RADIATION INDUCED SMALL BOWEL DISEASE

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INTRODUCTION

- Radiation therapy is not regularly indicated in the treatment of small bowel disease.
- Reasons are complex and related to the relative sensitivity of the small bowel to radiation, its mobility and the difficulty in defining the treated area.
- The small bowel is very susceptible to radiotherapy as doses that cause injury are very close to therapeutic doses.
- We discuss Radiation Induced Small Bowel Disease - pathophysiology, clinical presentation, prevention strategies and treatment.
INTRODUCTION

• Small bowel: consists of duodenum, jejunum, ileum
  • Extends from pylorus of stomach to ileocecal junction
  • Joins cecum (first part of large intestine) at ileocecal junction
  • Duodenum is the first and shortest (25cm) part. Most fixed part
  • Together ileum and jejunum 6-7 meters long in cadavers, shorter in living humans due to tonic contractions. Not fixed.
• Terminal ileum usually lies in the pelvis
• Small bowel is closely related to colon and rectum
• Radiotherapy indications include GI, Urological, Gynae cancers
• Pts subsequently develop GI side effects/injuries
• NB: injuries may overlap
RT INDUCED SMALL BOWEL DISEASE

• Injury to small bowel resulting from RT, excludes colon & rectum
• Radiation enteropathy / mucositis - describes disease process
• Pelvic radiation disease – describes the phenomenon of GI injury secondary to RT
• RT induced small bowel disease - is the most accurate description
• Two types of injuries exist: acute and chronic
ACUTE FORM

- Presents during or shortly after a course of radiotherapy
- Acute injury is due to damage to mitotically active intestinal crypt cells.
- Patients notice symptoms during the second week of treatment—when tissue damage and inflammation is probably at a maximum
- Symptoms peak by 4th-5th week—when histological changes are stable/improving
- Symptoms: colicky abdominal pain, bloating, loss of appetite, nausea, diarrhea and fecal urgency
CHRONIC FORM

- Develops between 18 months and 6 years after completed course of radiotherapy
- Chronic injury affects less mitotically active vascular endothelial and connective tissue cells.
- Chronic enteropathy presents in many different ways including post-prandial pain, acute or intermittent small bowel obstruction, nausea, anorexia, weight loss, bloating, diarrhea, steatorrhea and malabsorption of nutrients
PATHOGENESIS

- Complex injury type - repetitive injury, different healing
- Changes in small bowel
  - inflammation/cell death
  - persistent cytokine activation in submucosa
  - fibrosis of connective tissue with arteriolar endarteritis
  - tissue ischemia, mucosal friability, neovascularization, progressive fibrosis
  - multiple areas of dysfunction, stricturing disease
- Clinical presentation depends on
  - degree/extent of tissue damage
  - site of injury
Radiotherapy (Acute) → Mucosal Inflammation → Cell Death → Diarrhoea, Tenesmus, Urgency → Symptomatic Rx., Anti-Inflammatory, Anti-Diarrhoeals

Mucosal Inflammation (Chronic) → Cell Death → Diarrhoea, Tenesmus, Urgency → Symptomatic Rx., Anti-Inflammatory, Anti-Diarrhoeals

Atrophy → Fibrosis
Vascular Sclerosis
Bacterial Overgrowth → Bleeding, Malnutrition, Obstruction, Fistulae, Pain
PATHOGENESIS

- Intestinal damage is related to
  - radiation regime
  - size of treatment field
  - site of treatment field
  - area of normal bowel that is exposed
  - use of concurrent chemo
  - presence of radiation implants

- Decreased blood flow to bowel wall increases the risk of radiation injury.
PATHOGENESIS

- Patients at increased risk
  - Hypertension, DM, generalised atherosclerosis
  - Previous surgery
  - Chemotherapy (Doxorubicin, Methotrexate, 5Fu, Bleomycin - all increase sensitivity to RT)
  - Irritable bowel disorder (limited data)
  - Thin elderly females (more intestines in the pelvic area)
CLINICAL PRESENTATION

