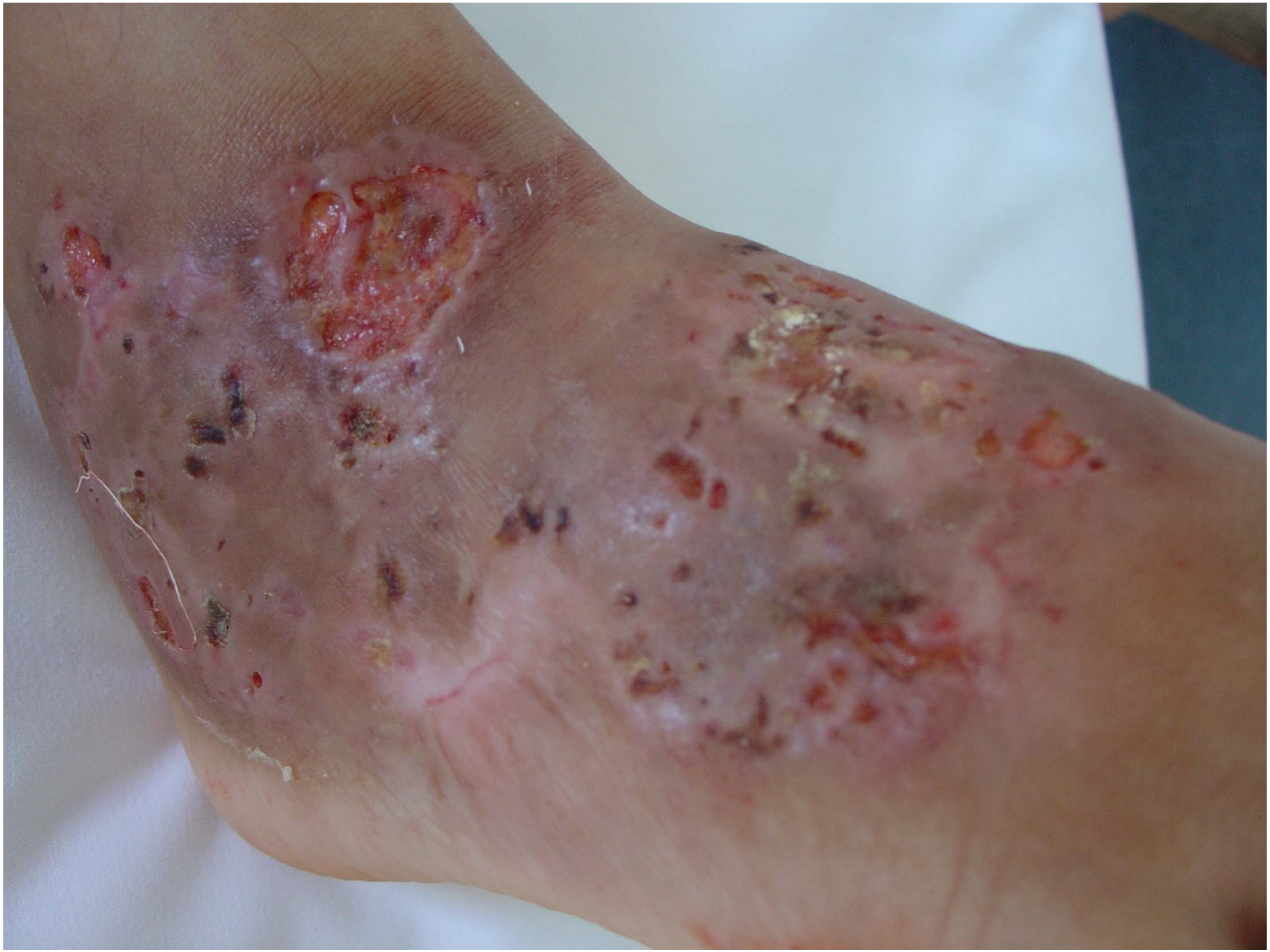




6 months later…

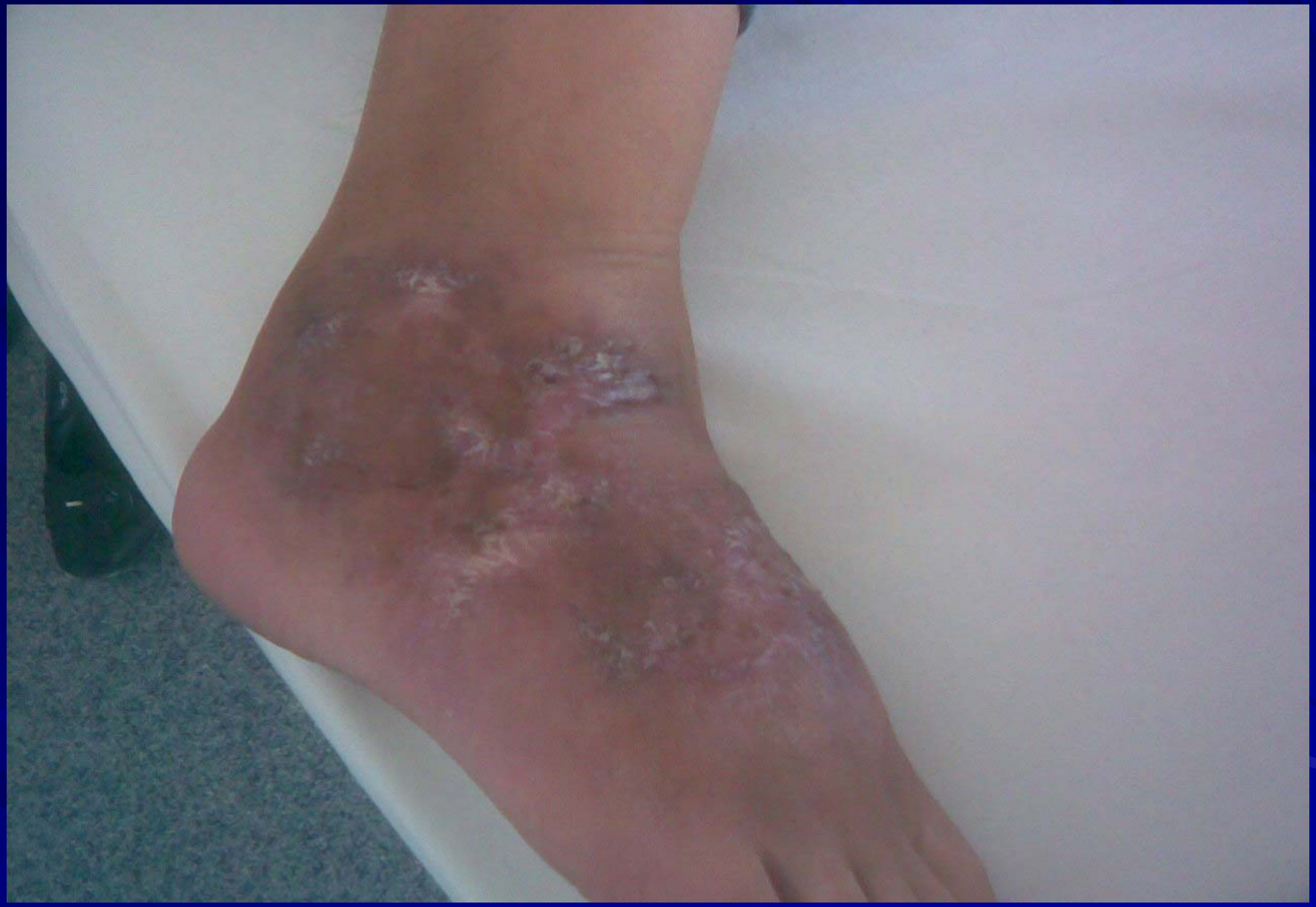
- Reactivation of skin lesions
- Clinical remission without mucosal healing at colonoscopy

