

When To Treat...

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Introduction

- Highlighting the difficulties of differentiation and treatment of intestinal TB (ITB) and Crohn's Disease (CD)

Mr VB – 27 year old male

- Born in India
- Moved to Australia 6 years ago
- Works in telecommunications

Presenting complaint

- Travelled to India for 2/12 over Dec 08 / Jan 09
 - Mumbai / Punjab (rural and city)
- No vaccinations or malaria prophylaxis
- Presented with 8/52 Hx
 - Lower abdominal pain, fever, rigors 6kg weight loss. Without diarrhoea or constipation
 - Brief improvement on norfloxacin / metronidazole
 - Referred to TNH ED with T 39.2

Any thoughts...



CT abdo /pelvis (05/03)

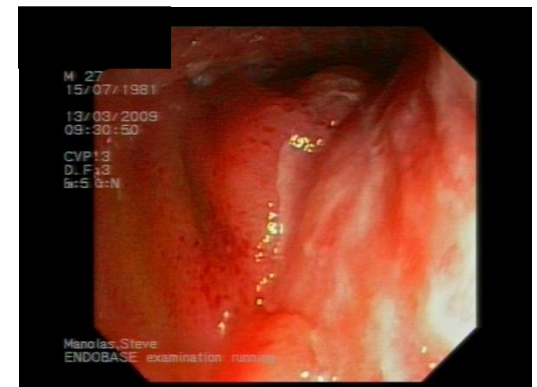
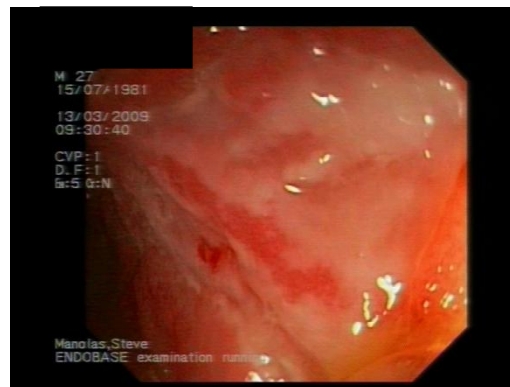
- Prominent circumferential thickening of 20cm of terminal ileum
- 3.5cm phlegmonous mass abutting the terminal ileum, 15.0cm from ileocaecal valve
- Centimetre mesenteric lymph nodes

Darn...

- Although specimen arrived fresh and personally delivered to the lab it was placed in formalin – cultures not available
- For repeat colonoscopy 7/7 later

Colonoscopy 13/03/09

- Macroscopic:
 - Mucosa appeared diffusely interspersed with purulent exudate at the terminal ileum
- Microscopic:
 - AFB / culture pending



OP review – 16/03/09

- 1st colonoscopy: TB PCR negative
- What would you do?...

Treatment

- For presumptive tuberculous enteritis
- HRZE with pyridoxine
- Took 3/12 to feel clinically better and to gain weight
- CT (10/06/09) :
 - Persistent terminal ileitis over 20cm
 - A reduction in size of the inflammatory phlegmon which abuts the terminal ileum (2x2x1.9)

Progress

- Returned to India Aug – Nov 09
- Completed 9/12 treatment on 16/12/09
- Wt gain 12 kg over period of treatment

Admitted 30/11 – 03/12/09

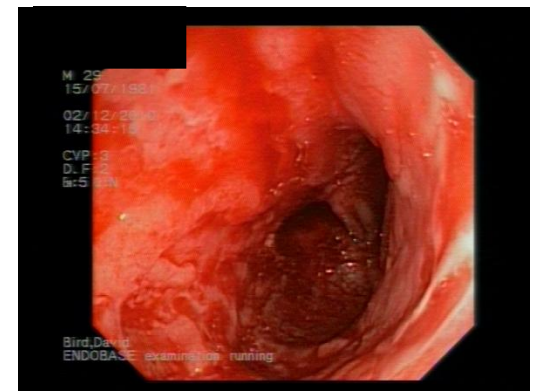
- 3/52 Hx
 - intermittent, generalised, abdominal pain (after eating, bowels 3x day)
 - No LOW, nausea, vomiting, fevers / chills / rigors
- Same as prior symptoms
- WCC 10.1, CRP 87

