Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

Name of the enterprise / Nature of the interest

Enterprise | Interest
--- | ---
none | none
What’s hot in the lower GI tract?

Roger Feakins
Lower GI tract

Iatrogenic disease
  - Medications and materials
  - Neutropenic enterocolitis
  - Graft-versus-host disease

Eosinophilia

Serrated lesions

microRNAs in Crohn’s disease

Prognostic factors

Inter-laboratory variability
Drugs facilitating anti-tumour immune response: “Immunomodulatory” colitis

<table>
<thead>
<tr>
<th>PI3Kδ inhibitors</th>
<th>Drugs targeting T cell inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Anti-CTLA-4 (cytotoxic T lymphocyte antigen 4)</td>
</tr>
<tr>
<td></td>
<td>• Anti-PD-1 (programmed cell death protein 1)</td>
</tr>
</tbody>
</table>
Idelalisib-associated Enterocolitis
Clinicopathologic Features and Distinction From Other Enterocolitides

Christine Y. Louie, MD,* Michael A. DiMaio, MD,* Karen E. Matsukuma, MD, PhD,†
Steven E. Coutre, MD,‡ Gerald J. Berry, MD,* and Teri A. Longacre, MD*

Idelalisib-associated Colitis
Histologic Findings in 14 Patients

Anna-Sophie Weidner, MD,* Nicole C. Panarelli, MD,* Julia T. Geyer, MD,*
Erica B. Bhavsar, BS,† Richard R. Furman, MD,† John P. Leonard, MD,† Jose Jessurun, MD,*
and Rhonda K. Yantiss, MD*
Original article

Clinical, Endoscopic, and Histologic Characteristics of Ipilimumab-Associated Colitis

Eduard Cornelis Verschuren *, Alfonsus Johannes van den Eertwegh ‡, Janneke Wonders *, Rob Michel Slangen §, Foke van Delft *, Adriaan van Bodegraven *, Il, Andra Neefjes-Borst †, b, Nanne Klaas de Boer *, b, e, a
Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies

Jonathan H. Chen, MD, PhD,* Maryam K. Pezhouh, MD, MSc,† Gregory Y. Lauwers, MD,‡ and Ricard Masia, MD, PhD*

PD-1 inhibitor gastroenterocolitis: case series and appraisal of ‘immunomodulatory gastroenterocolitis’

Raul S Gonzalez, Safia N Salaria, Caitlin D Bohannon, Aaron R Huber, Michael M Feely, Chanjuan Shi
Immunomodulatory colitis

FIGURE 2. Microscopic alterations. A, Stomach: there is expansion of the lamina propria and increased IELs with reactive epithelial changes. The inset shows increased IELs and apoptosis; B, Ileal biopsy: there is distinct blunting of the villi with expansion of the lamina propria by lymphoplasmacytic infiltrate with eosinophils and a few neutrophils involving the glandular epithelium. Note the flattened/cuboidal surface epithelium. C and D, Colonic biopsy shows expansion of the lamina propria with ill formed basal lymphoplasmacytic infiltrate and elongation of the crypts. D shows cryptitis, lymphocytic exocytosis, and apoptosis. IELs indicates intraepithelial lymphocytes.
Immunomodulatory colitis

Apoptosis

Intraepithelial lymphocytosis
<table>
<thead>
<tr>
<th></th>
<th>PI3Kδ inhibitors</th>
<th>Anti-CTLA4</th>
<th>Anti-PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMON CHANGES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neutrophil cryptitis / crypt abscess</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intraepithelial lymphocytosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>OTHER CHANGES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic crypt abscesses</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cryptolytic granulomas</td>
<td>+</td>
<td></td>
<td>(+)</td>
</tr>
<tr>
<td><strong>CHRONIC CHANGES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crypt changes</td>
<td>Rare</td>
<td>40%</td>
<td>If recurrent</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>-</td>
<td></td>
<td>If recurrent</td>
</tr>
</tbody>
</table>
Immunomodulatory colitis: chronic changes

