Medizinische Universität Graz

Inflammatory Bowel Disease and Dysplasia

Minisympózium: Patológia Gastrointestinálneho Traktu

SD-IAP, Košice, Slovakia, 6-7 June 2019

ENGIP

European Society of Pathology

Cord Langner MD
Diagnostic & Research Centre for Molecular BioMedicine
Institute of Pathology
Medical University of Graz, Austria

Agenda

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- **Normal Histology**
- **Basic Principles of IBD Diagnosis**
  - Ulcerative Colitis
  - Crohn's Disease
- **Difficulties in IBD Diagnosis and Differential Diagnosis**
- **Grading of Activity**
- **Dysplasia and Cancer**
- **Take Home Messages**

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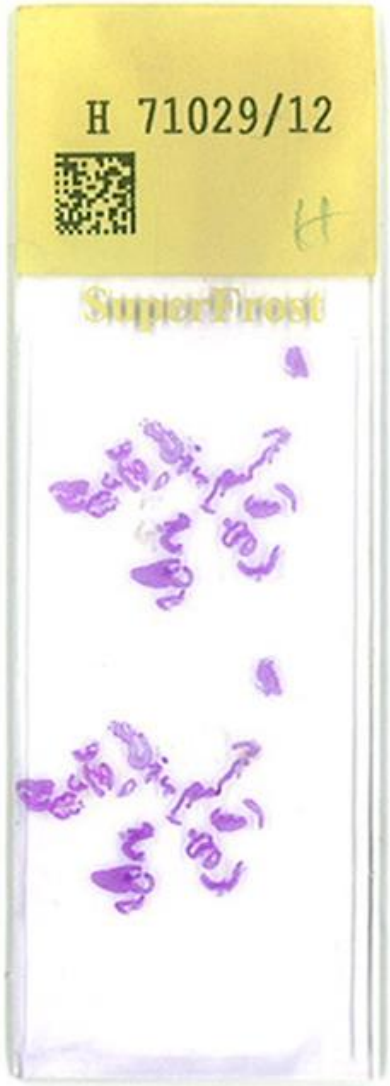
Normal Histology



- Mucosal architecture
- Cells in the lamina propria
  - Lymphocytes
  - Plasma cells
  - Macrophages
  - Eosinophilic granulocytes
  - Mast cells
  - Neutrophilic granulocytes

Normal Histology

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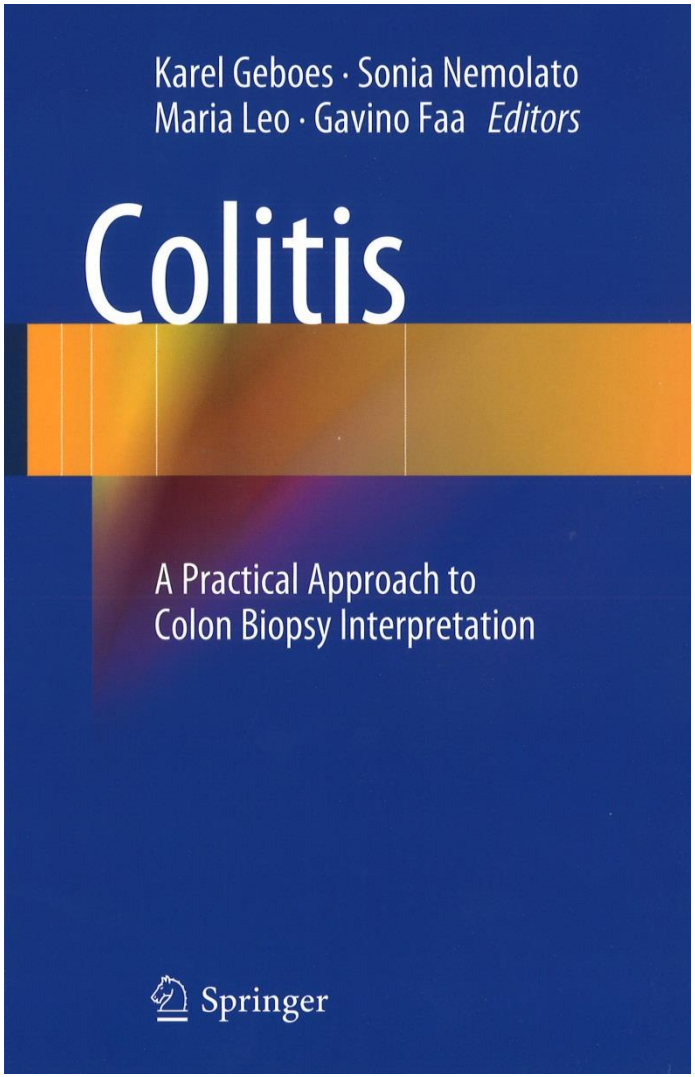
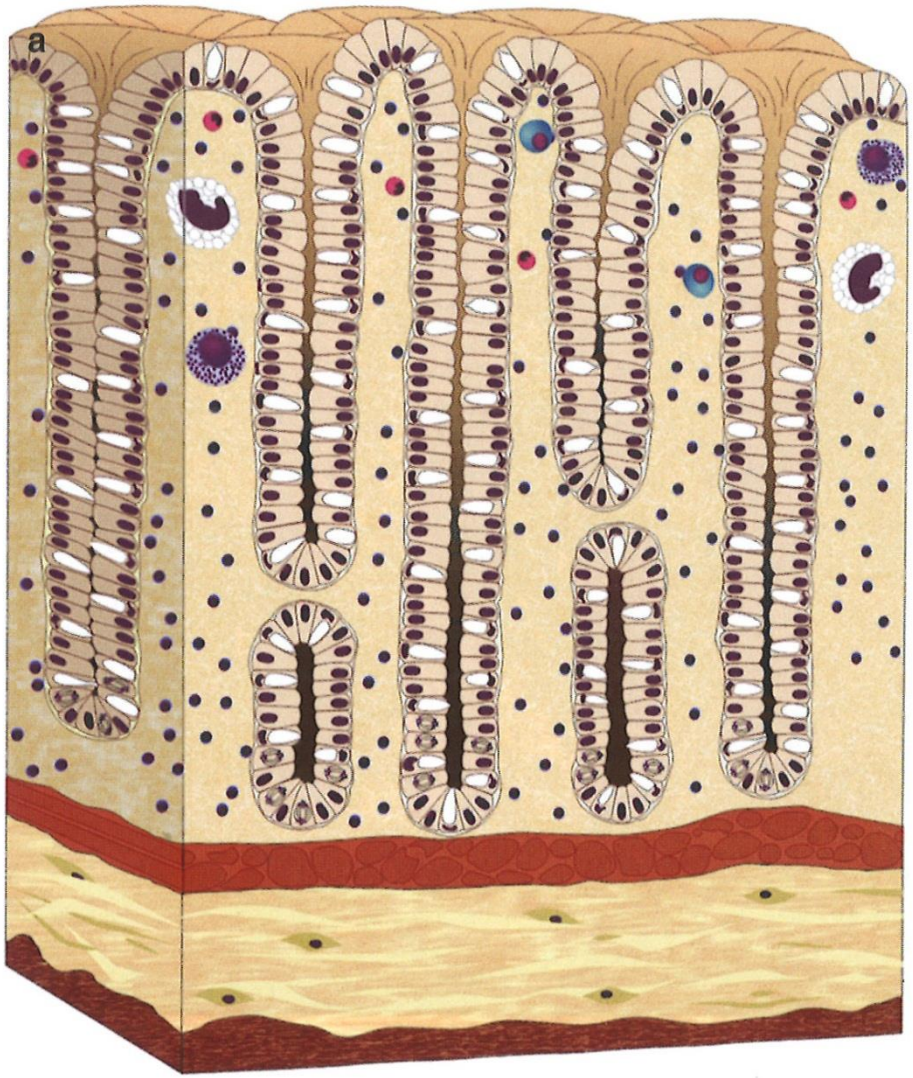
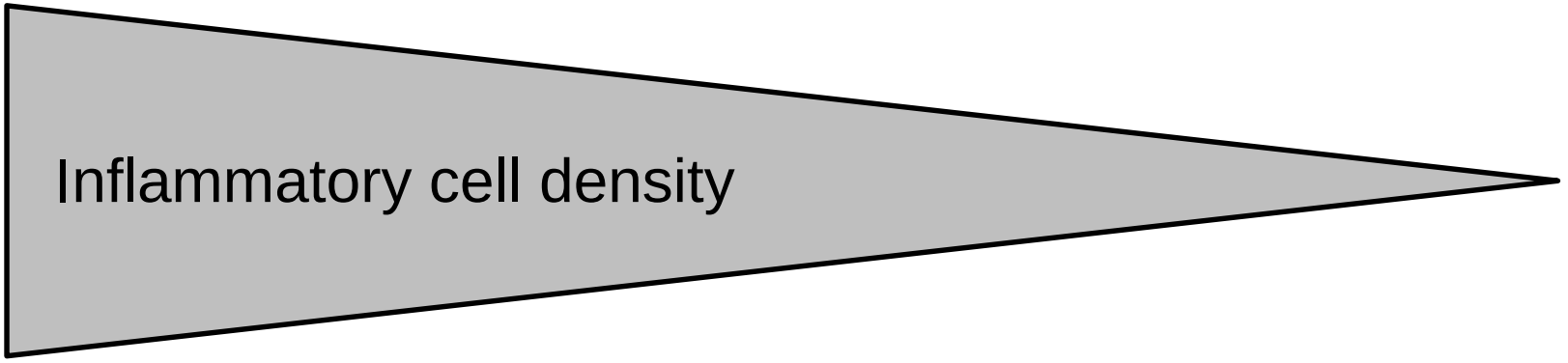


