GI pathology in immunosuppressed patients

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Bristol
Which “immunosuppressed patients”?

- HIV/AIDS patients
- Therapeutic immunosuppression
  - Oncology treatment
  - Transplantation:
    - Solid organ
    - Bone marrow
- [Not primary immunodeficiencies]
1. Antibody deficiencies
   - X-linked Agammaglobulinemia (XLA)
   - Common variable immunodeficiency (CVID)
   - Hyper IgM syndrome
   - Transient hypogammaglobulinemia of infancy (selected cases)
   - IgG subclass deficiency ± Selected IgA deficiency (selected cases)
   - Impaired specific antibody production with normal plasma immunoglobulin levels

2. Combined immunodeficiencies
   - All types of severe combined immunodeficiencies (SCID)

3. Other well-defined immunodeficiency syndromes
   - Wiskott–Aldrich syndrome
   - DNA repair defects; Ataxia-telangiectasia, Nijmegen breakage syndrome
   - Di George Anomaly
   - Primary CD4 deficiency
   - ICF syndrome

4. Diseases of immune dysregulation
   - X-linked lymphoproliferative syndrome (XLP)
Talk plan

• Diseases common to several immunosuppressed groups
  – Infection
  – Neoplasia
  – Drugs

• Diseases specific to certain immunosuppressed groups
Infection

• Bacteria
  – Infectious colitides
Objective To determine the spectrum and outcome of colorectal diseases occurring in adult liver allograft recipients.

Design A retrospective cohort analysis of clinical, microbiological and histopathological data regarding colorectal disease.

Patients Forty three out of 302 adult primary liver allograft recipients were transplanted and followed up (at median 42 months) at a tertiary referral centre/teaching hospital.

Results Out of 302 patients, 43 (14%) were investigated (by endoscopy and/or laparotomy) for symptoms of colorectal disease after orthotopic liver transplantation. The symptoms were: diarrhoea (n = 31); per-rectal bleeding (n = 5); and symptoms relating to pre-transplant activity of pre-transplant ulcerative colitis was unchanged or increased after orthotopic liver transplantation. Two further patients developed new-onset ulcerative colitis after orthotopic liver transplantation.

Conclusions Ulcerative colitis, C. difficile, cytomegalovirus infection and medications are the commonest colorectal causes of morbidity after orthotopic liver transplantation. Adult liver allograft recipients are, however, unlikely to show certain large bowel diseases encountered in other immunosuppressed groups. Amongst non-ulcerative colitis patients, those presenting with diarrhoea show a good outcome with appropriate management, whereas those with per-rectal bleeding have a more guarded prognosis. Eur J Gastroenterol Hepatol 14:231–236 © 2002 Lippincott Williams & Wilkins
<table>
<thead>
<tr>
<th>Cause of diarrhoea</th>
<th>Number of patients (%)</th>
<th>total $n = 31$</th>
<th>Median (range) onset after orthotopic liver transplantation, in months</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
<td>10 (32%)</td>
<td></td>
<td>1 (1–11)</td>
</tr>
<tr>
<td>Medication*</td>
<td>6 (20%)</td>
<td></td>
<td>6 (&lt;1–38)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>3 (10%)</td>
<td></td>
<td>1 (1–6)</td>
</tr>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>1 (3%)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>1 (3%)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td><em>De novo</em> ulcerative colitis</td>
<td>2 (6%)</td>
<td></td>
<td>9.5 (5–14)</td>
</tr>
<tr>
<td>Uncertain diagnoses</td>
<td>8 (26%)</td>
<td></td>
<td>2.5 (1–11)</td>
</tr>
</tbody>
</table>

*Four antibiotics, one iron replacement therapy, one mycophenolate mofetil.*
ZN+, thus: Mycobacteria
PAS +ve
2. 23M. MSM. 10 cms long stricture in rectum and anus, clinically & radiologically malignant. The surgeon was sharpening his scalpel in the MDTM helped by the usual confidently expressed diagnosis by the radiologist. A total of 20 separate biopsies, in two settings, showed fibrinopurulent exudate, granulation tissue and inflamed fibromuscular connective tissue with no mucosa, no granulomas and no tumour.

