Crohn’s Disease: Challenges and new therapeutic options

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Grey’s Hospital
Index patient

- 29 year old gentleman, Mr. N.S.
- **Main complaint:**
  Acute onset of severe, constant RIF pain, since previous night, associated LOA, no n&amp;v/diarrhoea.
  Four month history of severe, constant backpain, only partially relieved by analgesics. However, since the onset of abdominal pain, backpain ceased.
History: continued

- PMH: CD was diagnosed in 1999 → initially managed with sulfasalazine.
- In 2005 he was initiated on Asacol and prednisone 20mg dly.
Unsuccessful at induction of remission → azathioprine was gradually titrated upwards from 75mg dly to 150mg dly.

Patient became steroid dependent

Since February 2007 → lower back pain, spontaneous onset, non-progressive, radiating to R thigh, o/e normal alignment, tense paraspinals L > R, back non-tender, full ROM, hips FROM, Xray spine: NAD
History: continued

- PSH: incomplete bowel obstruction → intestinal resection with end-to-end anastomosis in 2000 and 2002

- Medication: Azathioprine 150mg dly, Prednisone 12,5mg dly, Asacol 800mg tds, Ca gluconate 1 bd, Ferrous sulphate, Analgesics

- Allergies: nil known

- Social: non-smoker, abstaining from alcohol, married, unable to maintain work due to his disease.

- Family Hx: nil of note
Examination

- Acutely ill, drowsy
- BP 59/36, HR 130, RR 24, temp 39’, mild deH2O
- No extra-intestinal features of Crohn’s disease
- CVS: bounding pulses, warm peripheries, regular, JVP →, apex 5ICS, HS normal, no murmurs, septic shock
- Chest: not distressed, clear, bilat br/s
- Abdomen: RIF tenderness, rebound & peritonism, no organomegaly, no perianal complications, PR: no stool, no blood, no mass
- Neuro: drowsy, no meningism, no focal signs
Clinical assessment

- 28 year old gentleman with chronic active Crohn’s disease, refractory to azathioprine as well as steroid-dependent, presenting now with septic shock and localized peritonitis in the right iliac fossa. Possible cause: abscess formation or perforation.
Investigations

FBC: WBC 7,1; HB 8,2; PLT 260; MCV 83,5
U&E: Na 141; K 4,1; Cl 110; Co2 26;
    urea 9,1; creat 95
LFT: ALP 57; Bil 7; Prot 61; alb 25; GGT 26;
    ALT 11
CMP:Corr Ca 2,36; Pho4 1,02; Mg 0,77

Ultrasound: Small collection on the right side of the pelvis
Initial management

- Resuscitation with voluven, IV fluids
- Ciprofloxacin 400mg q8h IV, Metronidazole 500mg
- Azathioprine 150mg dly po
- Hydrocortisone 100mg qid IV
- Urgent surgical consult
- CT abdomen: Right paracolic abscess, defect in wall at anastomosis between colon & terminal ileum
Crohn’s Disease: Challenges and New Treatment strategies
Introduction

- Idiopathic inflammatory bowel disorder.
- Hypothesis: Crohn’s disease occurs in a genetically predisposed patient, when various exogenous factors and host-factors cause dysregulation of the mucosal immune function.
Pathogenesis

- Genetic susceptibility:
  Polygenetic disease: 12 susceptibility regions
- Exogenous factors:
  Smoking; Hygiene hypothesis

Immunopathogenesis: Initiating events
1. Leaky epithelial barrier
2. Different pattern of toll-like receptor expression
3. Dendritic cells incorrectly recognize commensal bacteria as pathogens → initiate a Th1 immune response.
4. Epithelial cells activate effector-T cells
5. Activated T cells do not undergo apoptosis
Clinical presentation

A. Clinical presentation depends on disease location: Intestinal manifestations:

- 1. ileocolitis
- 2. jejunoileitis
- 3. colitis & perianal disease
- 4. gastroduodenal disease

B. Complications:

- Intestinal obstruction, free perforation, intra-abdominal abscess, fistula formation, massive hemorrhage, malabsorption, severe perianal disease

C. Extraintestinal manifestations
Extraintestinal manifestations
Extraintestinal manifestations
Extraintestinal manifestations

- **Cardiac**: myocarditis
- **Pulmonary**: pleuropericarditis, ILD
- **Hebatobiliary**: hepatic steatosis, 1’ **sclerosing cholangitis**, cholelithiasis, pancreatitis
- **Renal**: **nephrolithiasis**, hydronephrosis, fistulas, renal amyloidosis
- **Rheumatological**: migratory arthritis or **arthralgia**, ankylosing spondylitis, sacroiliitis
- **Dermatological**: **erythema nodosum**, **pyoderma gangrenosum**, metastatic crohn’s, aphthous stomatitis
- **Other**: Osteoporosis, **thromboembolisms**
Disease activity