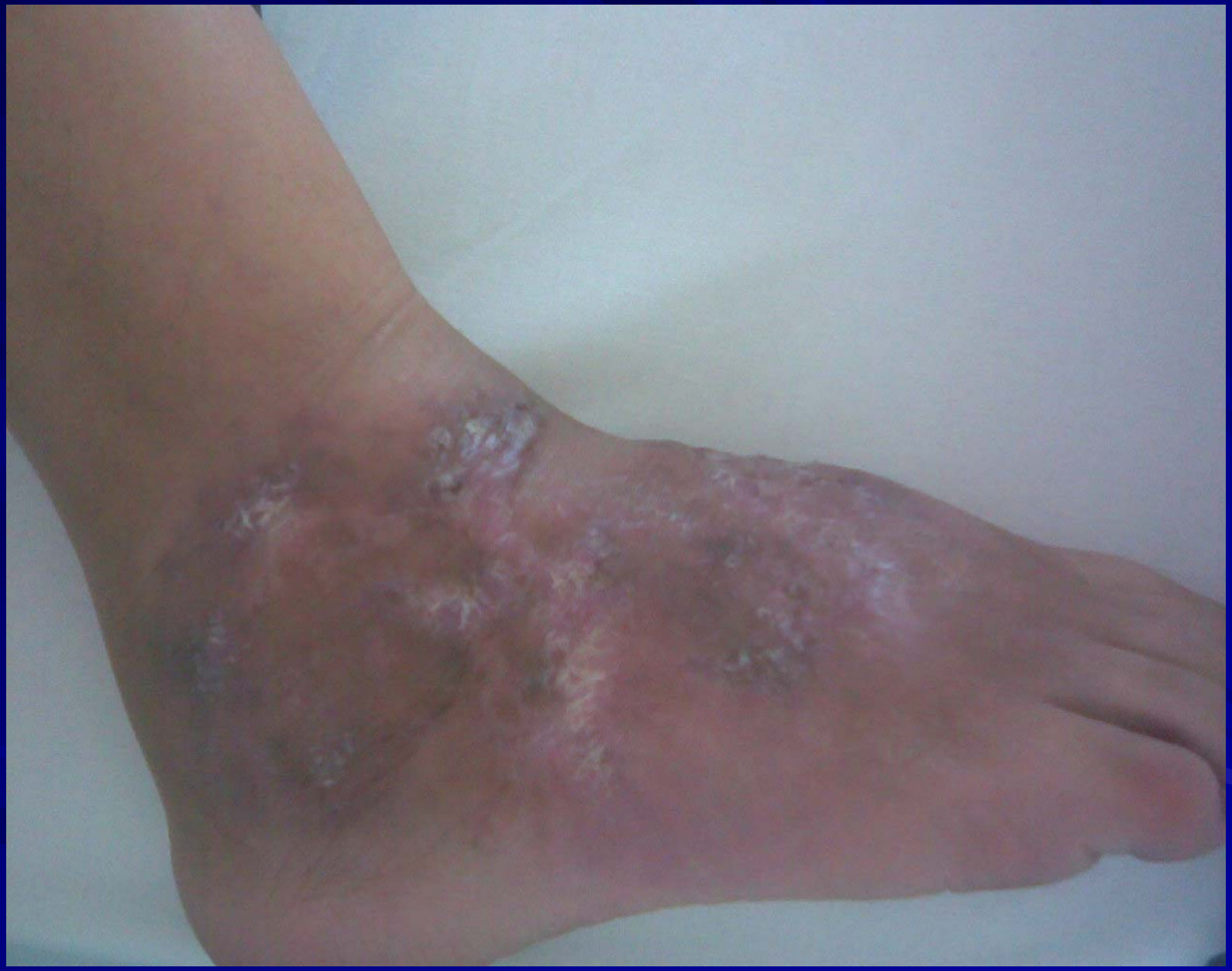




Treatment and outcome

- **A wound culture yielded colonies of meticilino resistent *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 corticostherapy), PCR-9.13.
- Colonoscopy: longitudinal ulcers in the rectum, no other injuries 30cm explorated.
- 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

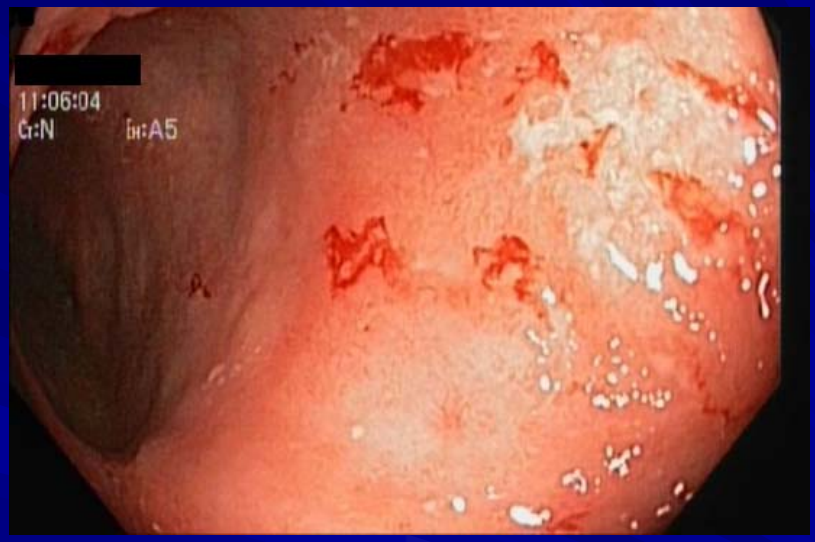
- Restart the initial IFX regimen (5mg/kgc every 8 weeks)