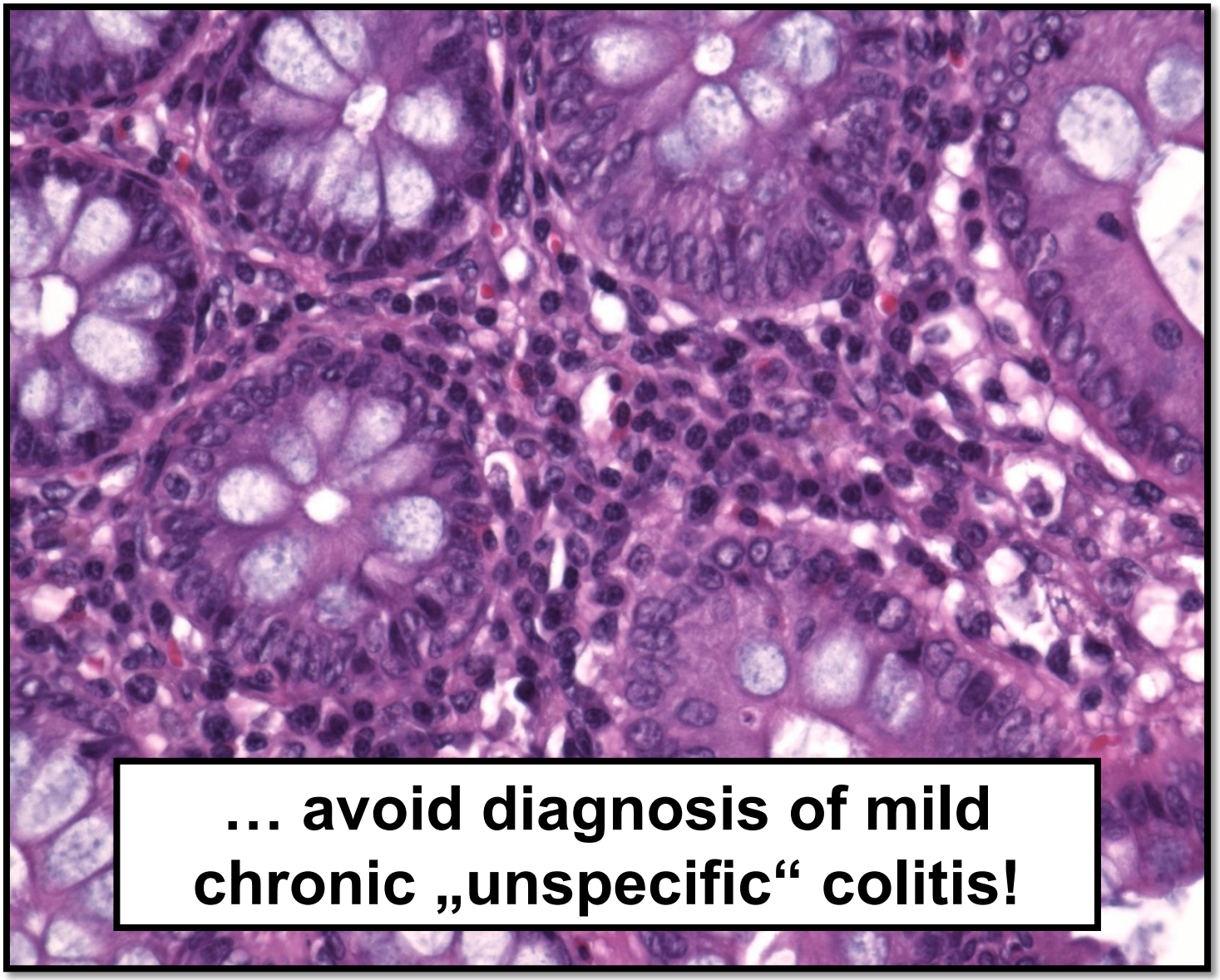


Normal Histology

- **Interindividual variability**
- **Intraindividual variability**
- **Regional variability**



Normal Histology



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Basic Principles of Histological IBD Diagnosis

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- Analysis of **multiple biopsies** allows a correct diagnosis of inflammatory bowel disease in 66-75% of newly diagnosed patients.
- Providing additional **endoscopic and clinical data** to the pathologist increases the diagnostic accuracy, allowing a final diagnosis in more than 90% of cases
- The histological features useful for a diagnosis of inflammatory bowel disease may be grouped into four categories:
  - **Mucosal (crypt) architecture**
  - **Lamina propria cellularity**
  - **Infiltration by neutrophils**
  - **Epithelial changes**

Basic Principles of Histological IBD Diagnosis

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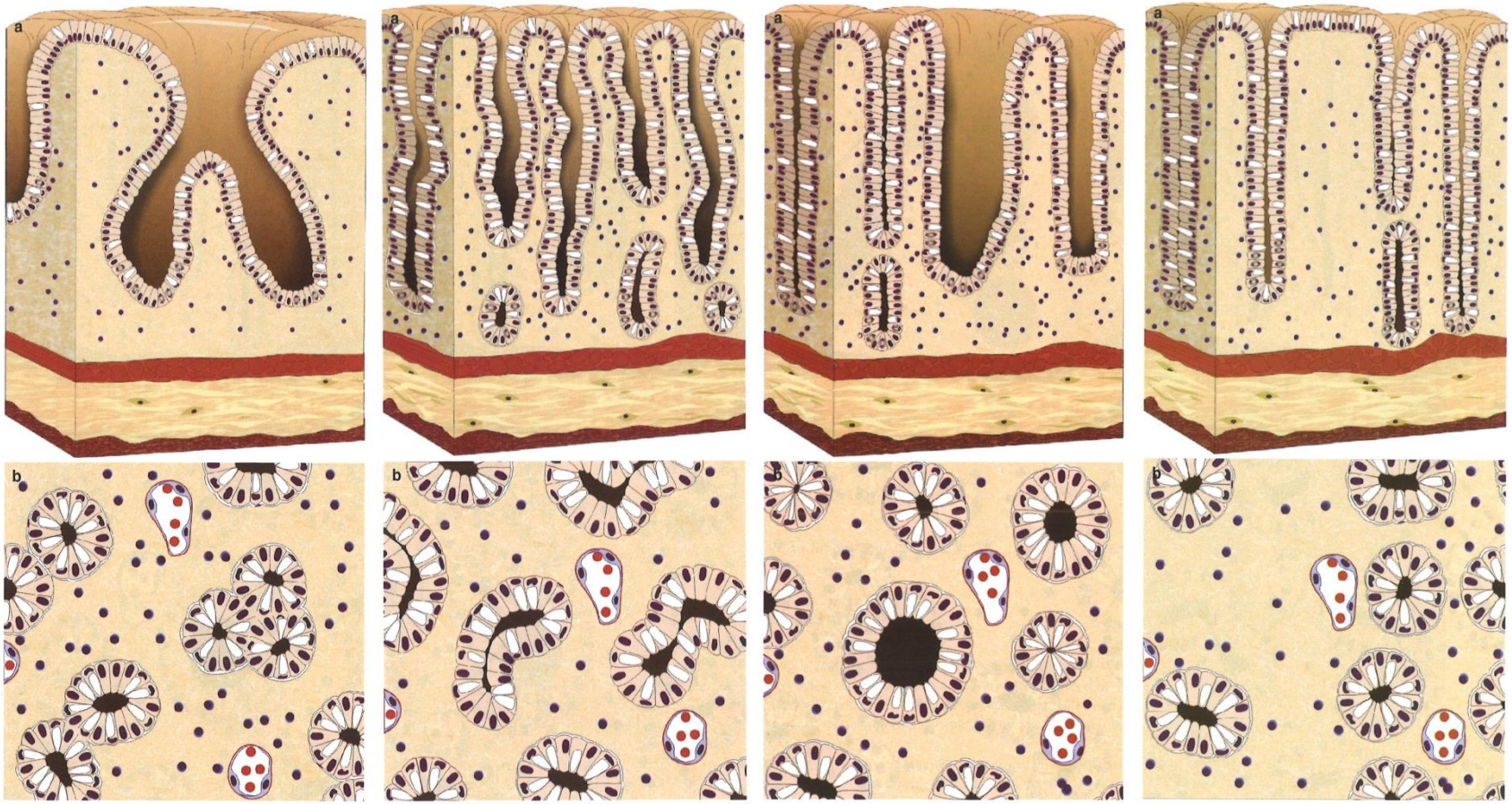
- **Abnormalities in mucosal (crypt) architecture**
  - Crypt distortion
  - Crypt branching
  - Surface epithelium irregularities (pseudovillous change)
  - Reduced crypt length (shortening)
  - Reduced crypt density

  } Atrophy

- Abnormalities in crypt architecture are particularly pronounced in ulcerative colitis (57-100% of cases), but may also occur in Crohn's disease (27-71% of cases)

Basic Principles of Histological IBD Diagnosis



Crypt Branching	Crypt architectural distortion	Variability in crypt internal diameter	Variability in the intercryptal distance

Basic Principles of Histological IBD Diagnosis

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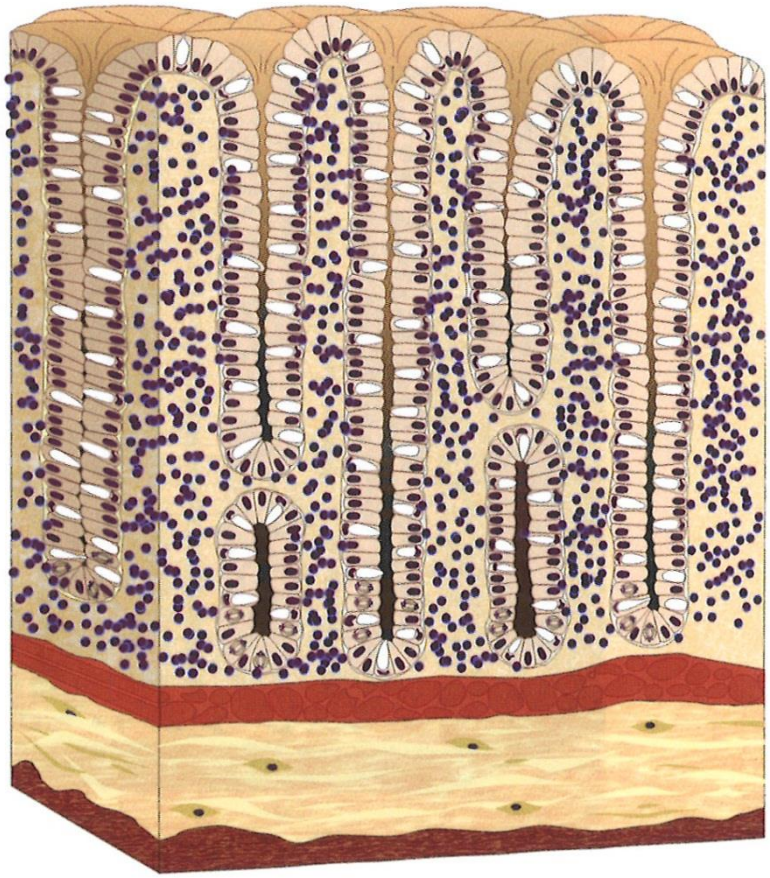
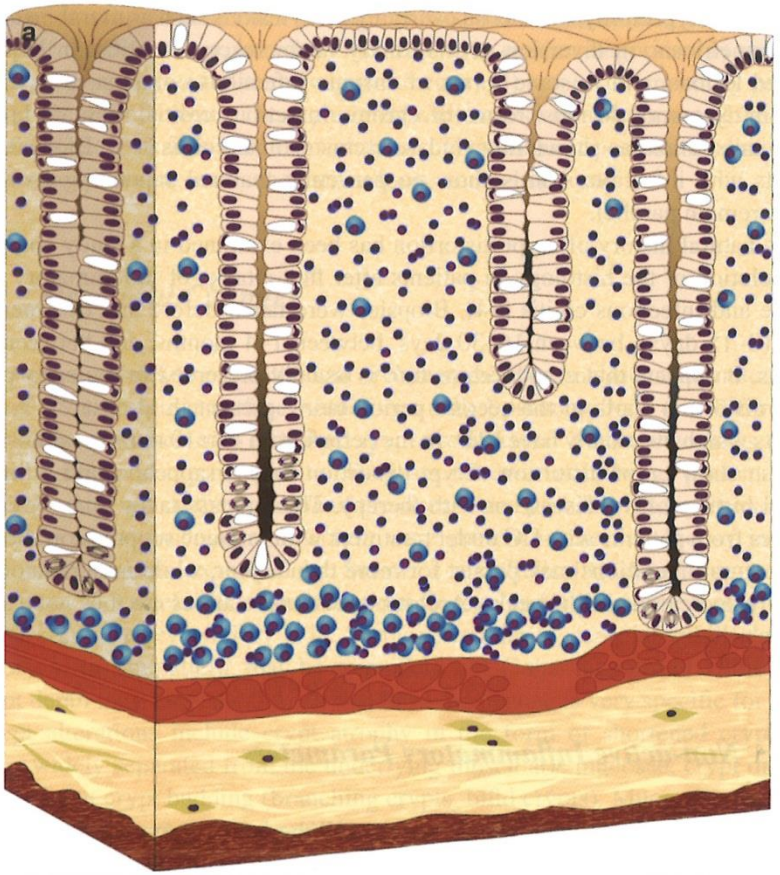
- **Lamina propria cellularity**
  - Transmucosal increase of inflammatory cells
  - Basal plasmacytosis