“H&E diagnosable” medications
H&E diagnosable medications

The substance is visible

- Iron pill gastritis
- Yttrium-labelled microsphere injury

- Polymers
- Pharmaceutical fillers
Hydrophilic Polymer–associated Ischemic Enterocolitis

Jesus A. Chavez, MD, Wei Chen, MD, PhD, Wendy L. Frankel, MD, and Christina A. Arnold, MD
Polymer-associated ischaemic enterocolitis

- Coating for intravascular devices
- Can dislodge ischaemia

Intestinal resections

- Visible polymer
- Submucosal vessels > elsewhere
- Basophilic serpiginous structures
- Chronic deposition:
  - Giant cell reaction
  - Less basophilic

*Chavez, Chen et al. 2017*
Hydrophilic Polymer–associated Ischemic Enterocolitis

Chavez, Jesus A.; Chen, Wei; Frankel, Wendy L.; Arnold, Christina A.
doi: 10.1097/PAS.0000000000000765

FIGURE 3. Hydrophilic polymers show altered morphology over time. Patient 1 had two separate bowel resections following her endograft repair. A, The characteristic polymer morphology was seen with the initial bowel resection performed 1 day after the aortic repair. B, Three months later, the polymers were fewer in number, less crisply basophilic, more amorphous in shape, and many were associated with a foreign body giant cell reaction.
Polymer

Hydrophilic Polymer–associated Ischemic Enterocolitis

Chavez, Jesus A.; Chen, Wei; Frankel, Wendy L.; Arnold, Christina A.
doi: 10.1097/PAS.0000000000000765

FIGURE 1. Characteristic morphology of hydrophilic polymers from patients with fenestrated Endografts. A, The polymers were only identified in vessels in areas of ischemia, and they were most commonly found in the submucosa (brackets). B, On highest power, the polymers displayed a serpiginous configuration with stippled basophilia. The polymers were turquoise on colloidal iron (C), pink on a von Kossa (D), and mucicarmine (E), and pale blue on trichrome (F).
Crospovidone and Microcrystalline Cellulose

A Novel Description of Pharmaceutical Fillers in the Gastrointestinal Tract

Sophia M. Shaddy, MD,* Michael A. Arnold, MD, PhD,*† Konstantin Shilo, MD,*
Wendy L. Frankel, MD,* Alan E. Harzman, MD,‡ Peter P. Stanich, MD,§
Aatur D. Singhi, MD, PhD,∥ Martha M. Yearsley, MD,* and Christina A. Arnold, MD*
Pharmaceutical fillers: crospovidone and microcrystalline cellulose

• Non-absorbable powders
  • facilitate drug delivery

• 9% GI specimens
  • Crospovidone: coral-shape with pink core and purple coat
  • Microcrystalline cellulose (MCC): clear, matchstick shape

Shaddy, Arnold et al. 2017
**Figure 2**

Crospovidone and Microcrystalline Cellulose: A Novel Deserialization of Pharmaceutical Filters in the Gastrointestinal Tract

Shaddy, Sophie M.; Arnold, Michael A.; Shilo, Konstantin; Franke, Wendy L.; Harzman, Alan E.; Stanich, Peter P.; Singh, Asut D.; Yearsley, Martha M.; Arnold, Christina A.


doi: 10.1097/PAS.0000000000000790

**FIGURE 2.** Crospovidone and MCC were most commonly seen in close approximation to each other in both processed medications and patient samples (not shown). A, oxycodone-acetaminophen (Percocet); B, omeprazole (Prilosec).
NEUTROPENIC ENTEROCOLITIS
Neutropenic Enterocolitis
New Insights Into a Deadly Entity

Taha Sachak, MD,* Michael A. Arnold, MD, PhD,†† Bita V. Naini, MD,‡
Rondell P. Graham, MBBS,§ Sejal S. Shah, MD,§ Michael Cruise, MD, PhD,‖
Jason Y. Park, MD, PhD,¶ Lindsey Clark, MD,** Laura Lamps, MD,**
Wendy L. Frankel, MD,* Nicole Theodoropoulos, MD,* and Christina A. Arnold, MD*
Neutrop(a)enic enterocolitis