Coronal and sagittal MRI images of the pelvis
2. This is before and after treatment, with eight weeks separating them. Note the massively thickened rectum before treatment (left) and the normal calibre rectum after treatment (right). What’s the diagnosis and what was the treatment?
32 year old male presented bloody diarrhoea

? IBD
Same patient 8 weeks later
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Time between biopsy &amp; LGV diagnosis (months)</th>
<th>Mucosal ulcers</th>
<th>Cryptitis</th>
<th>Crypt abscess</th>
<th>Crypt distortion</th>
<th>Granuloma</th>
<th>Plasma cell infiltrate</th>
<th>Giant cells present</th>
<th>Initial histological diagnoses/suggestions</th>
<th>Mode of initial LGV diagnosis</th>
<th>LGV DNA results from biopsy (date of biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
<td>Uncertain aetiology Possible IBD</td>
<td>Rectal swab</td>
<td>LGV Positive (September 2004) Negative (December 2002 &amp; June 2003)</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?IBD ?infective</td>
<td>Rectal swab</td>
<td>LGV Positive (May 03)</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?Due to prolapse ?IBD</td>
<td>Rectal swab</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uncertain aetiology</td>
<td>Clinical &amp; Serology WIF titre = 1:4000 Negative (September 2004) Inhibitory (December 2003)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?Infective ?Crohn's</td>
<td>Rectal swab</td>
<td>Positive</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exclude LGV</td>
<td>Clinical Rectal swab CT detected, not sent for LGV testing</td>
<td>LGV Positive</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td></td>
<td></td>
<td>minimal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Favours infective aetiology</td>
<td>Rectal swab</td>
<td>Negative (September 2004 and January 2005)</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
<td>?IBD. Exclude CT/LGV</td>
<td>LGV Positive (March 2005) Negative (June 2005)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diagnosed Crohn's 1999, thought to be recurrence</td>
<td>Rectal swab</td>
<td>Negative (November 2005)</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?Early ulcerative colitis</td>
<td>Rectal swab</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Viruses
Herpes simplex virus
71 female with heartburn. Previous hx of resected CRC.

OGD: Severe oesophagitis
CMV oesophagitis
(Patient was receiving 5FU-based chemoRx)
CMV

• HIV/AIDS, transplant and chemoRx patients:
  – Inflammation and viral inclusions
  – Crypt apoptosis alone
Sigmoid colonic tumour
Biopsies of sigmoid colonic tumour
CMV

• HIV/AIDS, transplant and chemoRx patients:
  – Inflammation and viral inclusions
  – Crypt apoptosis alone
  – Present as a focal lesion
Adenovirus
Viruses

• EBV – PTLD and smooth muscle tumours
• HHV8 – Kaposi sarcoma
• HPV – anal squamous neoplasia
Fungi and parasites
Cryptosporidium
Giardia
Leishmania
Neoplasia

• Lymphoid
• Epithelial
• Mesenchymal
Epstein Barr virus & Post-transplant lymphoproliferative disease (PTLD)

• Solid organ >> bone marrow
Monomorphic PTLD
Monomorphic PTLD

CD20

EBER
Polymorphic PTLD
Polymorphic PTLD

CD20

EBER
Polymorphic PTLD

EBER
Polymorphic PTLD
Polymorphic PTLD

EBER
Neoplasia

• Lymphoid
  – PTLD (polymorphic type can mimic Crohn’s disease)
Original Paper

Epstein–Barr virus infection in colorectal neoplasms associated with inflammatory bowel disease: detection of the virus in lymphomas but not in adenocarcinomas

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2 Gerhard-Domagk-Institut für Pathologie, Universitätsklinikum Münster, Germany
3 Pathologisch-Anatomisches Institut, Universität, Erlangen, Germany
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5 Institut für Pathologie, Auguste-Viktoria Krankenhaus, Berlin, Germany
6 Department of Cellular Pathology, Southmead Hospital, Bristol, UK
7 Department of Pathology, Gloucestershire Royal Hospital, Gloucester, UK
Neoplasia

• Lymphoid
  – PTLD (polymorphic type can mimic Crohn’s disease)
  – EBV driven GIT lymphomas and immunosuppression – e.g. IBD
  – HIV and lymphomas (primary effusion lymphoma – HHV8)
Neoplasia

• Epithelial
  – Anal squamous dysplasia and squamous cell carcinoma
Neoplasia

• Mesenchymal
  – Kaposi sarcoma (can be CD117 +ve but is DOG1 -ve)
In HIV/AIDS patients, EBV driven smooth muscle neoplasms:
- less pleomorphism
- low mitotic count
Drugs

• Diarrhoea and:
  – Antiretrovirals
  – Cyclosporine
  – Tacrolimus

• Mycophenolate mofetil (MMF)
MMF

• Oesophagus to Colorectum
• Histological patterns
  – GvHD like
  – IBD like
  – Combinations
  – (Dilated damaged crypts)
Talk plan

• Diseases common to several immunosuppressed groups
  – Infection
  – Neoplasia
  – Drugs

• Diseases specific to certain immunosuppressed groups
Gastrointestinal GvHD

- BMT rather than solid organ transplant patients
- Hallmark histological feature is apoptosis
  - Proliferative compartments
TABLE 1.