• Gastrointestinal symptoms
  • commonest for oncology patients
  • impact quality of life
  • under-reported
• NB – educate patients on S/E and self reporting
• Symptoms under recognized by doctors
• Alarm features – rectal bleeding, weight loss ➔ prompt gastro referral
• Surgeons need to be aware
  • prior radiotherapy is a risk factor for strictures and adhesions
  • Patients can present with sub-acute or intermittent bowel obstruction
PREVENTION STRATEGIES

• Use of modern imaging and radiotherapy techniques to minimize radiation exposure to normal tissues
  • IMRT (multiple beams, nonuniform dose across field)
  • image guided techniques (cone beam CT prior to Rx)
  • patient position (prone/decubitus) and positioning devices (belly board)
  • Full bladder

• Consider circadian rhythm effects
  • patients treated in the morning have more GI side effects, similar oncological therapeutic response
  • logistical problem – limited capacity for evening treatments

• Use of Statins and ACE inhibitors
  • In vitro studies show anti-inflammatory/fibrotic/thrombotic potential of statins in irradiated human cells
  • ACE inhibitors play a role in blood pressure homeostasis
Sketch of a multileaf collimator.
PREVENTION STRATEGIES

• Use of pro-biotics
  • help restore indigenous gut flora – NB for normal mucosa function
  • emerging evidence they may have radio-protective effect

• Surgical techniques
  • absorbable mesh slings- in early postop period these prevent the small bowel becoming adhered into the pelvis
  • space-occupying silicone prosthesis have been used to exclude the small bowel from pelvis
  • repeat surgery post radiotherapy – to remove implants, alternatively inflatable implants may be used
QUANTEC

• $V_{15} < 120\text{cc}$ – individual bowel loops
• Normal tissue constraint guidelines in clinical practice
TREATMENT

• Acute setting
  • Supportive- eg. loperamide, octreotide
  • Dietary – lactose free diet, low fat
• Chronic setting
  • Supportive Rx- symptom based eg. antimotility, analgesics, anti-emetics
  • antibiotics for small bowel bacterial overgrowth
  • Cholestyramine for bile salt malabsorption
  • Dietician consult- patients need sufficient caloric intake, vitamin & mineral supplements
  • In some patients parenteral support is necessary
  • Hyperbaric oxygen- decreases tissue hypoxia, encourage angiogenesis
  • Endoscopic therapies- argon plasma coagulation, enteroscopy
Treatment options for chronic radiation enteritis and rectal disease

- Nutrition
  - Low Fat
  - Elemental Diet
  - Lactose Free
  - Enteral & Parenteral Nutrition
- Rectal Disease
- Dysmotility
  - Antidiarrhoeals
  - Antispasmodics
  - Somatostatin Analogues
- Obstruction/ Fisutale
  - Resection
  - Bypass
  - Strictureplasty
- Bile Acid
  - Cholestyramine
  - Antibiotics
  - Probiotics
  - Prokinetic Agents
- Bacterial Overgrowth
  - Enemas
  - Steroids
  - 5-ASA
  - Short chain fatty acids
  - Butyrate
TREATMENT

- Surgery in post radiotherapy setting
  - Controversy: resection vs bypass
  - Resection with primary anastomosis - bowel ends viability and fistula formation
  - Bypassing - leave behind diseased bowel, prone to perforation + sepsis + fistula formation + blind loop syndrome
  - Challenging surgery due to adhesions & fibrosis
  - Difficult wound healing
  - Patients with strictures & bowel obstruction need surgery
  - Patients with extensive bowel involvement are at increased risk for high output stoma
  - Surgical candidates need thorough evaluation pre-op
  - Need dedicated/interested surgeons as part of the team
CONCLUSION

• New radiotherapy techniques decrease inadvertent exposure to adjacent normal tissue
• Preventative agents including ACE inhibitors and statins are an area of new research
• Treatment in acute phase is mostly supportive
• In the chronic phase – the key is to recognize and refer patients for specialist advice, eg gastroenterologist with interest in the field
• Patients need a targeted workup for the symptoms they have
• The small subset who require surgery should be directed to surgeons with experience in dealing with this challenging situation