79% death rate

Clinical criteria for diagnosis
- Neutropenia
- Wall thickness > 4 mm; length > 29 mm
- Fever > 38°C
- Abdominal pain

Pathology
- Right colon +/- other areas
- Patchy
- Necrosis, haemorrhage, ulceration, oedema
- Submucosa +++

Discordance with clinical in 40% cases

Sachak T 2017
Graft versus host disease - GVHD
Original Article

Diagnostic phrasing is independently correlated with the decision to treat for graft-versus-host disease: retrospective review of colon biopsies with rare apoptosis

Daniel J Rowan, Christopher P Hartley, Luis F Carrillo-Polanco, Kiyoko Oshima, Catherine E Hagen

First published: 22 July 2016  Full publication history
Colorectal GVHD – “iGVHD”

Crypt epithelial cell apoptosis
• Characteristic
• Number? > 6 per 10 contiguous crypts??

“iGVHD” - indeterminate for GVHD
• 6 apoptoses or fewer per 10 contiguous crypts
• Heterogeneous group
• “The use of the diagnostic category iGVHD [.....] allows treatment based on clinical judgement”

COLONIC EOSINOPHILIA
Primary Colonic Eosinophilia and Eosinophilic Colitis in Adults

Kevin O. Turner, DO,* † Richa A. Sinkre,* William L. Neumann, MD,* ‡ and Robert M. Genta, MD* §

Histopathology

Review

The pathology and causes of tissue eosinophilia in the gastrointestinal tract

James R Conner, Richard Kirsch ☐

First published: 26 May 2017  Full publication history
Eosinophils per high power field – colonic lamina propria

<table>
<thead>
<tr>
<th></th>
<th>Matsushita 2015</th>
<th>Turner 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right colon</td>
<td>4-14</td>
<td>7-17</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>-----</td>
<td>5-13</td>
</tr>
<tr>
<td>Left colon</td>
<td>0-6</td>
<td>2-10</td>
</tr>
</tbody>
</table>

Turner, Sinkre et al. 2017; Matsushita, Maruyama et al. 2015
## Thresholds for colonic eosinophilia?

<table>
<thead>
<tr>
<th>Colon Location</th>
<th>Turner 2017</th>
<th>Lee CM 1993</th>
<th>Odze 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right colon</td>
<td>&gt;50/hpf</td>
<td>20/hpf</td>
<td>60 per 10 hpf i.e. 6/hpf</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>&gt;35/hpf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left colon</td>
<td>&gt;25/hpf</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Many causes of colonic eosinophilia

- Parasites
- Allergy
- Hypereosinophilic syndromes
- Churg-Strauss
- IgG4-related disease
- Mastocytosis
- Drugs
- Vasculitis
- Connective tissue disorders
- IBD
- Tumours

Ulcerative colitis with eosinophils
Primary colonic eosinophilia

Rare +++

Histology
• Eosinophils: 40 to 1190 per hpf
• Intraepithelial eosinophils common
• Eosinophil crypt abscesses 7%

Turner, Sinkre et al. 2017
Micro RNAs (miR/miRNA) in IBD
miRNAs in Crohn’s fibrosis

Short noncoding RNAs
- Regulate post-transcriptional gene expression
- May influence development of fibrosis

Stricturing vs non-stricturing Crohn’s
- Serum and/or mucosal miRNA levels differ

Nijhuis A 2014
SERRATED COLORECTAL LESIONS
British Society of Gastroenterology position statement on serrated polyps in the colon and rectum

James E East,1 Wendy S Atkin,2 Adrian C Bateman,3 Susan K Clark,4 Sunil Dolwani,5 Shara N Ket,1 Simon J Leedham,6 Perminder S Phull,7 Matt D Rutter,8,9 Neil A Shepherd,10 Ian Tomlinson,11 Colin J Rees9,12
Serrated lesions: BSG position statement