Definition and Histologic Grading System for Gut

<table>
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<tr>
<th>Grade</th>
<th>Histological Features&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>I</td>
<td>Crypt abscesses with necrotic or atypical epithelial cells, in vicinity of inflammatory infiltrate composed of lymphocytes, plasma cells, immunoblasts, and occasionally eosinophils (see Fig. 3)</td>
</tr>
<tr>
<td>II</td>
<td>Individual crypt loss (see Fig. 4)</td>
</tr>
<tr>
<td>III</td>
<td>Loss of two or more contiguous crypts (see Fig. 5)</td>
</tr>
<tr>
<td>IV</td>
<td>Total denudation of epithelium (usually followed rapidly by bacterial or fungal superinfection)</td>
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Gastrointestinal GvHD

• Can include:
  – Acute inflammation
  – Granulomas?
Granulomas in GI GvHD?
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Gastrointestinal GvHD

• Other causes of apoptosis
  – Conditioning drugs (< Day 21)
  – Mycophenolate mofetil (MMF)
  – Viruses
Is the Presence of 6 or Fewer Crypt Apoptotic Bodies Sufficient for Diagnosis of Graft Versus Host Disease? A Decade of Experience at a Single Institution

Jingmei Lin, MD, PhD, Rong Fan, MD, PhD, Zijin Zhao, MD, Oscar W. Cummings, MD, and Shaoxiong Chen, MD, PhD

**Abstract:** Histopathology assessment is crucial for the diagnosis of graft versus host disease (GVHD), as the presence of crypt apoptosis is the cardinal criterion required. However, crypt apoptosis is not limited to GVHD; it also occurs in other conditions such as infection, drug reaction, or inflammatory reactions unrelated to GVHD. To better determine whether the presence of 6 or fewer apoptotic bodies is sufficient for the diagnosis of GVHD, we retrospectively reviewed 78 colon biopsies from 66 patients who received either hematopoietic stem cell (HSCT) or cord blood cell transplantation and whose colon biopsies exhibited apoptotic bodies. Among them, 41 cases contained 6 or fewer apoptotic bodies in the colon biopsy. These biopsies were compared with 141 colon biopsy controls that showed no significant pathologic changes as well as 16 colon biopsies with cytomegalovirus colitis from patients without a history of bone marrow transplantation. Among the 41 cases reviewed, 7 patients had coexisting GVHD in other organs (skin or liver). However, gastrointestinal symptoms of at least 4 HSCT patients whose colon biopsies contained 6 or fewer

**Key Words:** graft versus host disease, colon, cytomegalovirus colitis, apoptosis, transplantation


Transplantation, either hematopoietic stem cell (HSCT) or cord blood cell, is a potentially curative therapy in the management of immunohematopoietic disorders. However, the efficacy of this treatment is greatly impaired by graft versus host disease (GVHD), a donor-derived immune response against recipient antigens, resulting in significant morbidity and mortality.\(^1\) The gastrointestinal (GI) tract is one of the main target organs involved by GVHD. Unfortunately, GI GVHD may present with a variety of nonspecific symptoms; diagnosis based on clinical presentation alone is not reliable or specific.\(^2\) Gross endoscopic discordance with histologic findings exists\(^3,4\); therefore histopathology assessment is crucial to make a diagnosis of GVHD.
Control grp: Non-BMT patients investigated for GI symptoms or being followed up for colorectal polyps

Strikingly, the presence of a single or rare crypt apoptosis was seen in 21.3% (30 of 141) of the normal controls with a mean of 0.2 per 10 contiguous crypts and a maximum count of up to 5 per 10 contiguous crypts.
**TABLE 5.** Suggested Modified Histopathologic Criteria for Grading GVHD in Colon Biopsies