Basic Principles of Histological IBD Diagnosis



Increased transmucosal inflammation of the lamina propria



Basal plasmacytosis (and crypt shortening)

Basic Principles of Histological IBD Diagnosis

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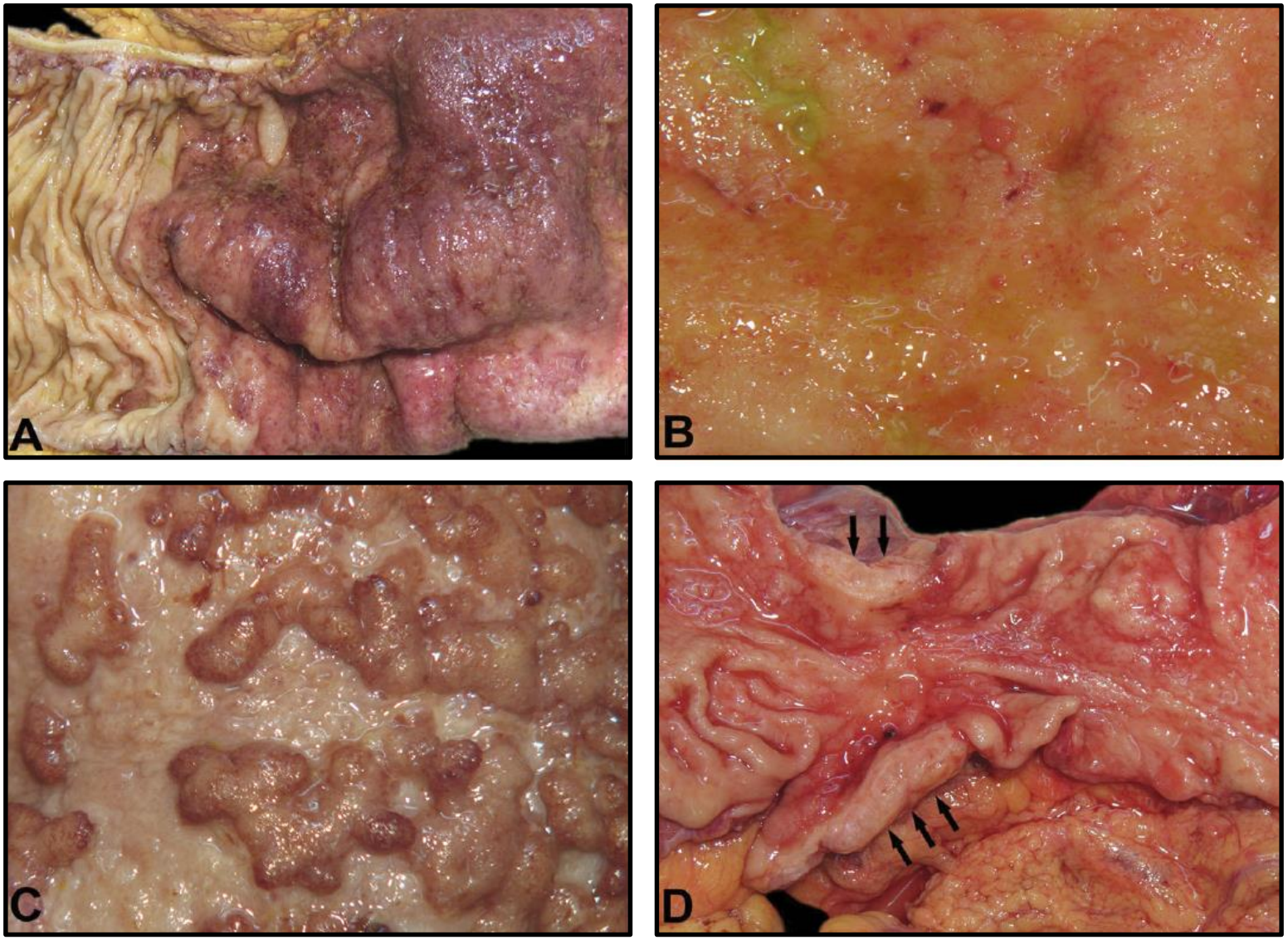
- **Lamina propria cellularity**
  - Transmucosal increase of inflammatory cells
  - Basal plasmacytosis
  - Non-necrotic epithelioid cell granulomas are present in approximately 20-50% of cases with Crohn's disease (DD cryptolytic granulomas in ulcerative colitis)
- **Neutrophils** (cryptitis / crypt abscess formation) = markers of disease activity
- **Epithelial changes:** epithelial damage and mucin depletion (at active sites), metaplastic changes (markers of chronicity)

Ulcerative Colitis: Key Histologic Features

- Diffuse (continuous) mucosal disease that begins in the rectum and spreads variably to the proximal colon (worse distally)
- Severe diffuse mucosal architectural abnormalities (crypt atrophy and distortion, decreased crypt density)
- Severe diffuse transmucosal increase of (predominantly mononuclear) inflammatory cells with basal plasmacytosis
- Epithelial abnormalities, such as surface epithelial damage and mucin depletion as well as Paneth cell metaplasia (in biopsies obtained distal to the hepatic flexure)
- Tissue fragments both within the same biopsy and within separately submitted specimens tend to show the same degree of inflammation
- Rare epithelioid cell granulomas, related to ruptured crypts

Ulcerative Colitis



Langner et al. Virchows Arch 2014

Ulcerative Colitis

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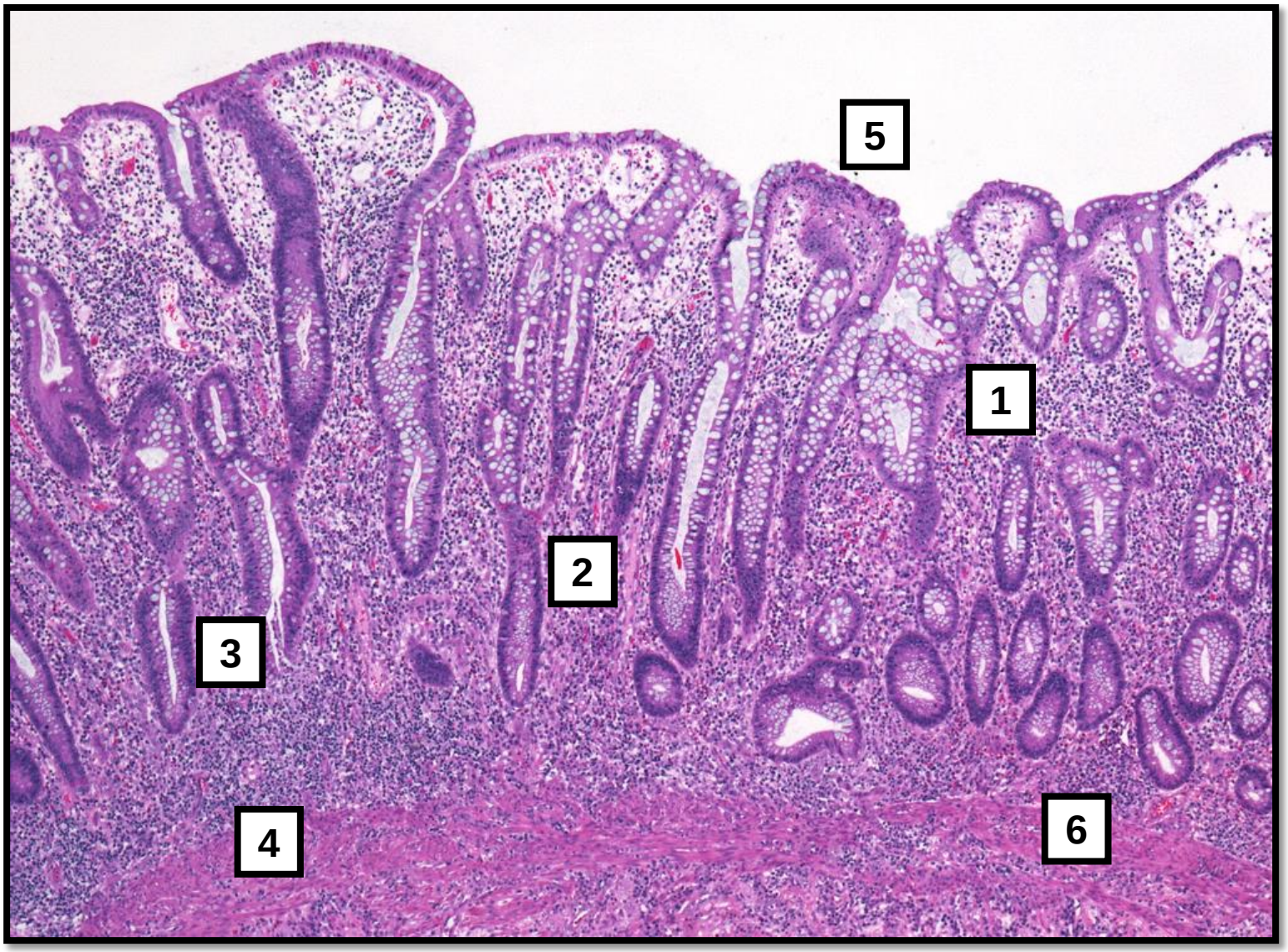
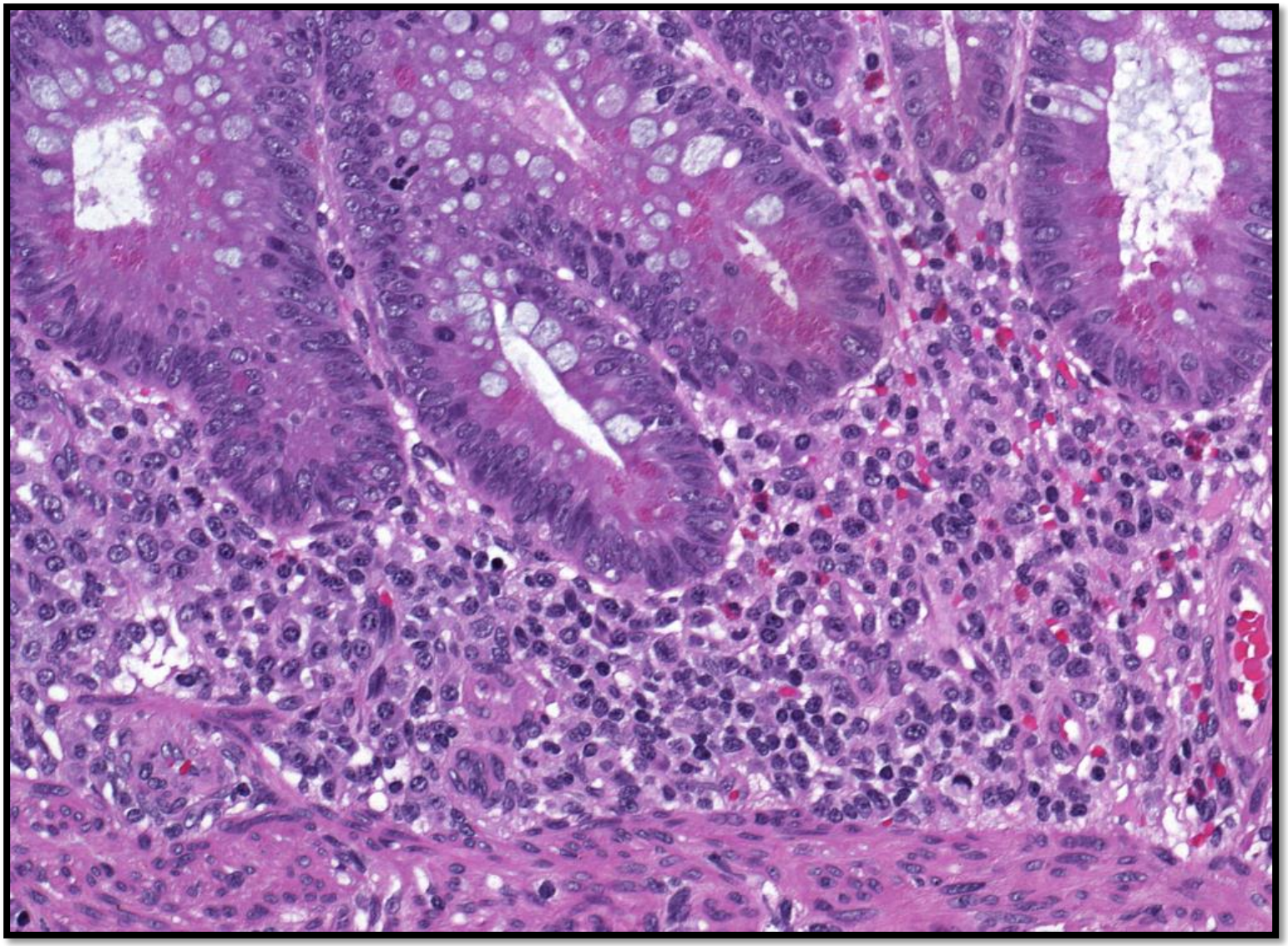