- Hyperplastic polyp
- Sessile serrated lesion (SSL)*
- SSL with dysplasia
- Traditional serrated adenoma (TSA)
- Mixed polyps

*synonyms: sessile serrated polyp (SSP); sessile serrated adenoma (SSA)

East JE et al 2017
Sessile serrated lesion vs hyperplastic polyp

Crypt features

- Dilatation at base
- Serration at base
- Branching (lateral)
- Horizontal extension of base (inverted “T”, “L”, anchor)
- Irregular distribution
- Herniation through muscularis mucosae
- Dysmaturation (variably defined)

How many crypts?

- WHO: minimum 3 crypts or 2 adjacent crypts
- AGA: 1 crypt
Traditional serrated adenoma
Management

“All polyps proximal to the rectosigmoid junction should be removed”

Surveillance – limited data

Repeat colonoscopy after 3 years if there are higher risk features, i.e.:

- SSL 10 mm or larger
- SSL with dysplasia
- Traditional serrated adenoma

East J et al 2017
Original contribution

Clinical, pathologic, and outcome study of hyperplastic and sessile serrated polyps in inflammatory bowel disease

Jeanne Shen MD, Joanna A. Gibson MD, PhD, Stephanie Schulte MD, Hema Khurana MD, Francis A. Farraye MD, MSc, Jonathan Levine MD, Robert Burakoff MD, MPH, Sandra Cerda MD, Taha Qazi MD, Matthew Hamilton MD, Amitabh Srivastava MD, Robert D. Odze MD, FRCPC, *
Serrated lesions in IBD

Frequencies in IBD

- Hyperplastic polyp - common
- SSP - uncommon
- Traditional serrated adenoma – rare

Implications

- No increased risk of significant future neoplasia

Lower incidence than non-IBD population?

Serrated mucosa?

Rubio 2007; Bossard 2007; Shen J 2015; Johnson DH 2014
Serrated lesions in IBD – associations with dysplasia

Negative for dysplasia
- Right > left
- BRAF mutation typical

LGD / indefinite
- Left > right
- KRAS mutation typical

Rubio 2007; Bossard 2007; Shen J 2015; Johnson DH 2014
COLORECTAL CARCINOMA - TUMOUR BUDDING
Access
To read this article in full you may need to log in, make a payment or gain access license (see right).

nature.com > Journal home > Table of Contents

Original Article


Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

International Tumor Budding Consensus Conference: agreement in 10 areas

1. H&E diagnosis (not immuno)
2. Single tumour cell / cluster of < 5 cells
3. Counted in 1 hotspot (area 0.785 mm²) at the invasive front
4. Not grade
5. Predicts LN metastases in pT1
6. Predicts survival in Stage 2
7. Intratumoral budding occurs
8. Three-tier system helps risk stratification
9. Multidisciplinary process
10. Guidelines/protocols

Lugli, Kirsch et al. 2017
CRC - PERINEURAL INVASION
Perineural Invasion Is a Strong Prognostic Factor in Colorectal Cancer

A Systematic Review

Nikki Knijn, MD,* Stephanie C. Mogk, BSc,* Steven Teerenstra, PhD,† Femke Simmer, PhD,* and Iris D. Nagtegaal, MD, PhD*
Perineural invasion in CRC

Meta-analysis:
• Important risk factor for local recurrence and for survival

Extramural > intramural?
• 3-tiered grading system
  • Pn0
  • Pn1a (intramural)
  • Pn1b (extramural)

Knijn N 2016; Ueno H 2013
INTER-LABORATORY VARIABILITY
Interlaboratory Variability in the Histologic Grading of Colorectal Adenocarcinomas in a Nationwide Cohort

Chantal C.H.J. Kuijpers, MSc,* †† Caro E. Sluijter, MSc, †‡ Jan H. von der Thüsen, MD, PhD, || Katrien Grünberg, MD, PhD, ¶¶ Martijn G.H. van Oijen, PhD, †# Paul J. van Diest, MD, PhD,* Mehdi Jiwa, MD, PhD,* † Iris D. Nagtegaal, MD, PhD, †§ Lucy I.H. Overbeek, PhD, † and Stefan M. Willems, MD, PhD* †
Impact of poor differentiation
  • pT1 CRC: consider resection
  • Stage II CRC: consider chemotherapy

Assessment of differentiation
  • Worst area? Predominant pattern?
  • Two categories?