<table>
<thead>
<tr>
<th>Grade Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate for GVHD</td>
<td>Rare crypt apoptosis (≤ 6 apoptotic bodies per 10 contiguous crypts)</td>
</tr>
<tr>
<td>Grade 1 GVHD</td>
<td>Increased crypt apoptosis without crypt/glands loss (≥ 7 apoptotic bodies per 10 contiguous crypts)</td>
</tr>
<tr>
<td>Grade 2 GVHD</td>
<td>Loss of individual crypt/gland with crypt apoptosis</td>
</tr>
<tr>
<td>Grade 3 GVHD</td>
<td>Loss of 2 or more contiguous crypts/glands with crypt apoptosis</td>
</tr>
<tr>
<td>Grade 4 GVHD</td>
<td>Extensive crypt loss with mucosal denudation or ulceration with crypt apoptosis</td>
</tr>
</tbody>
</table>
When assessing transplant patient GI biopsies

- Time from transplant?
- Transplant type?
- Underlying disease?
- GvHD elsewhere?
- MMF therapy?
- CMV, Adenovirus and EBV titres?
Cord Colitis Syndrome in Cord-Blood Stem-Cell Cell Transplantation

Alex F. Herrera, M.D., Gabriela Soriano, M.D., Andrew M. Bellizzi, M.D., Jason L. Hornick, M.D., Ph.D., Vincent T. Ho, M.D., Karen K. Ballen, M.D., Lindsey R. Baden, M.D., Corey S. Cutler, M.D., M.P.H., Joseph H. Antin, M.D., Robert J. Soiffer, M.D., and Francisco M. Marty, M.D.

Sequence-Based Discovery of *Bradyrhizobium enterica* in Cord Colitis Syndrome

Ami S. Bhatt, M.D., Ph.D., Samuel S. Freeman, B.S.E., Alex F. Herrera, M.D., Chandra Sekhar Pedamallu, Ph.D., Dirk Gevers, Ph.D., Fujiko Duke, B.S., Joonil Jung, Ph.D., Monia Michaud, M.Sc., Bruce J. Walker, B.S., Sarah Young, Ph.D., Ashlee M. Earl, Ph.D., Aleksander D. Kostic, Ph.D., Akinyemi I. Ojesina, M.D., Ph.D., Robert Hasserjian, M.D., Karen K. Ballen, M.D., Yi-Bin Chen, M.D., Gabriela Hobbs, M.D., Joseph H. Antin, M.D., Robert J. Soiffer, M.D., Lindsey R. Baden, M.D., Wendy S. Garrett, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Francisco M. Marty, M.D., and Matthew Meyerson, M.D., Ph.D.

Granulomas in GI GvHD?
Evaluating the association between histological manifestations of cord colitis syndrome with GVHD

S Shimoji, K Kato, Y Eriguchi, K Takenaka, H Iwasaki, T Miyamoto, Y Oda, K Akashi, and T Teshima

Cord colitis syndrome (CCS) is a recently proposed clinical entity characterized by a persistent diarrheal illness after cord blood transplantation (CBT), which is not caused by GVHD or CMV colitis. CCS is histologically characterized by chronic active colitis with granulomatous inflammation and Paneth cell metaplasia suggesting chronicity. However, the specificity of these pathological features to CCS remains to be validated. We conducted a retrospective study of 49 patients who had diarrhea and underwent diagnostic colonoscopy with biopsy following allogeneic hematopoietic SCT. None of the patients met the clinical criteria for CCS. Chronic active colitis with granulomatous inflammation and Paneth cell metaplasia was present in 12/33 (36%) patients with biopsy-proven GVHD, 4/6 (67%) patients with CMV colitis and 2/15 (13%) patients with nonspecific colitis. In patients with GVHD and/or CMV colitis, these pathological features were present in 4/8 (50%) patients after CBT and in 11/26 (42%) patients undergoing BMT or PBSCT. These results demonstrate that chronic active colitis with granuloma and Paneth cell metaplasia is not only a specific feature of CCS but also is present in GVHD and CMV colitis, irrespective of stem cell source.
Late-Onset Colitis after Cord Blood Transplantation Is Consistent with Graft-Versus-Host Disease: Results of a Blinded Histopathological Review

Filippo Milano 1,2,*, Howard M. Shulman 1,2, Katherine A. Guthrie 1,3, Ivy Riffkin 1, George B. McDonald 1,2, Colleen Delaney 1,2