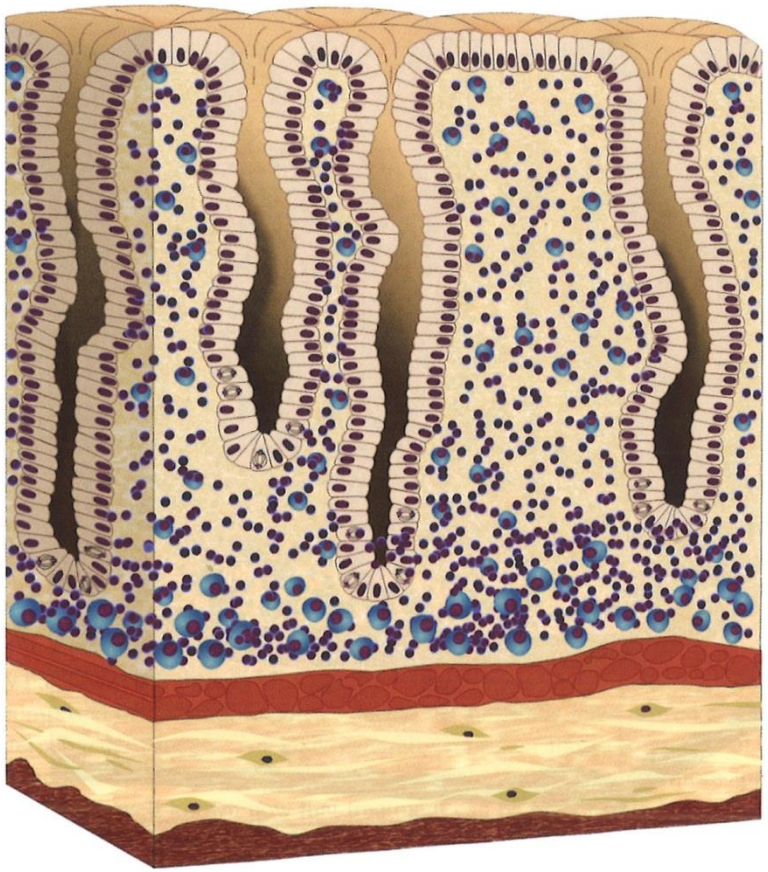
Langner Gastroenterol Clin North Am 2012