Kuijpers, Sluijter et al. 2016
FIGURE 5. Proportions of PD adenocarcinomas per laboratory in the subgroup of patients who could have been eligible for adjuvant chemotherapy solely based on the differentiation grade (n=2813 tumors). The asterisks indicate the laboratories that significantly differed from the reference laboratory (laboratory 25) on univariable logistic regression analysis.
Original Article

**Interlaboratory variability in the grading of dysplasia in a nationwide cohort of colorectal adenomas**

Chantal C H J Kuijpers, Caro E Sluijter, Jan H von der Thüsen, Katrien Grünberg, Martijn G H van Oijen, Paul J van Diest, Mehdi Jiwa, Iris D Nagtegaal, Lucy I H Overbeek, Stefan M Willems
Low grade or high grade dysplasia?
Interlaboratory variability in the grading of dysplasia in a nationwide cohort of colorectal adenomas

- Each circle = a lab
- Circle size = number of reports
- Dotted lines: average % with high-grade dysplasia (HGD)
  - 3.6% biopsies
  - 11.8% polypectomies
- Red and green bubbles = labs that diagnosed HGD less and more often than average
NEUROENDOCRINE TUMOUR (NET)
Mesenteric Tumor Deposits in Midgut Small Intestinal Neuroendocrine Tumors Are a Stronger Indicator Than Lymph Node Metastasis for Liver Metastasis and Poor Prognosis

Fata, Cynthia R. MD, MSPH; Gonzalez, Raul S. MD; Liu, Eric MD; Cates, Justin M. MD, PhD; Shi, Chanjuan MD, PhD

American Journal of Surgical Pathology: January 2017 - Volume 41 - Issue 1 - p 128–133
doi: 10.1097/PAS.0000000000000751
Original Articles
Mesenteric tumour deposits in midgut neuroendocrine tumour (NET)

- Jejunum and ileum

- Mesenteric tumour deposit: discrete irregular nodule(s), separate from main mass
  - Odds ratio for liver metastases: 16.68
  - Independent negative prognostic factor
  - Include in staging schemes?

Fata CR 2017
Mesenteric Tumor Deposits in Midgut Small Intestinal Neuroendocrine Tumors Are a Stronger Indicator Than Lymph Node Metastasis for Liver Metastasis and Poor Prognosis

Fata, Cynthia R.; Gonzalez, Raul S.; Liu, Eric; Cates, Justin M.; Shi, Chanjuan
doi: 10.1097/PAS.0000000000000751

FIGURE 1. Representative MTDs, completely replaced LN and peritoneal implant. A, An MTD with an irregular contour and associated fibrosis encasing large vessels. B, A higher-power view of another MTD showing a possible vein involved by tumor (blue arrows) and an entrapped nerve (yellow arrows). C, An LN completely replaced by NET with extranodal extension. D, A peritoneal tumor implant with partial mesothelial lining and containing no large vessels.
Summary

Iatrogenic disease
- Immunomodulatory drug colitis
- H&E diagnosable substances
- GVHD
- Neutropenic colitis

Improved definitions and diagnostic criteria
- Colonic eosinophilia
- Serrated lesions

Pathogenesis
- miRNAs and Crohn’s fibrosis

Additional prognostic factors
- Tumour budding (CRC)
- Perineural invasion (CRC)
- Mesenteric tumour deposits (NET)

Inter-laboratory variability
- CRC differentiation
- Adenoma grade
Thank you