Ileo-Colonic Tuberculosis: A Diagnostic Challenge

Falk Foundation, Istanbul, 2007

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South Africa
Introduction

• Gastroenterology in the developing world
  – High burden of enteric infections
  – Epidemic tuberculosis
  – Increasing IBD
Introduction

- Diagnosis of intestinal tuberculosis (ITB)
  - ITB vs IBD
    - Clinical evaluation
    - Endoscopy
    - Histology
    - Radiology
  - New Tools in TB diagnosis
  - IBD Genetics and Serology
  - Management Algorithm
Crohns – Tuberculosis Interface

• Pathogenic Similarities
  – TH-1 cytokine profile + granuloma formation
  – Impaired innate immunity
  – Host-bacterial interaction

• Phenotypic Similarities
  – Protean clinical manifestations
  – Differentiating CD from ITB

• Treatment of IBD
  – Immunosuppression and biological therapy in IBD patients from communities with high rates for TB
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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South Africa: TB Incidence 2004

- **≥ 900/100 000 population**
- **700 – 899/100 000 population**
- **500 – 699/100 000 population**
- **300 – 499/100 000 population**
- **≤ 299/100 000 population**

The map highlights the distribution of TB incidence across provinces in South Africa for the year 2004.
Gastro-intestinal Tuberculosis in SA

- Extra-pulmonary TB increase by 187% from 2000 to 2003
  
  - 50 patients with cavitating PTB
    - 46% abnormalities in the ileum and/or colon

- Intestinal TB in the presence of severe PTB goes undetected
TB Mortality

- “Diarrhoea attacking a person affected with phthisis is a mortal symptom”
  - Hippocrates

- Intestinal TB: 7.3% in-hospital mortality

- TB 5th most common cause of death W Cape, South Africa
Groote Schuur Hospital: 1980-2007

**IBD Epidemiology Cape Town**

- Crohns Disease – 2.6 / 100,000
- Ulcerative Colitis – 5 / 100,000

Wright J et al. SAMJ 1986
Clinical Dilemma: Crohns or ITB?

- Chronic ileo-colonic inflammation
- High TB prevalence environment
- Normal chest radiograph

- Endoscopy
- Histology
- Abdominal imaging

“Compatible with Crohn’s disease but TB cannot be excluded”
Clinical Features of Intestinal TB

- Young patients
- Insidious onset
- Constitutional symptoms
- Symptoms of ileo-colitis
- Abdominal mass
- Obstruction or perforation
- Malabsorption + protein losing enteropathy
Clinical Features of Intestinal TB

- Smoking

- Extra-intestinal manifestations
  - Extra-intestinal TB
  - Immune mediated phenomena
  - Thrombosis*

* Robson SC et al Brit J Haematol 1996
Peri-anal Disease in Tuberculosis

- Ulcerative lesions, verrucous lesions, sinuses and fistulas
- 17% of peri-anal fistulas tuberculous in origin
- 8% of colonic TB patients presented with ano-rectal disease
Chest Radiograph in Intestinal TB

- Normal chest radiograph in > 50% of cases of intestinal TB

Patel N et al. J Gastroenterol Hepatol 2004
Tuberculin skin testing (TST) in patients with ileo-colonic inflammation

**Positive**
- Cross reaction - BCG
- Cross reaction - other mycobact.
- Latent infection

**Negative**
- Anergy with tuberculosis
- HIV
- Anergy in Crohn’s disease*

TST – limitations in high TB prevalence environments

* Verrier Jones J *et al* Gut 1969
Ileo-colonic Tuberculosis

• Extent
  – Ileo-caecum
  – Ascending colon
  – Colon, ano-rectum, small intestine, upper GI
  – Diffuse or discrete
  – Skip-lesions

• Morphology
  – Ulcerating, hypertrophic, strictures

• Complications
  – Fistulas, perforations, abscess formation
Endoscopic Features of Tuberculosis