Ulcerative Colitis

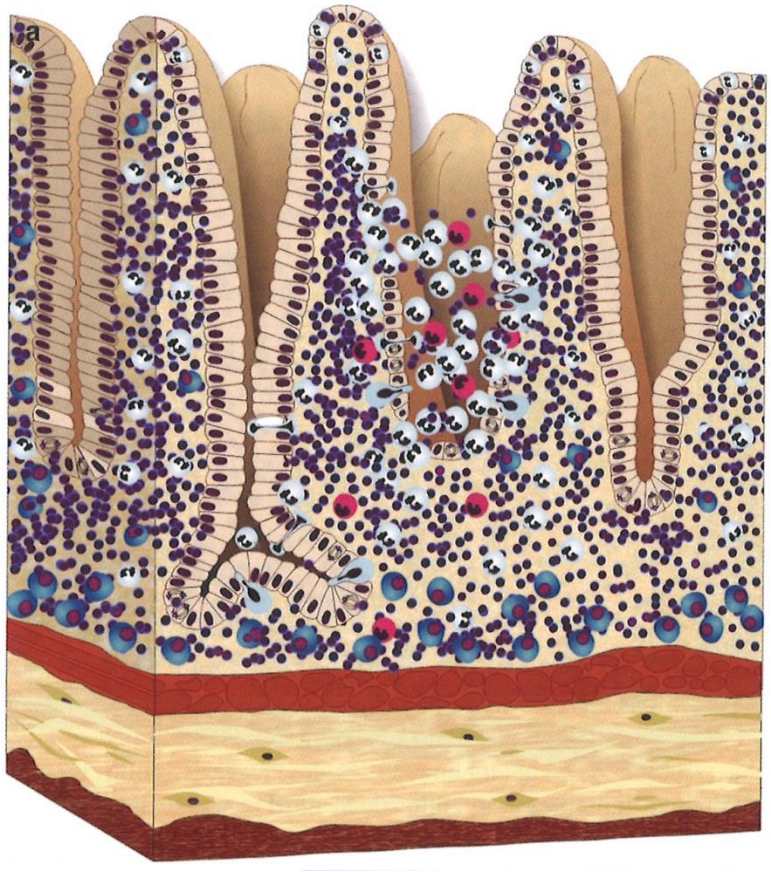


Langner Gastroenterol Clin North Am 2012

Ulcerative Colitis



Inactive ulcerative colitis



Active ulcerative colitis

Crohn‘s Disease: Key Histologic Features

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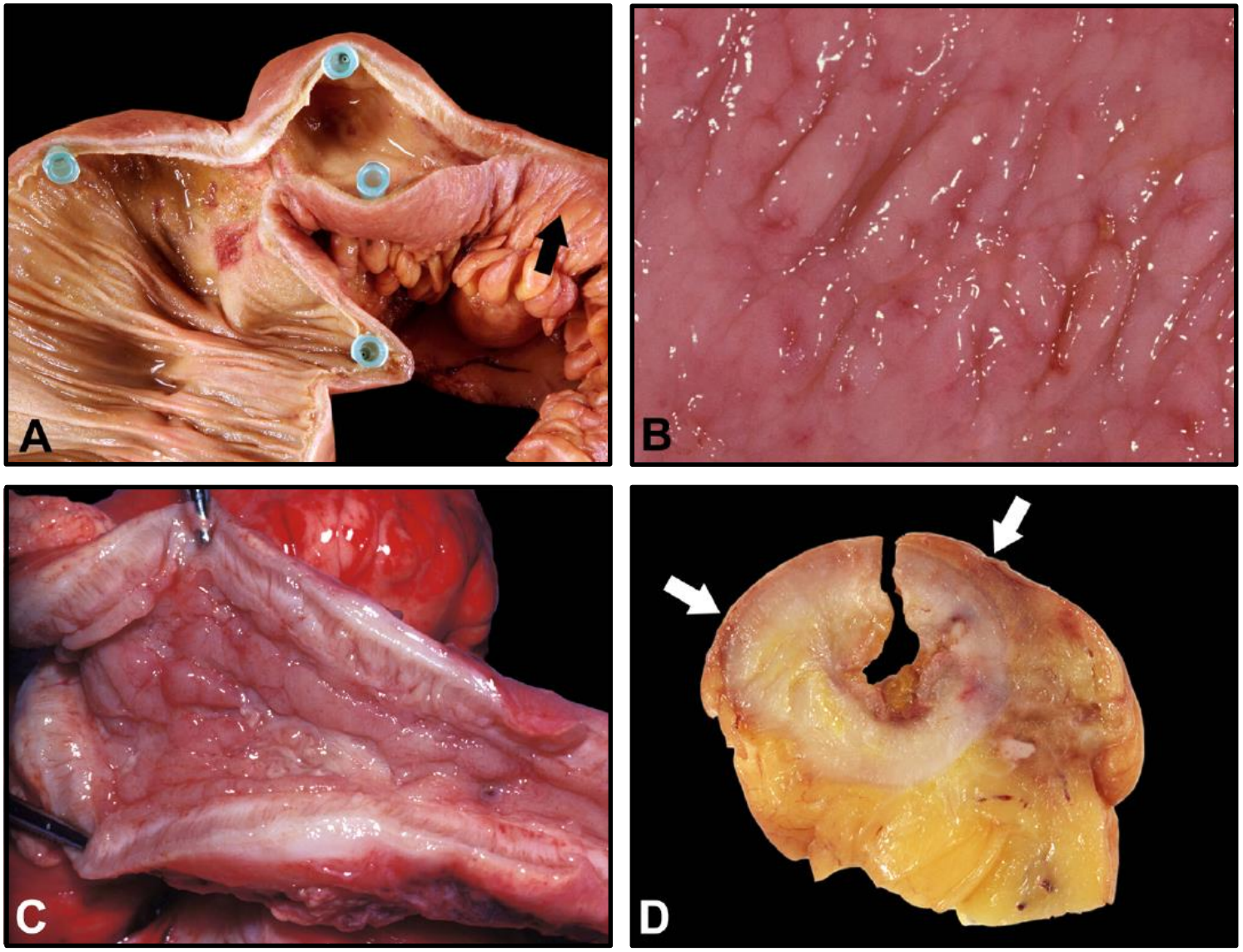
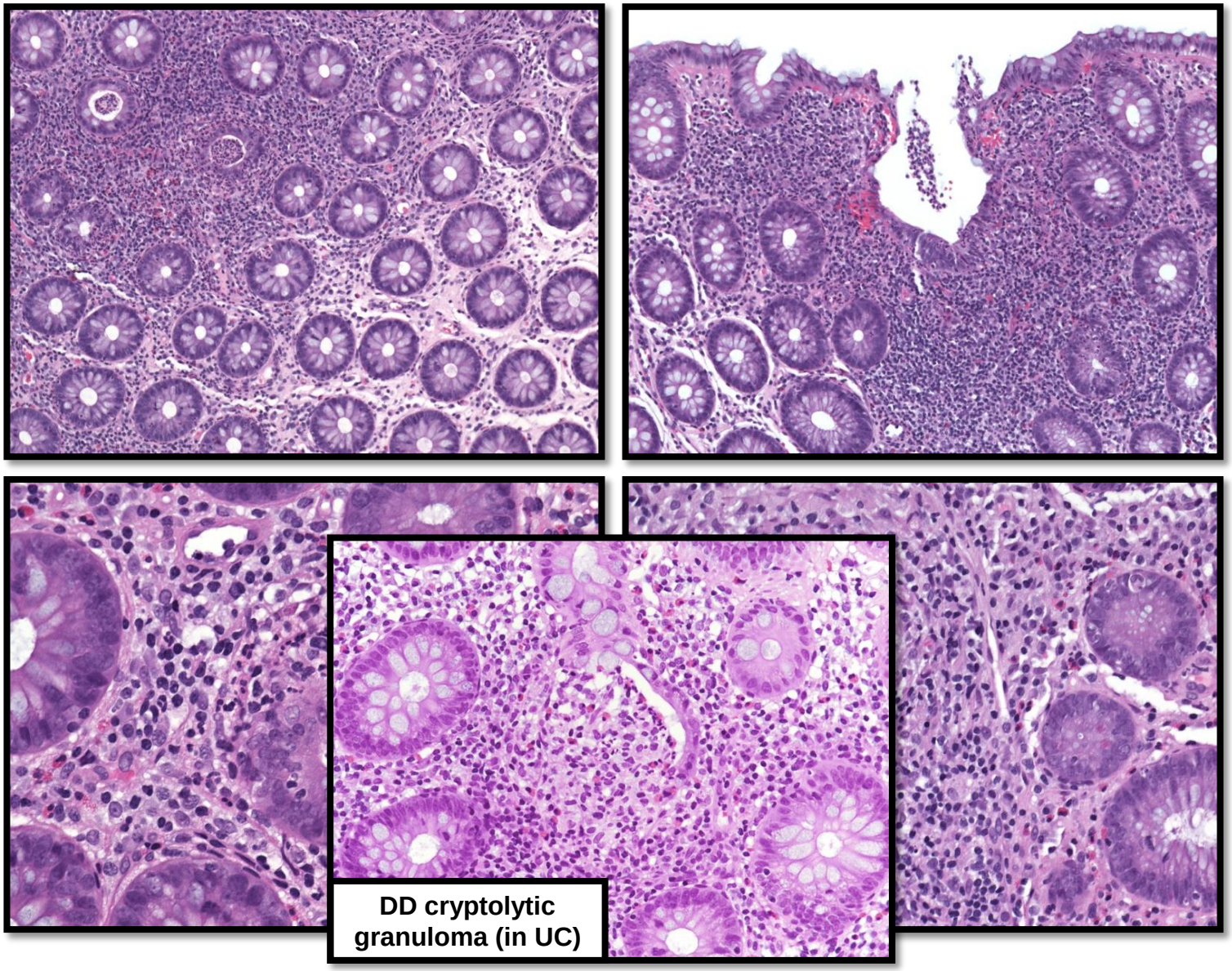
- Segmental (discontinuous) transmural disease (“skip lesions” with fissures, fistulae) with variable rectal involvement and variable disease severity (worse proximally)
- Focal (discontinuous) crypt architectural abnormalities (focal crypt distortion, branching etc.)
- Focal (discontinuous) inflammation (focal mononuclear expansion of the lamina propria, focal cryptitis). Focal or patchy inflammation may be observed in biopsies submitted from different parts of the bowel or may be present within tissue fragments of the same biopsy, not rarely within a single biopsy specimen
- Aphthous erosions/ulcers and deep fissures, any location
- Epithelioid cell granulomas (not crypt related) in approximately 20% of mucosal biopsies (up to 50% in resections)
- Transmural lymphoid aggregates as well as fibromuscular obliteration and nerve fiber hyperplasia in the submucosa on surgical specimens