CT 30/11/10

- Small bowel ileal wall thickening through to the caecum
- Large bowel wall thickening involving the distal sigmoid colon and proximal rectum (retracted on amendment – appearance most likely due to faecal loading)

Colonoscopy 03/12/10

- Macroscopic:
 - Ulcerated and inflamed areas in appendix orifice, terminal ileum and upper rectum
- Microscopic:
 - Terminal ileum - non-specific ulceration in mucosa, with underlying inflamed granulation tissue. No granulomas
 - Rectum - severe chronic active proctitis. No granulomas
 - No AFB; TB PCR negative



Gastro OP 09/12/10

- ASCA positive
 - suggestive but not diagnostic of Crohn's
- Presumed Crohn's
- Started 50mg prednisolone
- Commenced azathioprine 17/02 after returning from India

Ms OP – 30 year old female

- Referral from Gastroenterology Jan 11
- Immigrated from Turkey 2004 (suburban)
- Back to Turkey once for 3/12
- Past history
 - Abnormal screening CXR for Immigration in 2004
 - No prior treatment
 - Perianal fistula
 - Requiring 7 admissions over the last 6 years for surgical intervention

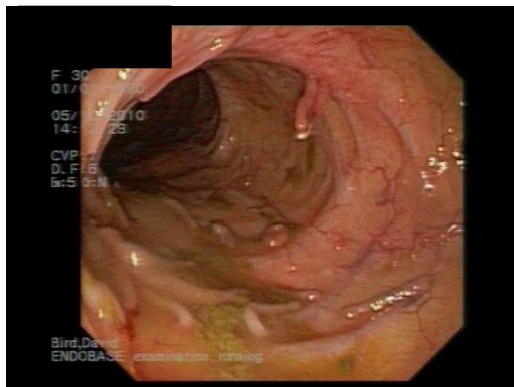
Initial surgical intervention

- September 2009 – LMO referral
 - Direct admit from general surgery clinic for perivaginal and perianal abscess drainage
- April 2010 – EUA pararectal sinus / curettage
 - Histopathology: Inflammatory tract with non-necrotising epithelioid granulomas – possible Crohn's
- May 2010 – MRI
 - Trans-sphincteric fistula extending into the left side of the perineum and the left natal cleft
 - Frank fluid throughout the fistulous tract

Colonoscopy 05/10/10

- Macroscopic
 - Multiple “worm-like” polyps, terminal ileitis
 - No evidence of colitis or proctitis
- Microscopic
 - Terminal ileum: active chronic ileitis with prominent granulomatous inflammation.
 - Caecal polyp / ascending colon: benign polypoid mucosa. No active inflammation. No granulomas
- TB PCR negative

Macroscopic



CT enteroclysis 03/12/10

- No evidence for small bowel thickening or obstruction or dilatation

ID OP review 17/01/11

- Referred for treatment of tuberculosis
- CXR
 - No parenchymal, hilar or pleural disease
 - RLL (apical segment) calcific opacity - likely benign healed granuloma
 - Small amount of scarring
- What to do?

Impression

- Ileal disease caused by Crohn's disease given concurrent perianal symptoms
- Latent TB
- Commenced on INH and mesalazine 2g bd

Mr SC – 48 year old male

- Referred to ID OP 10/01/11
- Turkish migrant 1984, returned 1990, 1999
- No allergies
- Smoker 20/d for 25 years

HOPC

- Unwell 12/12
 - Referred to Rheum for marked costochondral chest and thoracic back pain – coughing and movement
 - Dx Inflammatory arthritis
 - Norspan patches + methotrexate
- Subsequently
 - LOW > 10kg 9/12
 - 2 – 3/12 abdo pain esp after food

Further investigation

- CT (26/11/10):
 - 20cm thickened, walled distal ileum
 - DDx Crohn's disease and infective ileitis
- Colonoscopy (21/12/10):
 - Ulcerated, oedematous ileo-caecal valve mucosa that would not admit scope – ileitis
 - TB PCR negative
 - AFB / culture pending
- Gastroscopy:
 - H. pylori positive
- Referred to Gastro ? IBD / ITB

