Drug-Induced colitis

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Iatrogenic & Drug-induced pathology of the colon

1 Surgery
   – Adhesions
   – Motility disorders
   – Short bowel syndrome

2 Graft-versus-host-disease
   – Acute
   – Chronic
Iatrogenic & Drug-induced pathology of the colon

3 Radio-chemotherapy
   - Radiation rectitis
     • Acute
     • Chronic

4 Drugs
   - Bowel preparation for investigations
     - Oedema
     - Focal active colitis
   - Systemic of local treatment
Drug-Induced Colitis: The Problem

• Constipation is a frequent adverse event
  – > 280 drugs induce constipation in >3% of patients treated
  – Morphologic lesions: uncommon

• Diarrhoea is a frequent adverse event of drugs
  – 7% of all drug adverse effects
  – 4.1% in 5,669 pts with lansoprazole
  – More than 700 drugs have been implicated in causing diarrhoea
  – Colitis is less common and associated with less drugs
  – 80 cases registered in France in 1984-1994!
Drug-Induced Colitis: The Problem

• Prospective study: 59 pts with inflammatory diarrhoea
  – 35 drug-induced
  Siproudhis e.a. Gastroentérol Clin Biol 1998, 22, 778

• Prospective study: 88 consecutive pts with acute unclassified colitis
  – 46 (52.3%) IBD
  – 42 (47.7%) no relapse (50% drug-induced)
  Notteghem e.a. Gastroentérol Clin Biol 1993, 11, 811
Drug-Induced Colitis: Clinical Presentation

- **Acute Diarrhoea**
  - Usually during the first days of treatment
- **Chronic Diarrhoea**
  - Can appear long time after start of drug
- **Watery or inflammatory diarrhoea**
- **Colitis**
  - Inflammatory / Ischemic
Drug-Induced Colitis: Pathogenesis of diarrhoea & colitis

- **Secretory diarrhoea**
  - Antineoplastics, gold salts, biguanides, cardiac glycosides, prostaglandins

- **Shortened transit time**
  - Cisapride, erythromycin

- **Malabsorption of fat & carbohydrates**
  - Gold salts (auranofin)

- **Osmotic diarrhoea**
  - Lactulose, antacids, sugar substitutes
Drug-Induced Colitis: Pathogenesis of diarrhoea & colitis

- **Protein-loosing enteropathy**
  - Antineoplastics, antibacterials

- **Toxic and immunologic injury**

- **Promotion of infections**
  - Antibacterials, antineoplastics, immunosuppressive agents..

- **Allergic reaction**

- **Impairment of cell proliferation**
Drug-Induced Colitis: Pathogenesis of diarrhoea & colitis

- Clinical features and morphology can be influenced by the immune status of the patients
  - Immune competent
  - Immune disturbed
    - De novo colitis (UC) – flare up of colitis (UC) following liver transplantation for primary biliary cirrhosis
    - Colitis in transplant patients
Mofetil Mycophenolate & Chronic diarrhoea

• 3/20 pts with Crohn’s disease
  Hafraoui e.a. Gastroentérol Clin Biol 2002, 26, 17

• 26 pts (mean age 41.5yrs) with cadaveric organ transplant > persistent afebrile chronic diarrhoea
  – 13 infections (Campylobacter, CMV ..)
  – 13 Crohn’s-like morphology
Mofetil Mycophenolate & Chronic diarrhoea
Mofetil Mycophenolate & Chronic diarrhoea

- MMF is converted in its active metabolite: mycophenolic acid (MPA). MPA inhibits inositol-monophosphate dehydrogenase (IMPDH) which is necessary for the guanine synthesis in B- and T-lymphocytes.

- MMF (experimentally)

- MMF (in humans) can induce
  - Graft-versus-host-disease pattern (Papadimitriou et al. Transplant Proc 2001)
  - Crohn’s-like pattern (Dalle et al. Colorectal Dis 2004)
Mofetil Mycophenolate & Chronic diarrhoea : Mechanism

• MMF is converted into mycophenolic acid (MPA) and metabolized into 2 inactive metabolites
• A small part of this metabolite enters the biliary system (enterohepatic recirculation) – deconjugated and reabsorbed by enterocytes and metabolized into acyl glucuronide (AcMPA)
• AcMPA
  – Promotes release of IL-6 & TNFa
  – Causes impaired cell division by binding to elements of the cytoskeleton such as tubulin – individual variability
    • Responsible for impaired healing – explains ulcers in diclofenac treated patients and MMF treated patients
  – Binds to membrane proteins of enterocytes
Drug-Induced Colitis: Pathogenesis

- Vascular impairment
  - Cocaine & others
  - Anticoagulants
  - Reduced splanchnic flow due to cardiovascular drugs
  - Thromboses (oestrogens – progestagens)
- Physical event
  - Entrapment of pil
Drug-Induced Colitis: Pathogenesis