Crohn‘s Disease

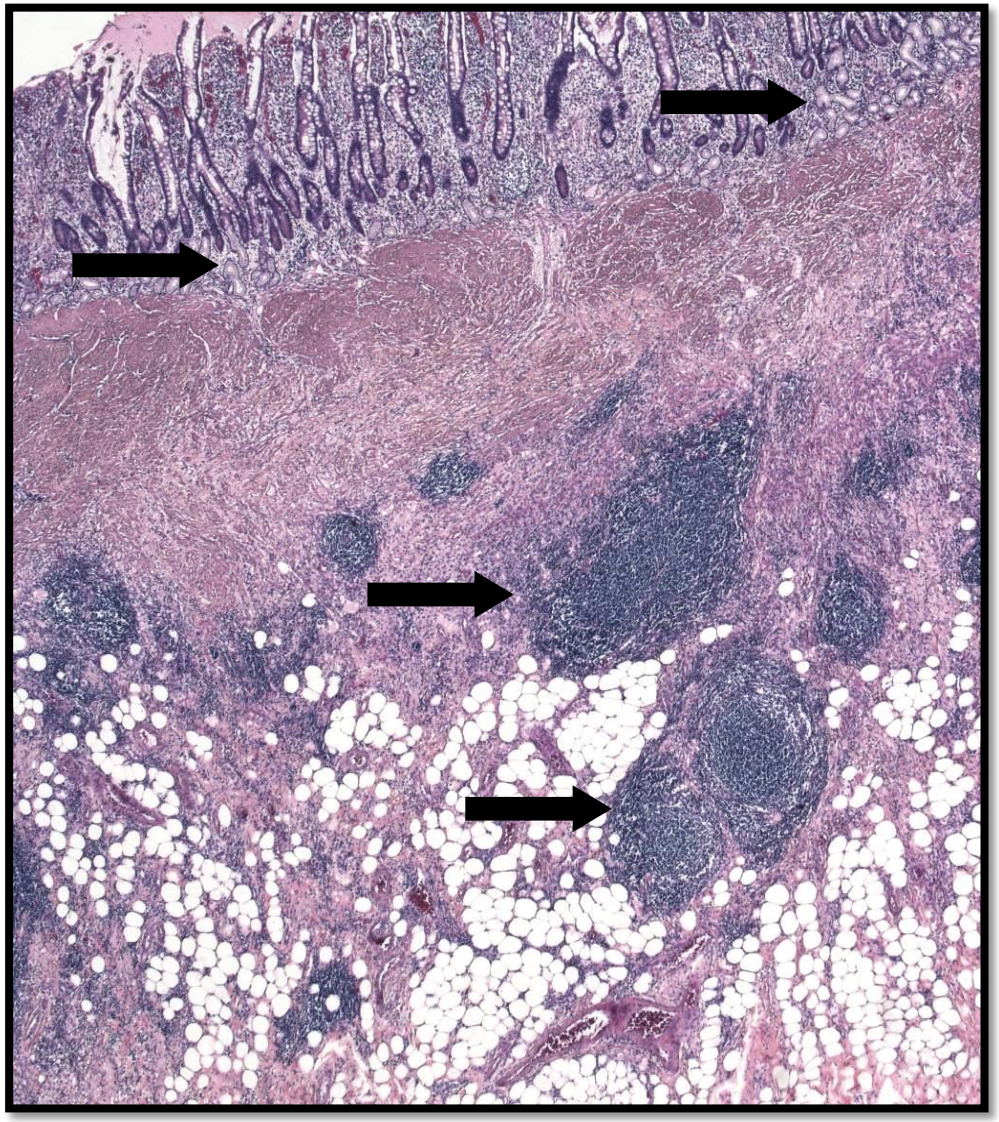


Langner et al. Virchows Arch 2014

Crohn‘s Disease



Crohn‘s Disease



Active Crohn‘s disease

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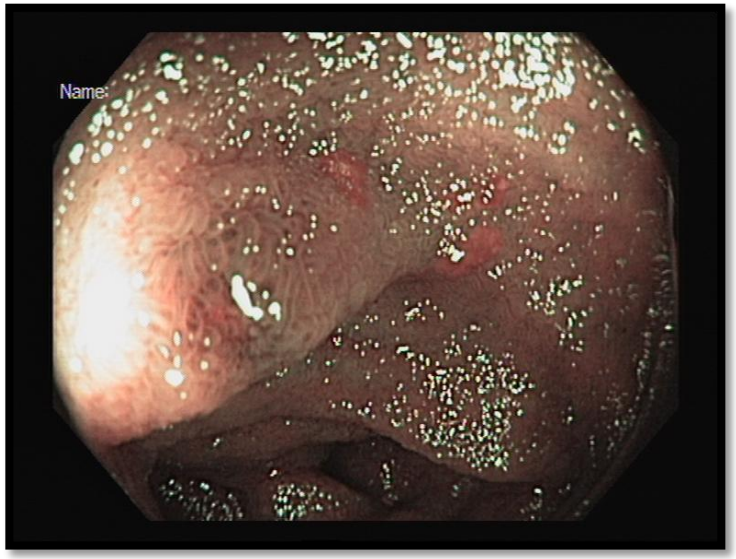
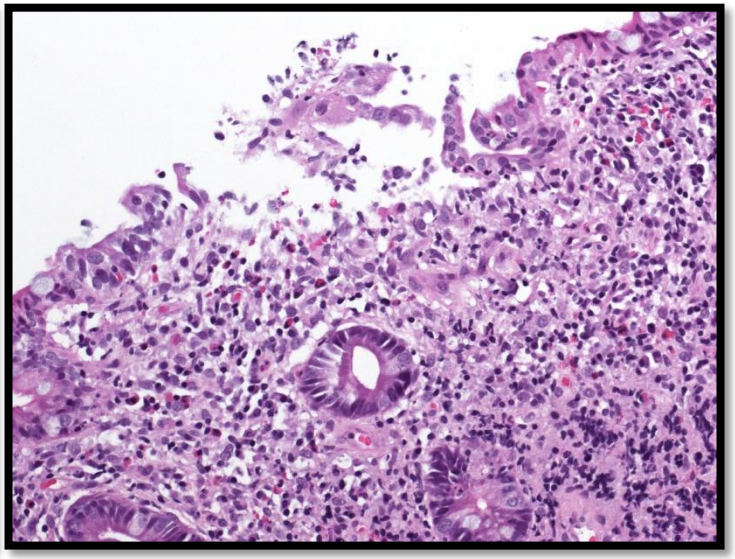
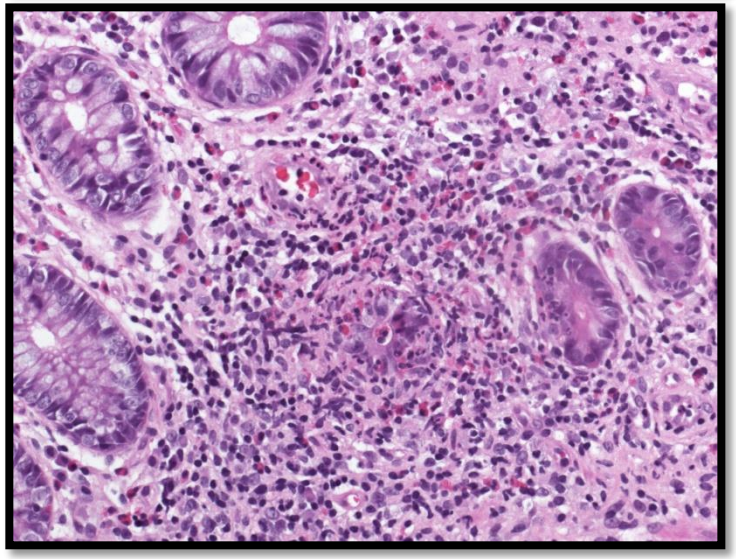
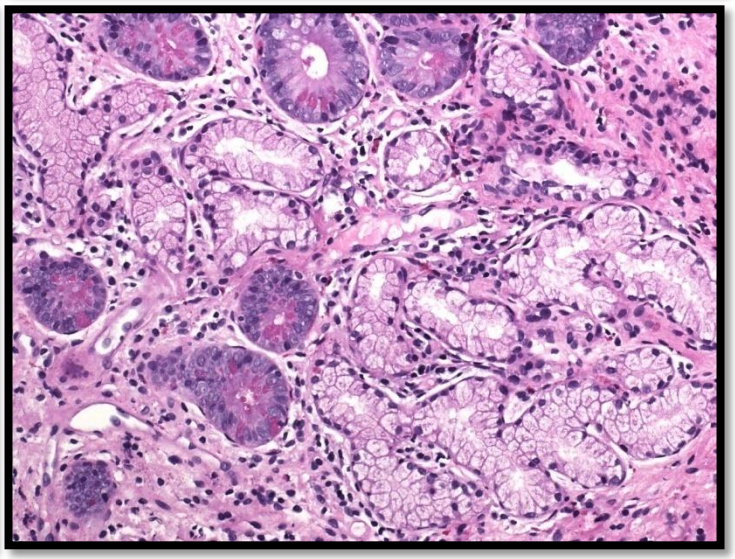
www.medunigraz.at/ENGIP

Case October 2012









Crohn‘s Disease: Distribution within the GI Tract

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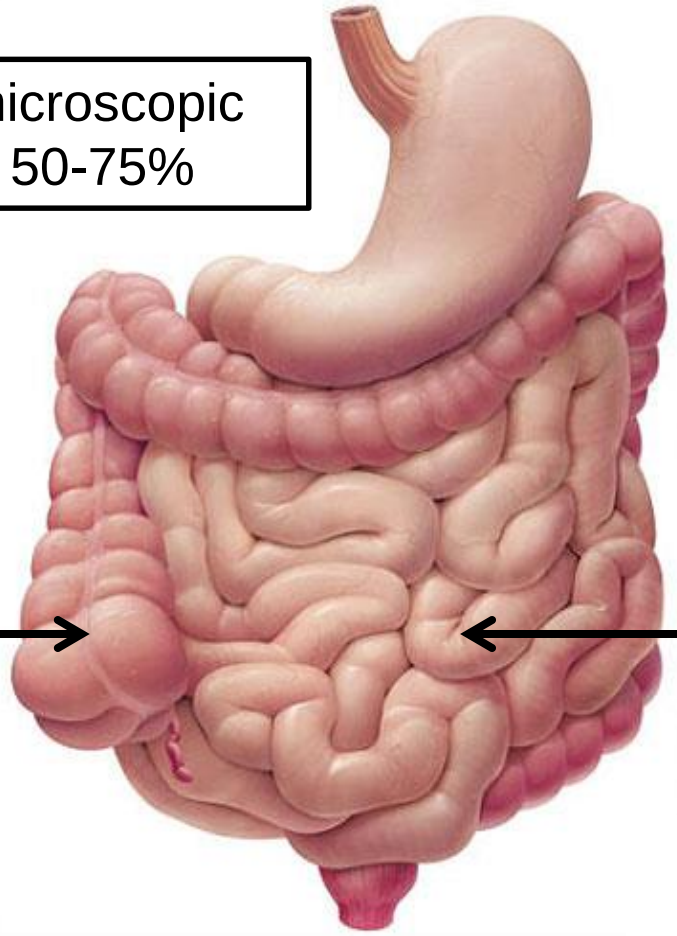
Stomach: microscopic lesions in 50-75%



Isolated large bowel CD in 15-25%

Isolated small bowel CD in 30-35%

CD affecting both small and large bowel in 40-50%

Upper Gastrointestinal Tract in Crohn‘s Disease

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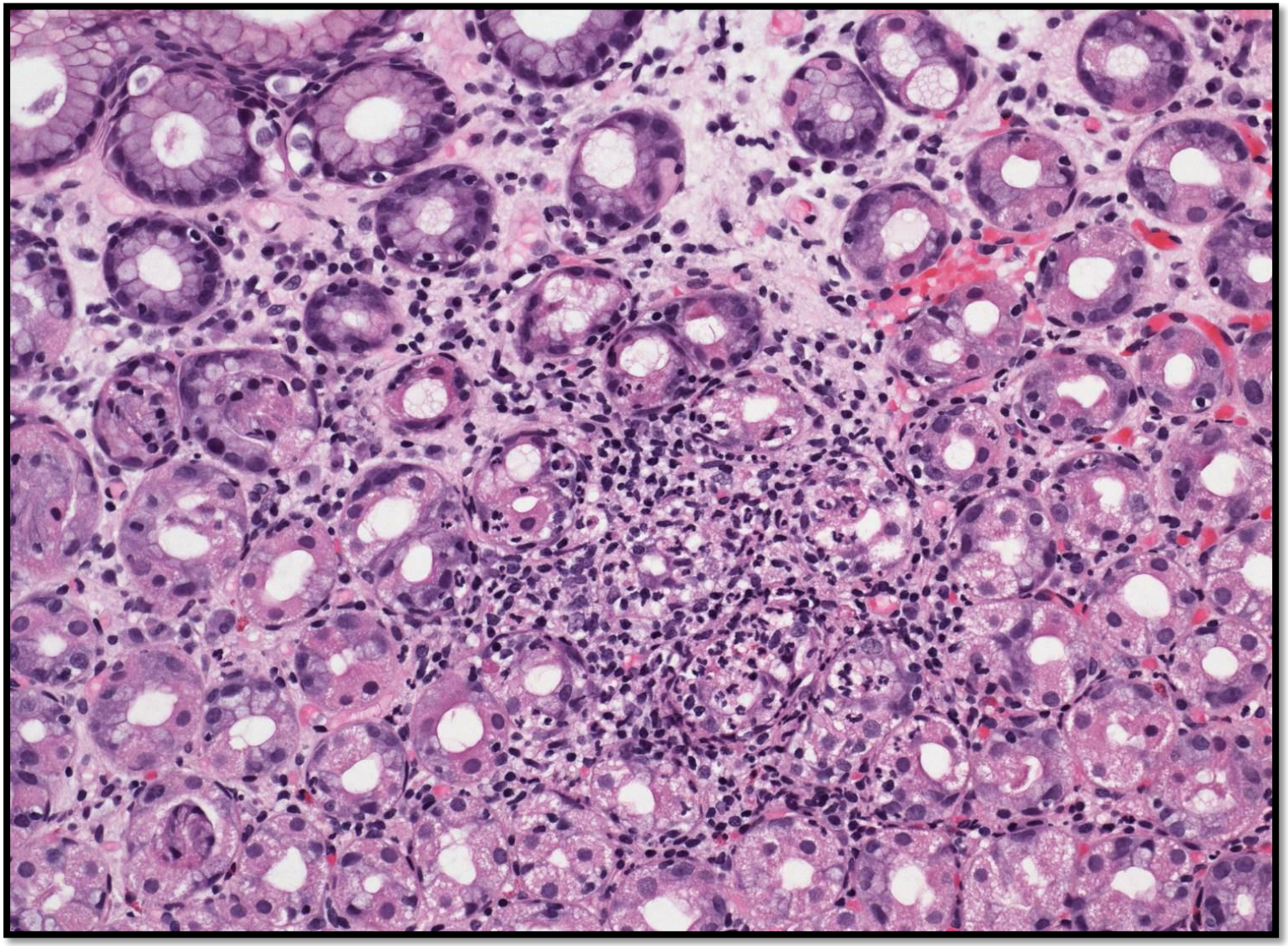

Upper GI Tract Involvement in IBD – Part 1

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Author	Crohn's disease	Ulcerative colitis
Oberhuber et al. 1997	Focal gastritis (antrum 48%, corpus 14%), granulomas 15%	Not analysed
Wright & Riddell 1998	Focal gastritis 31%, focal duodenitis 40%, granulomas 9%.	Not analysed
Oberhuber et al. 1998	Focal duodenitis in 43 cases (12%), 33 with granulomas Focal bulbitis in 73 cases (13%), 22 with granulomas Focal antrumgastritis in 238 cases (42%), 11 with granulomas Focal corpusgastritis in 113 cases (37%), 6 with granulomas	Not analysed
Yao et al. 2000	Microaggregates 55%, granulomas 18%	No microaggregates and no granulomas in 23 cases
Parente et al. 2000	Focal gastritis in 40/94 (43%) HP-negative cases, granulomas in 5 cases	Focal gastritis in 5/42 (12%) HP-negative cases, bust also in 11/57 (19%) HP-negative non-IBD control cases, no granulomas

Upper GI Tract Involvement in IBD – Part 2

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Author	Crohn's disease	Ulcerative colitis
Sharif et al. 2002	Focal gastritis in 28/43 (65%) children; granulomas in 6 (14%); mild to moderate chronic non-HP gastritis in 35%	Focal gastritis in 5/24 (21%) children; mild to moderate chronic non-HP Gastritis in 50%
Kundhal et al. 2003	Focal antrumgastritis in 52%	Focal antrumgastritis in 8%
Xin et al. 2004	Focal gastritis in 1/19 (5%)	Focal gastritis in 1/8 (12.5%)
Petrolla et al. 2008	Focal gastritis 36% CD ileitis vs. 5% non-CD ileitis	Not analysed
Lin et al. 2010	Not analysed	Focal gastritis in 17/59 (29%) cases, one case with granulomas
Sonnenberg et al. 2011	Focal gastritis in 11/208 (5%) cases	No focal gastritis in 280 cases
Hummel et al. 2012	Focal gastritis in 48/70 (69%) children; focal duodenitis in 13 (19%) children	Focal gastritis in 6/33 (18%) children; no focal duodenitis
Mc Hugh et al. 2013	13/25 (52%) children with focal gastritis have CD; 31/262 (11.8%) cases with focal gastritis (19 x IBD, of these 9 x CD and 9 x UC)	3/25 (12%) children with focal gastritis have UC; 31/262 (11.8%) cases with focal gastritis (19 x IBD, of these 9 x CD and 9 x UC)
Ushiku et al. 2013	Focal gastritis in 34/62 (55%) children; granulomatous gastritis in 9/62 (15%)	Focal gastritis in 17/57 (30%) children; no granulomatous gastritis