- Crohn’s disease activity index used for research purposes
- Combination of clinical assessment and laboratory features used in practice: symptoms, weight, Hb, albumin, ESR, CRP, WBC
Definitions

- **Remission**: Asymptomatic patients without inflammatory sequelae.
- **Chronic active CD**: Persisting/recurrent symptoms for > 6 months despite standardised therapy.
- **Steroid-dependent CD**: Need for c/s to maintain the pt in remission, after two unsuccessful attempts to withdraw c/s within the last 6 months.
- **Steroid-refractory CD**: Persisting clinical activity despite corticosteroids > 1mg/kg/day.
Management

1. 5-Aminosalicylic acid compounds
2. Corticosteroids
3. Antibiotics
4. Immunosuppressive agents
5. Biological agents
6. Surgical management
## 5 Aminosalicylic acid compounds

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<th>Azo-Bond:</th>
<th>Sulfasalazine</th>
<th>Sulfapyridine-5ASA Colon</th>
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<td>Olsalazine</td>
<td>5-ASA-5-ASA Colon</td>
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<td>Balsalazide</td>
<td>aminobenzoyl-alanin-5-ASA Colon</td>
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<th>Delayed Release:</th>
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<td>Claversal</td>
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<th>Sustained Release:</th>
<th>Pentasa</th>
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5 Aminosalicylic acid compounds

- Sulfasalazine effective in inducing remission in CD, esp colitis, ileocolitis (ECCDS)
- Sulfasalazine **not** effective for maintenance of remission (NCCDS)
- Asacol significantly ↓ relapse in pt in remission
- **Mechanism (5-ASA)**
  1. inhibition of NF-κB activity
  2. inhibits 5-lipoxygenase synthesis and therefore inhibits synthesis of leukotrienes
  3. free radical scavenger
Corticosteroids

- **Prednisone**: 17 wk course of prednisone (0.5-0.75mg/kg) induced remission in 60% pt (NCCDS)
- Maintenance therapy with low dose prednisone **not** effective (prednisone at 0.25mg/kg, NCCDS)
- Budesonide is effective at inducing remission (NEJM 1994) and prolongs time to relapse. Extensive first-pass metabolism

Antibiotics

- **Metronidazole**: perianal and fistulous CD, abscess
- **Ciprofloxacine** (500mg bd): perianal, fistulous CD
Immunosuppressive agents

**Indications:**
- Chronic active disease
- Steroid-dependent disease
- Long-term maintenance following a biological agent
- Prevention of immunogenicity to biological agents
- Prevention of post-operative recurrence
Azathioprine

- Not ideal induction agent d/t slow onset of action
- Effective maintenance of remission; Dose: 2 – 2,5mg/kg
- Side-effects:
  - bone marrow depression, esp leukopenia (↑ risk: TPMT deficiency, co-drugs: allopurinol, sulfasalazine)
  - pancreatitis, hepatitis, infection, lymphoma
  - if lacking the thiopurine methyltransferase → acc thioguanine metabolites

![Diagram showing the metabolic pathways of Azathioprine](image-url)
Methotrexate

- **Action:** inhibits dihydrofolate reductase resulting in impaired DNA synthesis & decreased production of IL 1
Methotrexate: Trials

- **Methotrexate for induction:** MTX 25mg IMI weekly. Improvement in Sx in 6 weeks. 17% of pt in methotrexate group had adverse event (aSx↑ALT, nausea, skin rash, P, optic neuritis).

- **Methotrexate for maintenance:** MTX 15mg IMI weekly, effective as maintenance, no severe adverse events reported in RCT.
Methotrexate

- **Side-effects:**
  - leukopenia, BM suppression
  - infection
  - hepatic fibrosis, ↑ ALT, hypersensitivity
  - teratogenic, mucositis, rash

- **Bone marrow toxicity:** a late complication of Rx. Median delay to neutropenia 16.9 months VERSUS onset within days to weeks

- **↑ Risk:** Drugs: C/S, NSAIDS, omeprazole, penicillin, Co-trimoxazole. Larger dose, ↓ renal Fx, ascites/oedema/effusion. IV contrast can precipitate toxicity

- **Treatment:** 1. stop MTX 2. Give folinic acid/leucovorin 3. Granulocyte CSF 4. Abs
Biotechnology agents