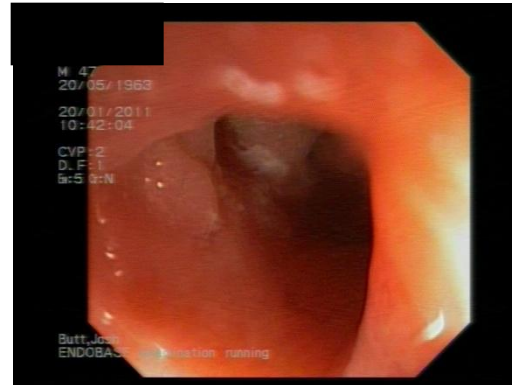
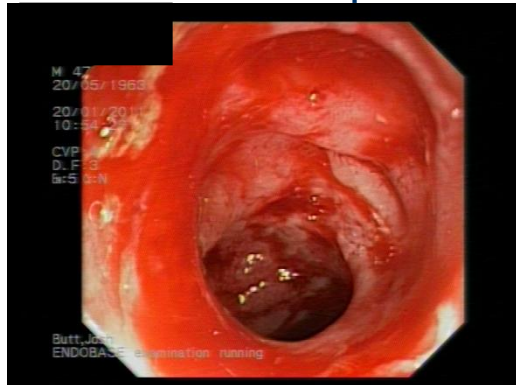


Elective Admission 17/01 – 29/01/11

- Investigation of terminal ileitis
- QFG
 - positive TB antigens 6.97 IU/ml (RR <0.35), mitogen 11.66 IU/ml (RR >=0.5)
- HIV / HBV negative
- Anti S. Cerevisiae IgG / IgA negative
- MRI spine 17/01/11
 - No evidence of infective process affecting the spine
- CT chest 27/01/11
 - No evidence of previous or current tuberculous infection

Endoscopy

- Colonoscopy
 - Macroscopic:
 - Strictured terminal ileum with evidence of mucosal ulceration
 - Microscopic:
 - Non-specific ulceration and severe inflammation. No granulomas



- CT enterocolitis
 - 20 cm ileitis involving distal/terminal ileum

Management

- Still unwell in hospital thus commenced on empiric HRZE
- Also commenced on 75mg prednisolone by Gastroenterology for ileitis
- ID OP review
 - TB culture negative
 - Improvement
 - Putting on weight
 - Some ongoing epigastric pain after meals

Distinguishing intestinal TB from Crohn's Disease



Difficulty in distinguishing

- Overlapping clinical, radiological, endoscopic and histological characteristics
- Chronic granulomatous diseases which affect the GI tract in a similar manner
- Both have an insidious onset that can go undiagnosed for years with divergent outcomes
- Low TB culture sensitivities do not aid in the diagnosis

Clinical features of both diseases

Symptoms / manifestations	Comment
Constitutional	fever, anorexia, LOW
Mucosal ulceration	diarrhoea, haematochezia, malabsorption, protein losing enteropathy
Transmural involvement	abdo pain, distension, vomiting due to luminal obstruction, palpable lump, intestinal perforation and perianal / intestinal fistulisation
Site of involvement	Predilection for ileo-caecal region, entire GIT
Acute presentation	Perforation, obstruction, abscess
Extraintestinal	Lung, LN, reactive polyarteritis, skin (erythema nodosum), eye (uveitis), liver, blood dyscrasias (anaemia, leukocytosis, thrombocytosis, inc CRP / ESR

Epstein D et al, 2007. Aliment Pharmacol Ther 25: 1373-1388;

Pulimood et al, 2011. World J Gastroenterology: 17(4); 433-443

Differentiation by Serology

- Anti-Saccharomyces cerevisiae Ab (ASCA)
 - ELISA for Ab resulting from macromolecular transport of food Ag fluctuating with intestinal permeability
 - Chronic inflammation increases rate of ASCA +
 - 1/14 (7%) in ITB wrt 49% in CD – recommend test for differentiation
 - Other studies have shown no significant differentiation value of this assay