1 Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
2 Departments of Pediatrics, Pathology, and Medicine, University of Washington School of Medicine, Seattle, Washington
3 Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

ABSTRACT
Cord colitis syndrome after umbilical cord blood transplantation (UCBT) involves late-onset diarrhea, absence of infection or GVHD, chronic active colitis, and granulomatous inflammation that responds to antibiotics. We tested the hypothesis that Seattle recipients of UCBT had late-occurring colitis distinct from GVHD and colitis in other allograft recipients. We conducted a blinded histological review of 153 colon biopsy specimens from 45 UCBT recipients and 45 matched allografted controls obtained between day +70 and day +365 post-transplantation. Diarrhea was the primary indication for biopsy in 10 UCBT recipients and 11 controls. No histological differences were seen between UCBT recipients and controls with diarrhea or between the entire cohort of UCBT recipients and their controls. Distorted mucosal architecture and apoptotic crypt cells typical of GVHD were common in both groups; Paneth cell metaplasia and granulomas were rare findings. Chronic active colitis was present in 58% of the UCBT recipients and in 62% of controls. No UCBT recipient with diarrhea was treated with antibiotics, and all recipients responded to systemic corticosteroids. Colitis occurring after day +70 in allografted controls was related to acute GVHD, independent of the source of donor cells. We could not identify a histologically distinct cord colitis syndrome in either the UCBT or the non-cord blood allograft recipients.

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Underlying condition requiring transplant

• BMT transplant
  – Lymphoma/leukaemia
Underlying condition requiring transplant

• Renal transplant
  – Amyloid
Underlying condition requiring transplant

- Liver transplant
  - Portal colopathy
  - Primary sclerosing cholangitis and IBD
Transplantation and IBD

• Does transplantation improve or worsen IBD?
Colorectal disease in liver allograft recipients – a clinicopathological study with follow-up
Newton A.C.S Wong\textsuperscript{a}, Andrew J. Bathgate\textsuperscript{b} and Christopher O.C. Bellamy\textsuperscript{a}

**Objective** To determine the spectrum and outcome of colorectal diseases occurring in adult liver allograft recipients.

**Design** A retrospective cohort analysis of clinical, microbiological and histopathological data regarding colorectal disease.

**Patients** Forty three out of 302 adult primary liver allograft recipients were transplanted and followed up (at median 42 months) at a tertiary referral centre/teaching hospital.

**Results** Out of 302 patients, 43 (14\%) were investigated (by endoscopy and/or laparotomy) for symptoms of colorectal disease after orthotopic liver transplantation. The symptoms were: diarrhoea ($n = 31$); per-rectal bleeding ($n = 5$); and symptoms relating to pre-transplant activity of pre-transplant ulcerative colitis was unchanged or increased after orthotopic liver transplantation. Two further patients developed new-onset ulcerative colitis after orthotopic liver transplantation.

**Conclusions** Ulcerative colitis, *C. difficile*, cytomegalovirus infection and medications are the commonest colorectal causes of morbidity after orthotopic liver transplantation. Adult liver allograft recipients are, however, unlikely to show certain large bowel diseases encountered in other immunosuppressed groups. Amongst non-ulcerative colitis patients, those presenting with diarrhoea show a good outcome with appropriate management, whereas those with per-rectal bleeding have a more guarded prognosis. *Eur J Gastroenterol Hepatol* 14:231–236 © 2002 Lippincott Williams & Wilkins
Transplantation and IBD

• Does transplantation improve or worsen IBD?

activity of pre-transplant ulcerative colitis was unchanged or increased after orthotopic liver transplantation. Two further patients developed new-onset ulcerative colitis after orthotopic liver transplantation.

• Immunosuppression helps but restoration of normal liver function has opposite effect.
Other specific associations

• Solid organ transplant patients
  – Gastric and duodenal ulcers
Other specific associations

• Solid organ transplant patients
  – Gastric and duodenal ulcers

• HIV/AIDS patients
  – Oesophageal and anal ulcers
  – Enterocolopathy (apoptosis and villous atrophy)
23M AML patient
• Pneumatosis coli:

• Colitis but no ...
Leukaemia and neutropenic colitis
Summary

• Rare and/or multiple pathology
• Clinical data are crucial – especially when considering GvHD
When assessing transplant patient GI biopsies

- Time from transplant?
- Transplant type?
- Underlying disease?
- GvHD elsewhere?
- MMF therapy?
- CMV, Adenovirus and EBV titres?