- **Infliximab**: chimeric IgG1 monoclonal antibody
  - Induction: 5 or 10 mg/kg IVI and week 0, 2, 6.
  - Maintenance: 5 or 10 mg/kg IVI every 8 weeks.
  - **Action**: neutralize TNF α, induce apoptosis in T lymphocytes, mediate AB-dependent cellular cytotoxicity and C’ fixation

- **Adalimumab**: human IgG1 mAb (100% human prot)
**Infliximab: side-effects**

- **Infections, esp TB, histoplasmosis**
  - Odds ratio 2.0 for serious inf;
  - NNH: 59, within a Rx period of 2 – 12 months

- **Lymphoma: non-Hodgkin’s, Skin cancers:**
  - squamous & basal cell CA → odds ratio 3.3;
  - NNH was 154 for 1 additional malignancy within a Rx period of 6 – 12 months

- **Multiple sclerosis, optic neuritis**

- **Acute infusion reactions, delayed hypers reactions**

- **Formation of auto-antibodies, eg ANF**
Other biotechnology agents

- **Natalixumab**: humanized IgG4 monoclonal antibody against α4 integrin (95% human). Action: neutralizes α4 integrin

- **Certolizumab pegol**: pegylated humanized monoclonal antibody F AB fragment.
Mild CD: Induction

- First line: budesonide or sulfasalazine
- Second line: Oral prednisolone 40 – 60mg dly
- Third line: Methotrexate 25mg weekly IMI
  - Azathioprine not ideal d/t slow onset of action
  - Infliximab 5mg/kg at weeks 0, 2, 6 or Adalimumab

Fulminant or refractory CD

- First line: IV corticosteroids 1mg/kg/day
- Second line: IV infliximab or adalimumab
- Surgery if obstructive complication or not able to tolerate medical therapy
Fistulising Crohn’s disease

- **First line**: Ciprofloxacin 500mg bd, metronidazole 1000mg – 1500mg dly
- **Second line**: Azathioprine 2.5mg/kg/day
- **Third line**: Infliximab
- **Fourth line**: Fistulotomy

Surgery

- Fibrotic strictures → bowel obstruction
- Internal fistulas complicated by abdominal abscess
- Enterovesical fistulas
- Enterocutaneous fistulas
Patient’s Progress

- **Week 2/day 10**: Pt developed a high-output enterocutaneous fistula. Mx: TPN, IV AB
- **Week 5/day 32**: Necrotizing fasciitis, abscesses ant & posterior to right ilia crest → Mx: debridement, TPN, Piperacillin-Tazobactam, metronidazole, Ciprofloxacin
- **Week 7/ Day 47**: Massive GIT bleed. Hb 9,7 → 6,5; Gastroscopy: no ulcer, oes candidiasis, Mx: IV PPI, transfusion, fluconazole
Patient’s Progress

- **Week 8/ day 49:** Initiated on methotrexate 25mg IMI weekly plus folic acid, long-term ciprofloxacin to induce fistula closure

- **Week 9/ day 62:** Febrile neutropenia, temp 39.5’, HR 135, lungs clear, CXR: NAD, u-dipstick : NAD. Mx: Piperacillin- Tazobactam, Metronidazole, Ciprofloxacin, stop MTX, stop azathioprine

- **Week 10/ day 65:** Poor response to AB, re-exploration of groin wound: clean, no pus collection, Hb: 8.7; WBC 0.4; neutro 0.1; PLT 90. Blood & u-MCS: no growth x4. Mx: Neupogen, Leucovorin, Piperacillin-Tazobactam, Metronidazole, Amikacin added
Patient’s Progress

- **Week 10/ day 68**: Piperacillin-Tazobactam substituted with meropenem, IV Fluconazole

- **Week 10/ day 69**: Fever & tachycardia resolved, minimal petechiae right knee. Pancytopenia persisted, WBC 0.4; Neutro 0.3; HB 7.3; PLT 36, MPV 10.7; RPI 0.7%. Smear: NCNC, no fragments, no PLT clumping; INR 1.22; APTT 24.6. Blood culture: repeatedly no growth, urea & creat: WNL. Mx IV AB, packed cells, K replacement
28yr old pt with Crohn’s disease, previously treated with azathioprine for one year, weekly MTX was initiated 20 days ago. Pt received daily folate as well as INH prophylaxis.

Febrile neutropenia and pancytopenia, not responding to leucovorin and neupogen.