• First endoscopic description of colonic TB
  – Ulcers with transverse orientation
  – Ileo-caecal destruction
  – Inflammatory polyps

Aoki G et al Endoscopy 1975
Differentiating CD from ITB

Prospective systematic colonoscopy study

CD n=44 vs ITB n=44

CD +1
1. Longitudinal ulcers
2. Cobblestoning
3. Apthous ulcers
4. Anorectal lesions

ITB -1
1. Transverse ulcers
2. Pseudopolyps
3. Patulous ICV
4. < 4 segments

PPV CD 94.9%

PPV ITB 88.9%

Lee et al. Endoscopy 2006;38:592-597
### ITB: Ultrasound, CT, MRI

<table>
<thead>
<tr>
<th>Wall thickening - asymmetrical</th>
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<tbody>
<tr>
<td>Abdominal nodes</td>
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<tr>
<td>- 12mm – 50mm</td>
</tr>
<tr>
<td>- Widespread</td>
</tr>
<tr>
<td>- Central necrosis</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Mesentry</td>
</tr>
<tr>
<td>- nodules/abscesses</td>
</tr>
<tr>
<td>Liver/spleen</td>
</tr>
<tr>
<td>micro-abscesses</td>
</tr>
</tbody>
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| In Crohn’s Disease....         |
| PSC, NAFLD, Gallstones        |
| Sacro-ileitis                 |
| Small regional nodes          |
| Fat wrapping                  |
| Wall thickening - symmetrical |

- Fat wrapping
- Wall thickening - symmetrical
56 year-old male
Pulmonary TB
Caecal Mass
Histology non-specific

Caecum after
9 weeks TB Therapy
Longitudinal CD Ulcer

Circumferential ITB Ulcer
28 Year-old Female
Entero-cutaneous Fistula
Following Appendicectomy
Caecum

Ziel Nielsen Stain
Barium Enema

- Caecal destruction
- Diseased TI
- Fistula to bladder
Barium Enema

Multiple Colon Strictures
18 Year-old Male
Ulcerating Skin Lesions
Bloody diarrhoea
...also previous TB in 2005

Crohns

or

TB?
Endoscopic Mucosal Biopsy in Colon TB

- Poor diagnostic yield
- Caseating granulomas – 33%
- Acid fast bacilli – 30%
- Positive TB culture - < 20%

- A number of OTHER histological features can be used to diagnose intestinal TB
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<tbody>
<tr>
<td></td>
<td>ITB (n=20)</td>
<td>CD (n=20)</td>
<td>ITB (n=33)</td>
</tr>
<tr>
<td>Caseous necrosis</td>
<td>40%</td>
<td>0%</td>
<td>36%</td>
</tr>
<tr>
<td>Confluent granulomas</td>
<td>60%</td>
<td>0%</td>
<td>42%</td>
</tr>
<tr>
<td>≥5 granulomas/biopsy site</td>
<td>40%</td>
<td>0%</td>
<td>45%</td>
</tr>
<tr>
<td>≥10 granulomas/biopsy site</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Large granulomas</td>
<td>Diameter &gt;200 μm</td>
<td>Diameter &gt; 400 μm</td>
<td>Area &gt;0.05 mm²</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>5%</td>
<td>51%</td>
</tr>
<tr>
<td>Submucosal granulomas</td>
<td>45%</td>
<td>5%</td>
<td>39%</td>
</tr>
<tr>
<td>Ulcers lined by bands of epithelioid histiocytes</td>
<td>45%</td>
<td>5%</td>
<td>61%</td>
</tr>
<tr>
<td>Disproportionate submucosal inflammation</td>
<td>65%</td>
<td>5%</td>
<td>-</td>
</tr>
</tbody>
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Epstein D et al Aliment Pharmacol Thera 2007 in press
Histological features, other than acid-fast bacilli and caseating granulomas, are useful in differentiating intestinal tuberculosis from Crohn’s disease.