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Selected Difficulties in Histological IBD Diagnosis

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- Ulcerative colitis and Crohn's disease show overlapping morphological features, and a precise diagnosis may be difficult, if not impossible in 10-15% of cases
- **Terminology: Indeterminate colitis (on resection specimens) or IBD unclassified, IBDU (on biopsies)**
- In fact, there is no single pathognomonic histological feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histological observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn's disease

Selected Difficulties in Histological IBD Diagnosis

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	Infectious colitis	UC active phase	UC in remission	Crohn's disease
Crypt architectural abnormalities / basal plasmacytosis	- / (+)	+++	++/+	+/(+)
Metaplastic Paneth cells / mucin depletion	-	++	++ / (+)	(+)
Mononuclear cells ↑	(+)	+++	-	(+)
Neutrophils	+++	+++	-	++
Granulomas / giant cells	(+)	(+)	-	++
Continous morphologic changes	(+)	+++	++ / (+)	-
Discontinous morphologic changes	+	-	- / (+)	++

Selected Difficulties in Histological IBD Diagnosis

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- **Terminology: Indeterminate colitis (on resection specimens) or IBD unclassified, IBDU (on biopsies)**
- In fact, there is no single pathognomonic histological feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histological observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn's disease
- Differential diagnosis between ulcerative colitis and Crohn's disease may also be challenging when patients are under therapy: mucosal healing in ulcerative colitis may cause discontinuous inflammation (and "rectal sparing")

Rectal Sparing and Skip Lesions in Ulcerative Colitis: A Comparative Study of Endoscopic and Histologic Findings in Patients Who Underwent Proctocolectomy

Mee Joo, MD and Robert D. Odze, MD, FRCPC†*

TABLE 1. Clinical, Demographic, and Pathologic Features of the 56 Study Patients

Parameter	Result
Mean age at colectomy (y) (range)	42 (19-77)
Male/female	28/28
Mean age at UC diagnosis (y) (range)	32 (9-68)
Tobacco use [n (%)]	9 (16.1%)
Alcohol use [n (%)]	15 (26.8%)
Mean duration of UC ± SD (mo) (range)	93 ± 80.4 (6-336)
Mean follow-up duration ± SD (mo) (range)*	33 ± 42 (3-156)
Indication for colectomy [n (%)]	
Refractory disease	45 (80.4%)
Fulminant colitis	10 (17.8%)
Perforation	1 (1.8%)
# Preoperative endoscopies	168
Mean No. of endoscopies per patient ± SD (range)	3 ± 2 (1-10)
# Preoperative biopsies	512
Mean No. of biopsies per patient ± SD (range)	9.1 ± 9.3 (1-49)
Extent of disease [n (%)]	
Pancolitis	36 (64.3%)
Subtotal	12 (21.4%)
Left-sided	8 (14.3%)
Mean colitis score ± SD, biopsies	2.7 ± 0.9†
Mean colitis score ± SD, resections	3.2 ± 0.8†
Medication use [n (%)]	
Corticosteroids	53 (94.6%)
Aminosalicylates	48 (85.7%)
Immunomodulators	34 (60.7%)
Anti-TNF-α	8 (14.3%)
Enema therapy (steroid or aminosalicylates) [n (%)]	33 (58.9%)

*calculated as the duration of time from the first visit to the colon resection.
†$P < 0.01$ for comparison of biopsies and resections.

TABLE 2. Prevalence Rates of Rectal Sparing and Patchiness of Disease in the Study Patients

	Endoscopy (%)	Biopsy (%)	Colectomy (%)
Rectal sparing	18 (32.1)	17 (30.4)*	3 (5.4)**
Absolute	N/A	3 (5.4)	0 (0)
Relative	N/A	14 (25)*	3 (5.4)**
Patchiness of disease	17 (30.4)	14 (25)*	6 (10.7)
Absolute	NA	2 (3.6)	4 (7.1)
Relative	NA	12 (21.4)*	2 (3.6)

NA indicates not applicable.
*$P < 0.01$ compared with endoscopy series.
**$P < 0.05$ compared with biopsy series.

Joo & Odze. Am J Surg Pathol 2010

PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis

E V Loftus Jr, G C Harewood, C G Loftus, W J Tremaine, W S Harmsen, A R Zinsmeister, D A Jewell, W J Sandborn

Gut 2005;**54**:91–96. doi: 10.1136/gut.2004.046615

Table 1 Endoscopic characteristics of inflammatory bowel disease among PSC-IBD cases

	PSC-UC (n = 61)	PSC-CD* (n = 5)	PSC-IC† (n = 5)	Total (n = 71)
Pancolitis	56 (92%)	2 (40%)	4 (80%)	62 (87 %)
Rectal sparing	32 (52%)	3 (60%)	2 (40%)	37 (52%)
Ileitis	19/37 (51%)	3/4 (75%)	1/4 (25%)	23/45 (51%)

*These patients were found to have: (1) colonic stricture requiring right hemicolectomy, later with ulcers at anastomosis; (2) perianal fistula, ileal stricture, and contracted caecum; (3) aphthous ulcers in the distal colon; (4) pancolitis which was patchy on biopsy; and (5) linear ulcers on one colonoscopy but pancolitis on four subsequent procedures.

†These patients were found to have: (1) aphthous ulcers throughout the colon; (2) linear ulcers on one colonoscopy but pancolitis seen subsequently; (3) focal inflammation endoscopically in the descending colon and hepatic flexure but diffuse inflammation on biopsy; (4) proximal colitis elsewhere but pancolitis here; and (5) patchy histological inflammation with a single granuloma, diffuse pancolitis on subsequent examinations.

PSC-IBD, inflammatory bowel disease associated with primary sclerosing cholangitis; CD, Crohn's disease; IC, indeterminate colitis; UC, ulcerative colitis.

Loftus et al. Gut 2005

PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis

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Gut 2005;**54**:91–96. doi: 10.1136/gut.2004.046615

Table 2 Clinical features and outcomes of PSC-IBD (cases) and controls with CUC

	PSC-IBD (n = 71)	Comparison CUC (n = 142)
Demographics and clinical features		
Males (n (%))	46 (65%)	92 (65%)
Age at IBD diagnosis (y) (median (range))	32 (9–73)	28 (6–80)
Age at PSC diagnosis (y) (median (range))	42 (10–71)	NA
Pancolitis (n (%))	62 (87%)	76 (54%)
Rectal sparing (n (%))	37 (52%)	8 (6%)
Ileitis (n (%))	23/45 (51%)	10 (7%)
Outcomes		
CRN total (n (%))	18 (25%)	15 (11%)
Low grade dysplasia (n (%))	8 (11%)	7 (5%)
High grade dysplasia (n (%))	3 (4%)	4 (3%)
Colorectal cancer (n (%))	7 (10%)	4 (3%)
IBD diagnosis to CRN (y) (median (range) interval)	12.7 (0.3–41)	12.1 (1 day–5.8)
PSC diagnosis to CRN (y) (median (range) interval)	4.9 (0.03–20)	NA
Surgery (n (%))	31 (28%)	66 (46%)
IPAA (n (%))	14 (13%)	43 (30%)
Brooke ileostomy (n (%))	5 (7%)	21 (15%)
Ileorectal anastomosis (n (%))	7 (6%)	0 (0%)
Pouchitis (n (%))	10/14 (71%)	13/30 (30%)
Stomal varices (n (%))	2/5 (40%)	0 (0%)

PSC-IBD, inflammatory bowel disease associated with primary sclerosing cholangitis; CUC, chronic ulcerative colitis; CRN, colorectal neoplasia; IPAA, ileal pouch-anal anastomosis; NA, not applicable.

Loftus et al. Gut 2005

Dig Dis Sci (2013) 58:2608–2614
DOI 10.1007/s10620-013-2697-7

ORIGINAL ARTICLE

Medizinische Universität Graz

The Phenotypic Expression of Inflammatory Bowel Disease in Patients with Primary Sclerosing Cholangitis Differs in the Distribution of Colitis

David F. Schaeffer · Lay Lay Win · Sara Hafezi-Bakhtiari · Maria Cino · Gideon M. Hirschfield · Hala El-Zimaity

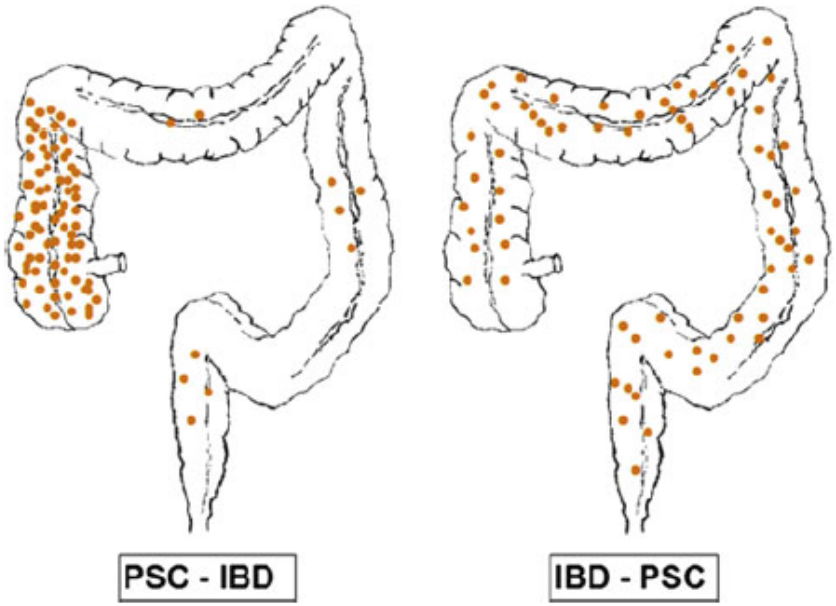


Fig. 2 The distribution of colitis depends on primary disease presentation. If liver disease precedes the colitis (PSC-IBD) the colitis has a right-sided predominance. When colitis precedes liver disease (IBD-PSC), the pattern is predominantly pancolitic in distribution