Differentials:
- Methotrexate induced myelosuppression
- Azathioprine induced myelosuppression
- Opportunistic infection eg TB, Histoplasmosis
Patient’s Progress

- **Week 11/ day 70:**
  - Sudden depressed LOC. Pinpoint pupils bilaterally, no meningism, globally depressed tone, left hemiparesis, plantars equivocal bilaterally;
  - → no response to naloxone,
  - → required intubation for airway protection
  - → IV fluids, Platelets, FDP, urgent CT brain
Patient’s Progress

- Large R parieto-occipital ICH with smaller ICH on the L occipital lobe with oedema
- Mass effect & midline shift to left
- Infarct left external capsule (subcute)
- CD pt with extensive bilateral ICHs, as well as an infarct
Neurologic manifestations of IBD

- CVD d/t thrombosis and thromboembolism
- Cerebral vasculitis, necrotizing angiitis
- Immune mediated neuropathy and cerebral demyelination

**Question arises:** Could this patient have had cerebral vasculitis/necrotizing angiitis which resulted in ICHs in the presence of significant thrombocytopenia?
Patient’s Progress: Differentials

- **Clinically:** frothy sputum, bibasal crepitations, PO2 16.19 kPa on T-piece
- **Neurogenic pulm oedema**
- **LRTI:** Pneumocystis, TB, aspiration
- **ILD:** related to MTX or Crohn’s D
- **Alveolar haemorrhage, ALI**
Patient’s Progress

- **Week 11/ day 71**: Not for neurosurgical intervention due to extensive haemorrhages and thrombocytopenia. Supportive management with mannitol, dexamethasone, IV antibiotics.

- **Week 11/ day 72**: Patient rested in peace surrounded by his family & friends.
References

- Baumgart DC. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007;369:1641-57
- Harrison’s Principles of Internal Medicine, 16th edition
- Kumar and Clark
References

- Oral budesonide for active Crohn’s. NEJM 1994;331:836
- Feagan BG. A Comparison of Methotrexate with placebo for the maintenance of remission in Crohn’s Disease. NEJM 2000;342:1627-32
References

- Bongartz T. Anti-TNF Antibody therapy in Rheumatoid arthritis and the Risk of Serious Infections and Malignancies. JAMA 2006;295: 2275-2285
Thank you
Disease activity cont.

- **Mild-moderate**: ambulatory pts tolerating oral meals without dehydration or >10% weight loss

- **Moderate to severe**: failure to respond to treatment for mild disease, fever, weight loss, abd pain /tenderness, intermittent N&V without obstruction, significant anaemia

- **Severe to fulminant**: persisting sx on c/s, high fevers, persistent vomiting, intestinal obstruction, rebound tenderness, cachexia, abscess
Azathioprine

- **Dose**: 2 – 2,5mg/kg
- **Action**: azathioprine → 6- mercaptopurine → thiopurine → inhibitor of purine ribonucleotide synthesis & cell proliferation, inhibits immune response
- Not ideal induction agent d/t slow onset of action
- Effective maintenance of remission
- Possibly effective in fistula closure
Methotrexate

Methotrexate for maintenance: MTX 15mg IMI weekly. At week 40, 65% pt in remission in MTX group versus 39% in placebo group. P 0.04. No severe adverse events.

Side-effects:
- leukopenia, bone marrow suppression
- hepatic fibrosis, raised transaminases
- hypersensitivity pneumonitis
- teratogenic
- mucositis, rash, nausea, diarrhoea
- infection
“Top-down“ Therapy

- Use of Anti-TNF agents early in the course of CD. Larger studies needed to assess safety and efficacy.
Methotrexate

- **Action:** inhibits dihydrofolate reductase resulting in impaired DNA synthesis & decreased production of IL 1

- **Methotrexate for induction:** MTX 25mg IMI weekly. After 16 weeks: 39% in MTX vs 19.1% in placebo group in remission. P 0.025. 17% of pt in methotrexate group had adverse event (aSx↑ALT, nausea, skin rash, pneumonia, optic neuritis). Improvement in Sx in 6 weeks in methotrexate group
Biotechnology agents

Mechanism of action:

- Infliximab, adalimumab, certolizumab pegol: neutralize TNF α
- Infliximab and adalimumab also induce apoptosis in T lymphocytes in vitro and mediate antibody-dependent cellular cytotoxicity and complement fixation
- Natalixumab neutralizes α4 integrin
**Methotrexate: bone marrow suppression**

- Bone marrow toxicity with MTX a late complication of Rx. Median delay to neutropenia 16.9 months
- Drugs that can cause BM suppression if combine with MTX: corticosteroids, NSAIDS, omeprazole, penicillin, Co-trimoxazole.
- **Treatment:** stop MTX
  - Give folinic acid
  - Granulocyte colony stimulating factor if poor response or pt severely ill
  - ABs according to local guidelines.