TB PCR on Endoscopic Mucosal Biopsy

- Formalin-fixed paraffin embedded samples
- Confirmed intestinal TB
- PCR $\geq 22\% - 75\%$

Amarapurkar et al. J Assoc Physicians India 2004
Gan et al. Am J Gastroenterol 2002
Anand et al. Am J Gastroenterol 1994
New Tools for TB Diagnosis

- Interferon-gamma release assays
  - Quanti-FERON-TB Gold ®
  - T-Spot TB ®

- Skin patch test

- Antibody tests

- Antigen recognition tests
  - Lipoarabinomannan (LAM)

- Rapid culture systems
Anti-*Saccharomyces cerevisiae* Antibody Does Not Differentiate Between Crohn’s Disease and Intestinal Tuberculosis

Govind K. Makharia • Vikas Sachdev • Rajiva Gupta • Suman Lal • R. M. Pandey

Fig. 1  Bar diagram showing the positivity of ASCA and ANCA in healthy controls and patients with Crohn’s disease and intestinal tuberculosis

DOI 10.1007/s10620-006-9527-0

ORIGINAL PAPER
NOD2 Mutations in Intestinal TB and Crohn's Disease

- NOD2/CARD15 gene polymorphisms not associated with CD in SA
  
  Zaahl MG et al
  Molec Cell Probes 2005

- NOD2 not associated with pulmonary TB
  
  Stockton JC et al
  FEMS Immunol Med Microbiol 2004

- NOD2 not associated with intestinal TB
  
  Watermeyer G Unpublished

- NOD2 mutations not found in ITB or CD in South Africa
Why the difficulty in diagnosing colonic TB?

- Protean clinical manifestations
- Normal chest radiograph
- Extra-pulmonary TB often pauci-bacillary
- Sub-mucosal disease
- Limited colonic inflammatory response
- Limitation of TB diagnostics
Conclusion

• Diagnosis of ITB based on combination of:
  – Clinical evaluation
  – Imaging
  – Systematic endoscopy
  – Systematic histological evaluation
  – Objective responses to treatment
Is this Crohns or Intestinal TB?

“ It is impossible to diagnose abdominal tuberculosis with any degree of certainty, since the disease mimics many other abdominal conditions and histological confirmation may be equivocal”

Walsh J
1909 Trans Natl Assoc Prev Tuberc 5:217-222
Intestinal TB remains a diagnostic challenge
Chronic Ileo-colonic Inflammation

Caseating granulomas or acid-fast bacilli absent
No TB at an extra-intestinal site

- Previous TB / TB contact
- Abnormal chest x-ray
- HIV positive
- Positive test for latent TB
- TB lesions on endoscopy
- TB lesions on histology
- Abdominal imaging with features of TB

- No past TB / No TB contact
- Normal chest x-ray
- HIV negative
- Negative test for latent TB
- Crohns lesions on endoscopy
- Crohns lesions on histology
- Abdominal imaging with features of CD

Treat for TB x 8 wks

TB culture +
and / or
Clinical improvement
Inflammatory markers ↓

Complete therapy

Treat for CD x 8 wks

TB culture Θ
and
Clinical improvement
Inflammatory markers ↓

Continue therapy
Chronic Ileo-colonic Inflammation

Caseating granulomas or acid-fast bacilli absent
No TB at an extra-intestinal site

Treat for TB x 8 weeks
Treat for CD x 8 weeks

TB culture negative
Poor clinical response
Clinical deterioration
↑ inflammatory markers

Re-evaluate
• Chest radiograph
• Abdominal imaging
• Endoscopy + histology + culture
• Consider laparoscopy

Revise therapy accordingly
• Change to TB therapy
• Step up CD therapy
• Consider surgery