- Physical event
  - Entrapment of pil
    Male pt; 17yrs; abdominal complaints for some months; lab : ferrisprive anemia > treatment : vitamins, iron
    Hospitalisation for subobstruction with vomiting
Drug-Induced Colitis: Pathogenesis

- **Physical event**
  Hospitalisation for subobstruction with vomiting
  Final diagnosis: Crohn’s disease with stricture
  Symptoms partly due to entrapment of vitamin pill
Drug-Induced Colitis: Lesions, Distribution, Macroscopy, type

- **Distribution**
  - Colon & other segments of GI tract
  - Small intestine and upper GI tract
  - Colon alone (rectum, right or left colon, total colon)

- **Macroscopy**
  - Normal
  - Solitary ulcer
  - Segmentary colitis pancolitis (fulminant)
Drug-Induced Colitis

Lesions of the large Intestine: Type (1)

• Erosions and ulcers
  – NSAIDs, KCL

• Strictures
  – KCL, Pancreatic enzyme replacement

• Microscopic colitis
  – Variety of drugs

• Pseudomembranous colitis
  – Antibiotics, neoplastic agents, PPIs
Drug-Induced Colitis

Lesions of the large Intestine: Type (2)

- Neutropenic enterocolitis
  - Cytosine arabinoside, cisplatin, vincristine, adriamycin, mercaptopurine, -FU
- Malakoplakia
  - Corticosteroids
- Sigmoid diverticular perforation
  - Corticosteroids
Drug-Induced Colitis

Lesions of the large Intestine: Type (3)

- **Ischemic colitis**
  - Digitalis, diuretics, ergotamine, cocaine, Kayexalate, glutaraldehyde, sumatriptan, $\alpha$-interferon, dopamine, methysergide, NSAIDs

- **Focal active colitis**
  - NaPO4, NSAIDs

- **Epithelial atypia mimicking dysplasia**
  - IV cyclosporin

- **Apoptosis**
  - NSAIDs, NaPO4, Laxatives, -FU
Drug-Induced Colitis: Lesions, type & distribution & evolution

- **Microscopy**
  - Normal
  - Infectious-type colitis
  - IBD-like pattern
  - Microscopic features

  **Highly Variable**
  - Oedema
  - Ischemic-type colitis
  - Microscopic colitis

- **Evolution**
  - Complete remission after elimination of offending agent
Occasionally combination of mechanisms
Same drug: different lesions or combinations
- Erythromycin
  - Transit time via motilin receptor
  - Bacterial overgrowth (antibiotic)
NSAIDs & Colitis

• Significant clinical problem
  – Elderly patients
  – 2 months – 5 yrs after onset of treatment
  – Diarrhoea, blood in the stool
  – Small intestine and colon

• Pathogenesis
  – Decreased mucosal prostaglandins
  – Enterohepatic circulation
NSAIDs & Colitis
Gibson e.a. Arch Internal Med 1992, 152, 625

- Non-specific ulceration: caecal,
  - Oxyphenbutazone, slow-release diclofenac, ibuprofen, distal ulcers naproxen
- Constipation & perforation
  - Indomethacin, ketoprofen, naproxen
- Hypersensitivity reaction (allergic colitis with eosinophils)
  - aspirin
- De novo colitis
- Focal active colitis
- Reactivation of quiescent IBD
NSAIDs & Non-specific ulceration
NSAIDs & Non-specific ulceration
NSAIDs & Colitis: Morphology

- **Architecture**
  - Distorsion

- **Epithelium**
  - Well preserved

- **Inflammation**
  - Chronic
    - Basal plasmacytosis = absent
  - Limited active inflammation
Antibacterials & Colitis

- Normal
- Oedema
- Infective-type colitis
- Pseudomembranous colitis
Drug-Induced Colitis: Patterns

• Infective-type colitis
  – Antibacterials
  – NSAIDs
  – Cyclosporin

• Ischemic-type colitis
  – Cardiovascular drugs (diuretics, digoxin, antihypertensive drugs…)
  – Oral contraceptives
  – Ergot alkaloids
  – NSAIDS
  – others
Ischemic colitis in Young patient etiology

- Drugs
- Vasculitis
- Infections
- Hypovolemic/hypoperfusion syndrome
- Coagulopathy
- Anorexic behaviour
Ischemic colitis in Young patient etiology

- Preventza OA et al. J Gastrointest Surg 2001; 5: 388-392
- N : 39 young adults (25 female) presenting with ischemic colitis
  - 13 oral contraceptives
  - 19 : unknown etiology
  - 4 vasoactive drugs
  - 4 vascular thrombi
  - 2 vasculitis
  - 4 hypovolemia
Pharmacologic agents and Colon Ischemia

- **Vasoconstriction** – arterial spasm – non-occlusive ischemia
- **Vasopressin** – Terlipressin
- **Decongestants**
  - Pseudoephedrine (segmental ischemic colitis, involving the splenic flexure)
- **Ergot alkaloids** - Methysergide maleate
- **Illicit/ Controlled drugs**
  - Cocaine
  - Amphetamines (Methamphetamine = speed, …)
- **Antibiotic-associated hemorrhagic colitis**
- Antibiotics
- Appetite suppressants : phentermine