AFB and Culture

- Thought to help identify ITB, however...
- Studies are case series
 - Presence of AFB has low sensitivity (25 – 36% intestinal biopsies) with specificity of 100%; PCR sensitivity was 65.4 % and the sensitivity of caseification necrosis was 34.6%
 - Sensitivity of tissue culture 21 – 54.5%, specificity 100%
 - 19 pts tissue culture sensitivity and AFB positivity were 21% and 84%, respectively, while the sensitivity of caseification necrosis was 84%
- Other studies indicate that MTB cultured < 20% of biopsies
- Need evaluation for use with intestinal TB

Role of endoscopy

- Advantageous as it allows visualisation and biopsy of the mucosa
- Diagnostic yield increases with a number of biopsies taken (recommended > 8)
- Whilst “skip lesions” and pancolitis are usually indicative of Crohn’s
- Up to 44% of patients with ITB can have lesions in > 2 sections and 5% have a pancolitis

Comparative endoscopic findings

- First systematic prospective analysis in 88 pts

Four features of CD	Four features of ITB
Anorectal lesions	Transverse ulcers
Longitudinal ulcers	Pseudopolyps
Aphthous ulcers	Involvement of < 4 segments
Cobblestone appearance	Patulous ileo-caecal valve

- +1 for CD features, -1 for ITB features
- CD if $N > 0$, ITB $N < 0$
- Correct 87.5%, incorrect 8%, indeterm 4.5%
- PPV for CD 94.9% and 88.9% for ITB

More recent prospective study

- Univariate, bivariate, multivariate analysis of 106 pts

Table 3. Types of involvement in patients with Crohn's disease and intestinal tuberculosis

Variable	CD (n=53)	Intestinal tuberculosis (n=53)	OR (95% CI)	P value
Skip lesions	35 (66%)	9 (16.9%)	0.10 (0.04–0.26)	<0.001
Erythema	14 (26.4%)	5 (9.4%)	0.29 (0.09–0.87)	0.02
Friability	14 (26.4%)	0	—	<0.001
Aphthous ulcers	29 (54.7%)	7 (13.2%)	0.12 (0.04–0.32)	<0.001
Linear ulcers	16 (30.1%)	4 (7.5%)	0.18 (0.05–0.61)	0.005
Deep ulcers	18 (33.9%)	27 (50.9%)	2.01 (0.91–4.41)	0.07
Superficial ulcers	27 (50.9%)	9 (16.9%)	0.19 (0.08–0.48)	<0.001
Nodularity	13 (24.5%)	26 (49%)	2.96 (1.29–6.76)	0.01
Cobblestoning	9 (16.9%)	0	—	<0.001

CD, Crohn's disease; CI, confidence interval; OR, odds ratio.

Pathology findings

Crohn's Disease	Intestinal Tuberculosis
Granulomas -More likely single lesions -Pericryptal granulomatous inflammation	Granulomas -Confluent, large granulomas >400mm -Submucosal -> 4 in a given Bx site -Caseation
Architectural distortion distant from granulomatous inflammation	Bands of epithelioid histiocytes lining ulcers
	Disproportional submucosal inflammation

- Underlies importance of taking multiple biopsies

MTB PCR in biopsies

- Retrospective studies
- IS6100 primer for MTB
- ITB
 - PCR positive results in 22% (13/60), 30% (6/20), 45% (18/40), 64% (25/39) and 75% (27/36)
 - Sensitivity 30 – 75%, specificity 95 – 100%
- Three included CD biopsies
 - PCR positive in 0% (0/30), 0% (0/26) and 5% (1/20)
- PCR may have utility in histologically non-diagnostic cases

Radiology in differentiation

Crohn's Disease	Intestinal Tuberculosis
Symmetrical bowel wall thickening	Asymmetrical caecal wall thickening
Long, eccentric strictures w/o significant prestenotic dilatation	Short, concentric, smooth strictures with significant prestenotic dilatation
Fibrofatty proliferation of mesentery	Inflammatory mass centred around the caecum and enveloping the TI
Regional mesenteric lymph nodes (3 – 8mm)	Small, homogenous pre-caecal lymph nodes
Hypervascular mesentery (comb sign)	No vascular engorgement
High density ascites	Abscesses
Extraintestinal involvement: fatty liver, gallstones, PSC, sacro-ileitis	