Epstein D et al
Aliment Pharmacol Thera 2007 in press
Tuberculosis and HIV

• Risk of developing TB = 36% per annum

• TB dissemination
  – ascites, nodes, hepato-splenic disease

• Smear negative

• Current Challenges
  – Diagnosis of TB in HIV
  – Immune reconstitution syndrome on ARVs
  – MDR and XDR TB
Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zellar, Jason Andrews, Gerald Friedland

Summary

Background The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

Methods We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

Results From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis; 67% (28 of 42) had a recent hospital admission. All 44 patients with XDR tuberculosis who were tested for HIV were co-infected. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 6–37) among the 42 patients with confirmed dates of death. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74–95) patients with XDR tuberculosis had similar strains.

Conclusions MDR tuberculosis is more prevalent than previously realised in this setting. XDR tuberculosis has been transmitted to HIV co-infected patients and is associated with high mortality. These observations warrant urgent intervention and threaten the success of treatment programmes for tuberculosis and HIV.
**XDR Tuberculosis — Implications for Global Public Health**

Mario C. Raviglione, M.D., and Ian M. Smith, M.B., Ch.B.

In early 2005, physicians at a rural hospital in KwaZulu-Natal, a province of South Africa, were concerned by a high rate of rapid death among patients infected with the human immunodeficiency virus (HIV) who also had tuberculosis. A study revealed the presence not only of multidrug-resistant (MDR) tuberculosis but also what came to be called extensively drug-resistant (XDR) tuberculosis. XDR tuberculosis is caused by a strain of *Mycobacterium tuberculosis* resistant to isoniazid and rifampin (which defines MDR tuberculosis) in addition to any fluoroquinolone and at least one of the three following injectable drugs: capreomycin, kanamycin, and amikacin. Of 53 patients with XDR tuberculosis, 55% claimed they had never been treated (implying that they had primary infection with an XDR strain of *M. tuberculosis*); two-thirds had recently been hospitalized; and all 44 who underwent testing were HIV-positive. All but one of the patients died of tuberculosis, with a median survival period of only 16 days from the time the first sputum specimen was collected. Genotyping analysis revealed that 85% of the 46 isolates tested belonged to the KwaZulu-Natal (KZN) family of tuberculosis strains, which had been recognized in the province for a decade.¹

These alarming findings attracted much attention at the International AIDS Society conference in Toronto in August 2006. But this was not the first time that XDR tuberculosis had been identified. A March 2006 report by the Centers for Disease Control and Prevention and the World Health Organization (WHO) documented the presence of XDR tuberculosis in at least 17 countries. Though not representative, the data showed that 10% of MDR tuberculosis isolates were in fact XDR tuberculosis. More representative data from the United States, the Republic of Korea, and Latvia showed that 4%, 15%, and 19%, respectively, of MDR tuberculosis isolates were XDR strains.²

In the fall of 2006, international experts agreed on the laboratory case definition of XDR tuberculosis; a framework for action on the clinical management of suspected XDR tuberculosis;
Latent Tuberculosis in Cape Town

- 77 asymptomatic volunteers
- No active TB
- HIV negative

- 66% TST ⊕ cut-off 5mm
- 64% TST ⊕ cut-off 10mm
- 58% TST ⊕ cut-off 15mm
New Tools for TB Diagnosis

• Interferon-gamma release assays
  – In-vitro IFN-gamma release
  – MTB specific antigens (ESAT 6, CFP-10)
  – Quanti-FERON-TB Gold ®
  – T-Spot TB ®

• Antigen Recognition
  – Antigen capture ELISA
  – Lipoarabinomannan (LAM)
  – Urine test promising
Barium Contrast Studies in Intestinal TB

• Fleischner sign
  – a thickened patulous ICV combined with a narrowed terminal ileum

• Stierlin’s sign
  – a rapid emptying of contrast through a gaping ileo-cecal valve into a shrunken or “amputated” caecum

• Retraction of the caecum out of the pelvis