- **Chemotherapeutic agents**
  - Vinca alkaloid and taxane classes (inhibition of microtubule assembly/ischemic colitis)
- **Anticoagulants**
  - Bleeding – intramural hematoma
  - (relation with cholesterol crystal embolism)
- **NSAIDs**
  - Non-selective NSAIDs
  - Selective cyclooxygenase inhibitors (rofecoxib, meloxicam)
- **Migraine headache medication**
  - Serotonin receptor agonists (naratriptan, sumatriptan, Alosetron hydrochloride, Tegaserod)
Pharmacologic agents and Colon Ischemia

- Hyperlipemic agents
  - Statins
- Hormonal therapies
  - Flutamide (anti-adrogenic)
  - Estrogens and oral contraceptives
- Hypotensive and hypovolemic drugs
  - Anti-hypertensive drugs (reserpine, methyldopa..)
  - Diuretics
  - Digoxin
  - Laxative osmotic agents
- Ganglion blockers – alpha-adrenergic blockers, catecholamines
- Anti-arrhythmic drugs
- Psychotropic drugs
  - Tricyclic antidepressants, Phenothiazines, barbiturates
Drug-Induced Colitis: Patterns

- Eosinophilic colitis
  - Aspirin
  - Psychotropic drugs (carbamazepine)
  - Ticlodipine

- Microscopic colitis (Lymphocytic more common)
  - Proton pump inhibitors
  - H2 receptor antagonists
  - NSAIDs
  - Ticlodipine
  - Veinotonics
  - Carbamazepine
Lymphocytic ileo – colitis : Case History

• Female patient °1944
• Clinical History
  – *Stenosis of a renal artery and the celiac trunk*
  – *Arterial hypertension*
  – *Migraine*
  – *Treatment : Cafergot, omeprazole, tiberal, plavix (clodipogrel)*
  – *Current complaints : headache and diarrhea*
• *Endoscopy : Ischemia?*  > normal aspect
Lymphocytic ileo - colitis
Conditions associated with lymphocytic colitis

- Enteric infections
- Gluten
- Autoimmune diseases
- Drugs
  - Alpha-glucosidase inhibitor (diabetes)
  - Acarbose
  - Anticoagulants
  - Ticlodipine
  - Clodipogrel
  - H2 receptor antagonists
    - Rantidine
    - Cimetidine
  - Proton pump inhibitors
  - Lansoprazole
  - Cholesterol lowering agents
    - Simvastatin
  - Antiepileptic drugs
    - Carbamazepine
  - Anti Parkinson drug
    - Levodopa benserazide
  - NSAID
    - Piroxicam beta cyclodextrin
  - Anti-serotonin agent
    - Oxetorone
  - Selective serotonin reuptake inhibitors
    - Sertraline
    - Paroxetine
  - Anti-androgenic
    - Flutamide
  - Phlebotonic drugs
    - Flavonoid extract
  - Cyclo 3 fort
  - Vinburnine
  - Ferrous sulphate (Tardyferon)
  - Antipsychotic
    - Clozapine (collagenous colitis)
Collagenous colitis
Drug-Induced Colitis: Patterns

- IBD-like pattern: Crohn’s disease without granulomas
  - Mycophenolate mofetil
- IBD-like pattern: Crohn’s disease with granulomas
  - Diclofenac
  - Clofazimine
- IBD-like pattern: Ulcerative colitis
  - Diclofenac
  - Amionogluthemide (antineoplastic agent)
Drug-Induced Colitis: Patterns

- Non-specific ulcer
- Colon
  - NSAIDs
  - Antineoplastic agents (methotrexate)
- Rectum
  - Suppositories (analgesics …)
Drug-Induced Colitis: Patterns

- Surinfections
- Opportunistic infections (CMV…)
- Neutropenic colitis
Drug-Induced colitis: Patterns

• Specific patterns
  – Crypt epithelial cell apoptosis
  – fluorouracil
  – NSAIDs (diclofenac, mefenamic acid)
  – Cyclosporin
  – Colchicine
  – Ranitidine
  – Ticlodipine
  – Mofetil
Drug-Induced colitis: Patterns

- **Specific patterns**
  - Surface epithelial cell apoptosis
    - Contact laxatives (with or without pseudomelanosis)
Drug-Induced colitis: Patterns

• Specific patterns
  – Pancreatic enzyme supplements and colonic strictures
Drug-Induced colitis: Patterns

- Specific patterns
  - Clofazimine and crystal-storing histiocytosis
  - (pseudo)melanosis coli
  - Kayexalate-sorbitol colitis
Drug-Induced colitis: Patterns
Kayexalat-sorbitol colitis
Drug-Induced colitis: Diagnosis & conclusion

• THINK

• CLINICO-PATHOLOGICAL COLLABORATION
  – Clinical history
  – Relationship in time between onset of symptoms and start of drug and resolution after withdrawal

• CHALLENGE