Role of laparoscopy

- No systemic laparoscopic study comparing ITB and CD has been conducted

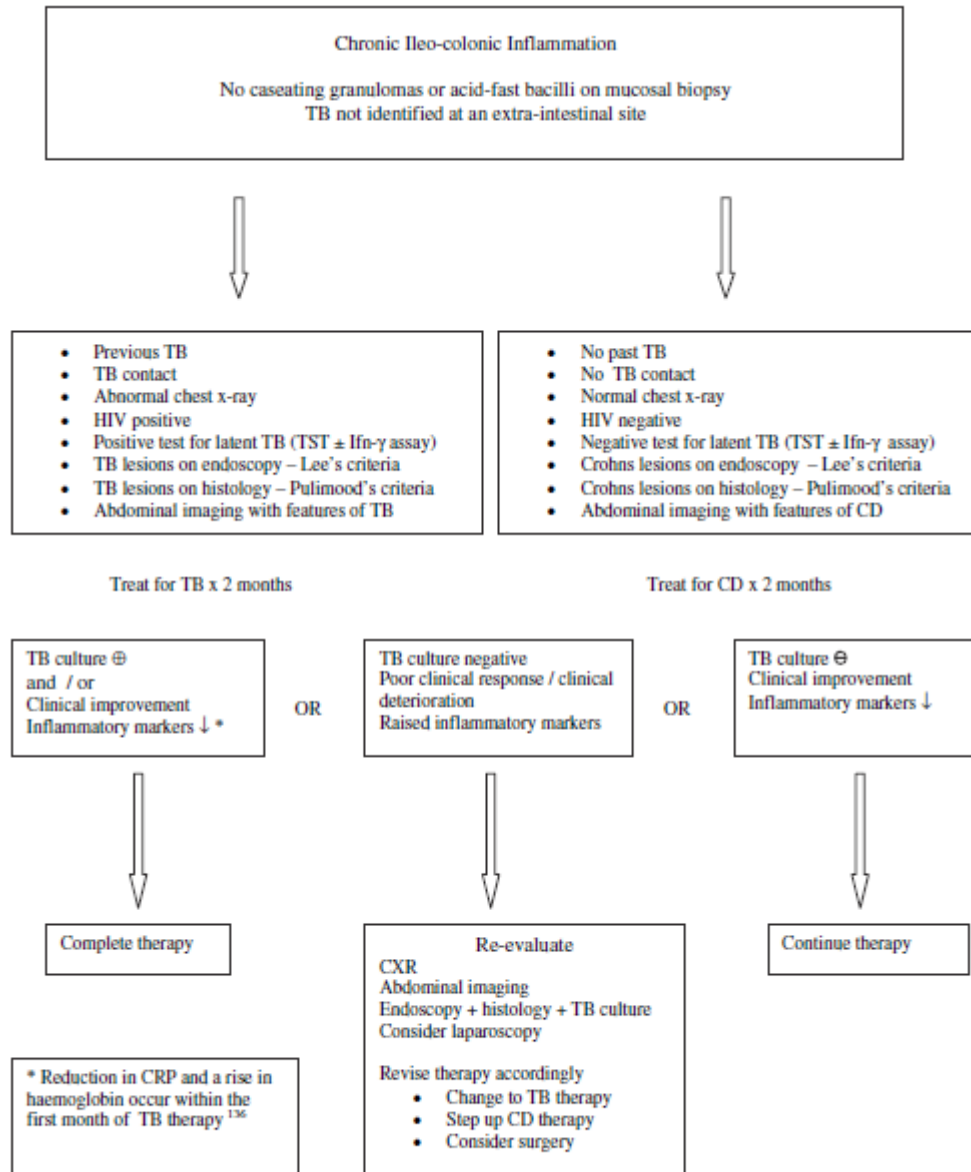


Figure 11. Treatment algorithm: CD vs. ITB.

Conclusions

- Differentiation between intestinal tuberculosis and Crohn's disease is complex
- Negative test results do not necessarily exclude infection
- Requires evaluation on a case-by-case basis regarding the need for treatment of either condition in the setting of the other
- Further investigation is definitely warranted