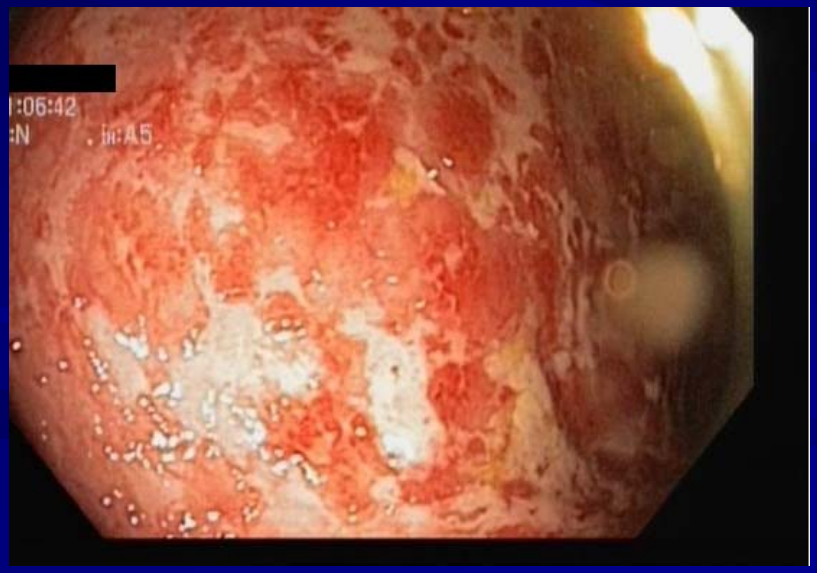
January 2013 (one year after the last flare)

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

- Clinical presentation: 6-7stools/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/kgc
- Budenofalk foam 6 mg 1/day
- Increasing the dose of IFX to 10mg/kgc
- Shortening the interval between administration of IFX to 4 wk
- Salofalk 4g/day

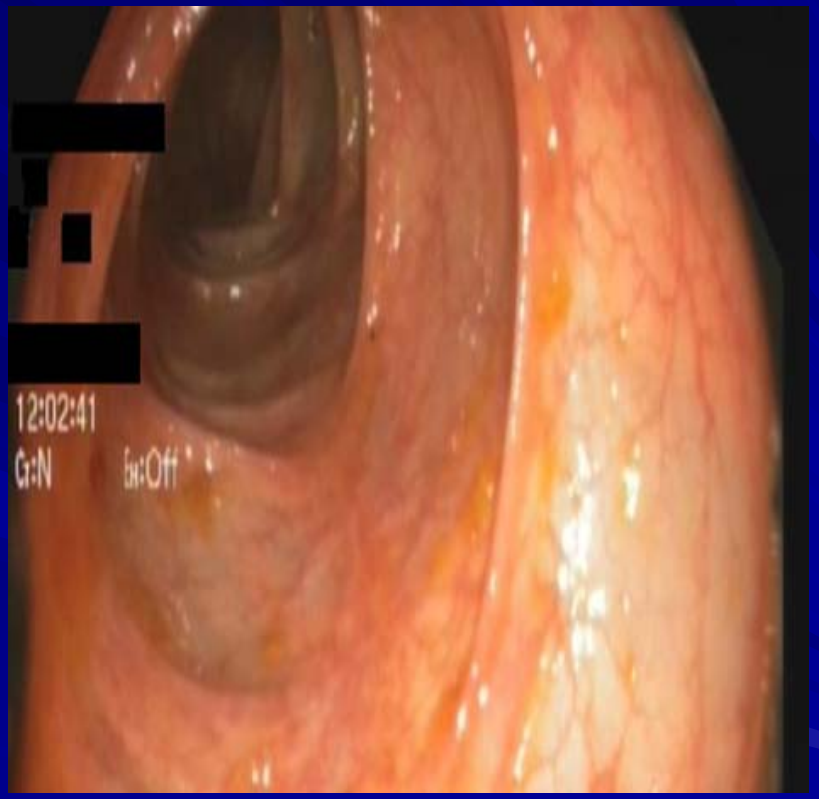
The chosen regimen was:

- **IFX 10mg/kgc at 8 wk**
- **Budenofalk foam 6mg/day**
- **AZA 2.5mg/kgc**
- **Salofalk 4 g/day**

Follow-up

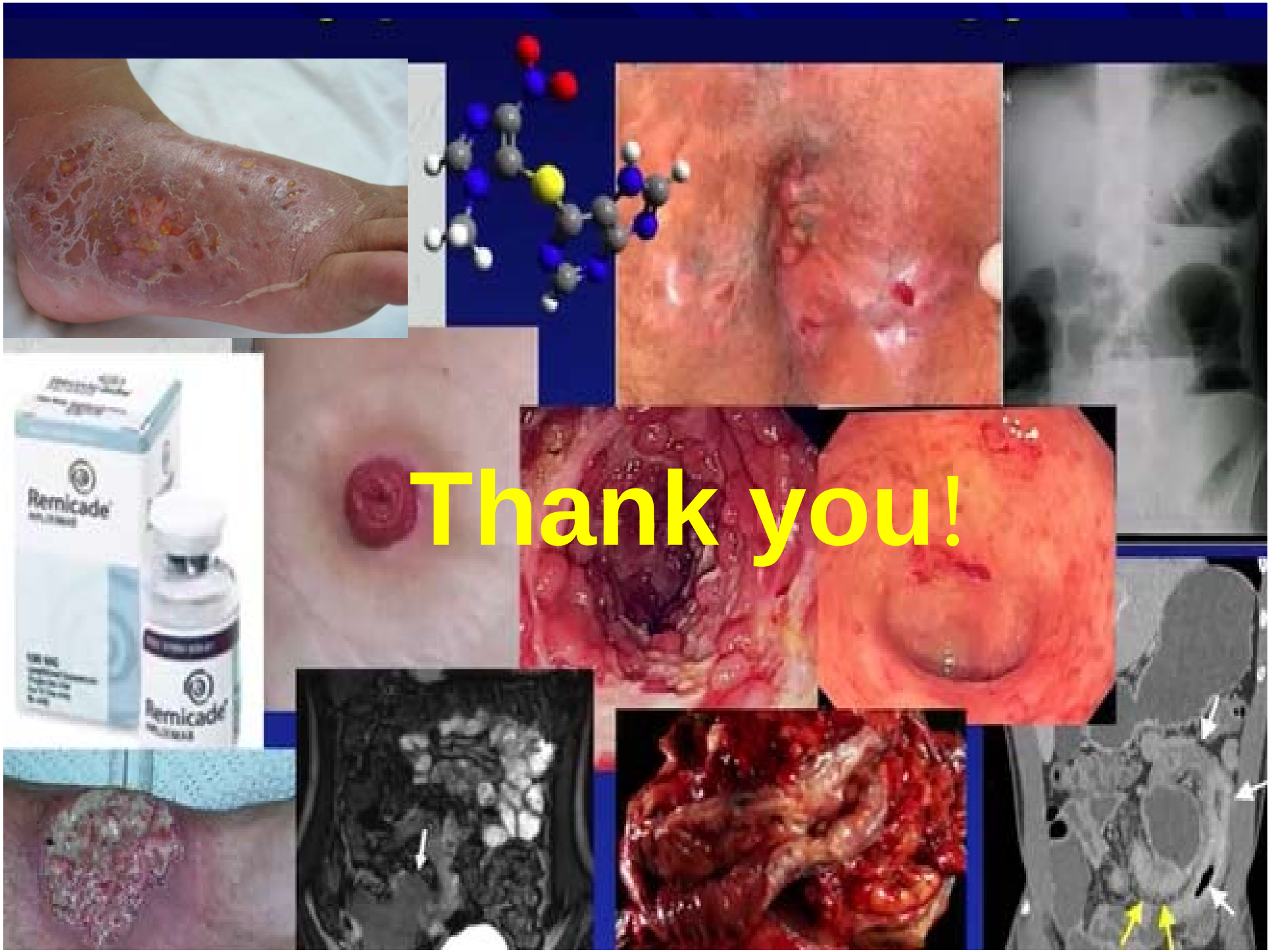
March 2013 (after 3 months of IFX dose escalation)

- Favorable outcome under IFX 10 mg/kgc+rectal foam Budenofalk
- Clinical and endoscopic remission which allows dose reduction of IFX to 5mg/kgc



Conclusions

- 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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Thank you!