Table 3 Pathologic features of colitis in PSC-IBD patients and IBD-PSC patients

Feature	Primary liver diagnosis [PSC-IBD; ($n = 56$)]	Primary colonic diagnosis [IBD-PSC; ($n = 41$)]
Extent of disease [n (%)]		
Pancolitis	19 (33)*	23 (56)*
Right sided	30 (53)**	8 (20)**
Left sided	7 (12)	10 (24)
Proctitis	0 (0)	0 (0)
Colitis grade [mean (%)]		
Grade 0—negative	0 (0)	0 (0)
Grade 1—mild	48 (86)	39 (95)
Grade 2—moderate	8 (14)	2 (5)
Grade 3—severe	0 (0)	0 (0)
Eosiniophilic infiltrate[a] [mean ± SD]		
Right	45 ± 14	29 ± 18
Left	18 ± 9	27 ± 16
Overall	63 ± 25	56 ± 34
Ulcer [mean (0)]	0 (0)	0 (0)

PSC primary sclerosing cholangitis, *IBD* inflammatory bowel disease

[a] Eosinophil count/3 hpf

* $p = 0.002$; ** $p = 0.018$

Schaeffer et al. Dig Dis Sci 2013

Medizinische Universität Graz

Distinctive inflammatory bowel disease phenotype in primary sclerosing cholangitis

A Boudewijn de Vries, Marcel Janse, Hans Blokzijl, Rinse K Weersma

Table 2 Phenotypic features primary sclerosing cholangitis - inflammatory bowel disease *n* (%)

Ref.	IBD (*n*)	PSC-IBD (*n*)	Proctitis		Leftsided		Pancolitis		Backwash		Rectal Sparing		Diagnosis IBD
			IBD	PSC-IBD	IBD	PSC-IBD	IBD	PSC-IBD	IBD	PSC-IBD	IBD	PSC-IBD	
Olsson *et al*[9], 1991	1445	55	552 (38.2)	3 (5.5)	NA	NA	893 (61.8)	52 (94.5)	NA	NA	NA	NA	IBD[1,2]
Loftus *et al*[11], 2005	142	71	NA	NA	NA	NA	76 (53.5)	60 (84.5)	10 (7.0)	20 (28.2)	8 (5.6)	34 (47.9)	IBD[1,2]
Kaplan *et al*[14], 2007	0	36	NA	NA	NA	NA	NA	17 (47.2)	NA	4 (11.1)	NA	2 (5.6)	IBD[1,2]
Sokol *et al*[15], 2008	150	75	138 (92.0)	68 (90.7)	130 (86.7)	68 (90.7)	91 (60.7)	49 (65.3)	36 (24.0)	14 (18.7)	20 (13.3)	15 (20.0)	IBD[1,2]
Joo *et al*[31], 2009	40	40	0	0	14 (35.0)	3 (7.5)	18 (45.0)	34 (85.0)	3 (7.5)	4 (10.0)	10 (25.0)	11 (27.5)	IBD[1,2]
Sano *et al*[32], 2010	60	20	18 (30.0)	1 (5.0)	19 (31.7)	1 (5.0)	21 (35.0)	7 (35.0)	NA	NA	NA	NA	IBD[1,2]
Ye *et al*[25], 2011	63	21	NA	NA	NA	NA	35 (55.6)	20 (95.2)	2 (3.2)	9 (42.9)	1 (1.6)	8 (38.1)	IBD[1,2]
Jørgensen *et al*[33], 2012	0	110	NA	NA	NA	3 (2.7)	NA	60 (54.5)	NA	17 (15.5)	NA	73 (66.4)	IBD[1,2]
O'toole *et al*[35], 2012	2649	103	209 (7.9)	1 (1.0)	649 (24.5)	23 (22.3)	663 (25.0)	56 (54.4)	NA	NA	NA	NA	IBD[1,2]
Boonstra *et al*[12], 2012	0	380	NA	9 (2.4)	NA	34 (8.9)	NA	219 (57.6)	NA	NA	NA	NA	IBD[1,2]
Boonstra *et al*[12], 2012[3]	80	80	4 (5.0)	2 (2.5)	16 (20.0)	2 (2.5)	35 (43.8)	52 (65.0)	2 (2.5)	4 (5.0)	1 (1.3)	8 (10.0)	IBD[1,2]
Schaeffer *et al*[34], 2013	0	97	NA	0	NA	17 (17.5)	NA	42 (43.3)	NA	NA	NA	NA	IBD[1,2]
Sinakos *et al*[30], 2013	0	129	NA	NA	NA	16 (12.4)	NA	76 (58.9)	NA	15 (11.6)	NA	31 (24.0)	IBD[1,2]
Mean			28.8%	13.4%	39.6%	18.8%	47.5%	64.7%	12.3%	16.7%	9.9%	30.9%	

[1]IBD Endoscopic findings; [2]IBD Histological findings (biopsies); [3]Subgroup analysis. PSC: Primary sclerosing cholangitis; IBD: Inflammatory bowel disease; NA: Not available.

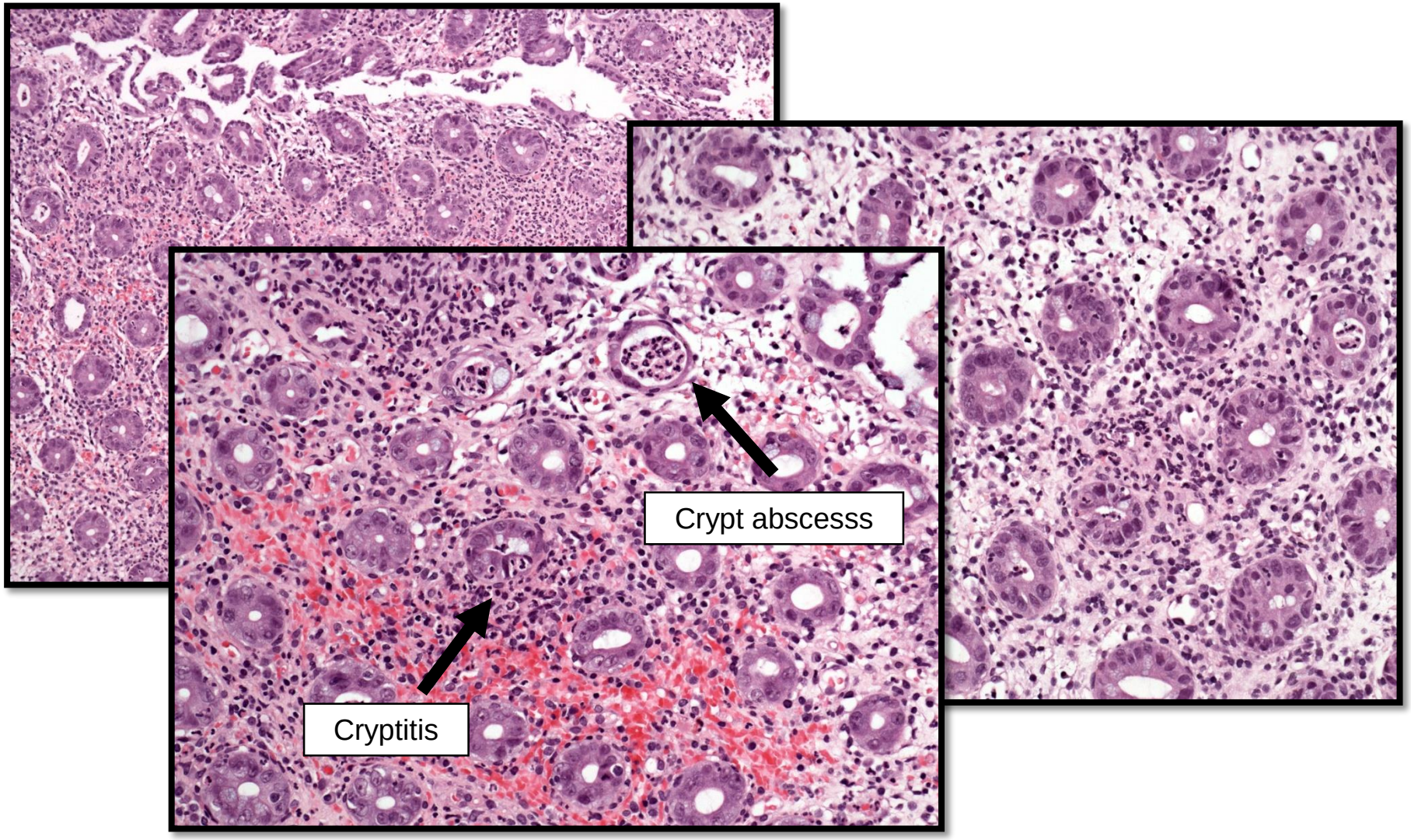
De Vries et al. World J Gastroenterol 2015

Differential Diagnosis

- **Prolonged infection**

  In early-onset IBD (2-6 weeks after the first symptoms), the classical histological features may not be fully established yet

Infectious Colitis



Infectious Colitis

Please note:
In early-onset IBD (2-6 weeks after the first symptoms), the classical histological features may not be fully established yet, whereas in prolonged infection mild features indicating chronic disease may be observed.

Differential Diagnosis

- **Prolonged infection**

  In early-onset IBD (2-6 weeks after the first symptoms), the classical histological features may not be fully established yet

- **Superinfection in established IBD**
  - Bacterial infection
  - Virus infection, particularly CMV

AP&T Alimentary Pharmacology and Therapeutics

Medizinische Universität Graz

Review article: cytomegalovirus and inflammatory bowel disease

K. Sager*, S. Alam*, A. Bond*, L. Chinnappan* & C. S. Probert*,†

Results

Cytomegalovirus reactivation is common in patients with severe colitis, with a reported prevalence of 4.5–16.6%, and as high as 25% in patients requiring colectomy for severe colitis. The outcome for this group of patients appears worse than that for patients without reactivation; however, reported remission rates following treatment with anti-viral therapy are as high as 71–86%.

Conclusions

Evidence, although not conclusive, supports testing for CMV colonic disease in cases of moderate to severe colitis, by processing biopsies for haematoxylin and eosin staining with immunohistochemistry and/or, CMV DNA real-time polymerase chain reaction; and if present treating with ganciclovir.

Sager et al. Aliment Pharmacol Ther 2015

Medizinische Universität Graz

Detection of Cytomegalovirus in Patients with Inflammatory Bowel Disease: Where to Biopsy and How Many Biopsies?

Jeffrey D. McCurdy, MD, PhD, Felicity T. Enders, PhD,† Andrea Jones, MD,‡ Jill M. Killian, BS,† Edward V. Loftus, Jr, MD,* David H. Bruining, MD,* and Thomas C. Smyrk, MD‡*

TABLE 1. Sensitivity of H&E Stains for Detecting CMV in Patients with IBD with a Positive Diagnosis by IHC

Population	Prospective n/N (%; 95% CI)	Retrospective n/N (%; 95% CI)
Overall	16/63 (25; 15–36)	27/61 (44; 32–57)
Low-grade CMV[a]	8/45 (18; 7–29)	11/43 (26; 13–39)
High-grade CMV[b]	8/18 (44; 22–67)	16/18 (89; 74–100)

[a]Low-grade defined as 4 or fewer CMV inclusions from the biopsy with the highest viral density.

[b]High-grade defined as 5 or more CMV inclusions from the biopsy with the highest viral density.

Mc Curdy et al. Inflamm Bowel Dis 2015

Virchows Arch (2015) 466:533–539
DOI 10.1007/s00428-015-1741-8

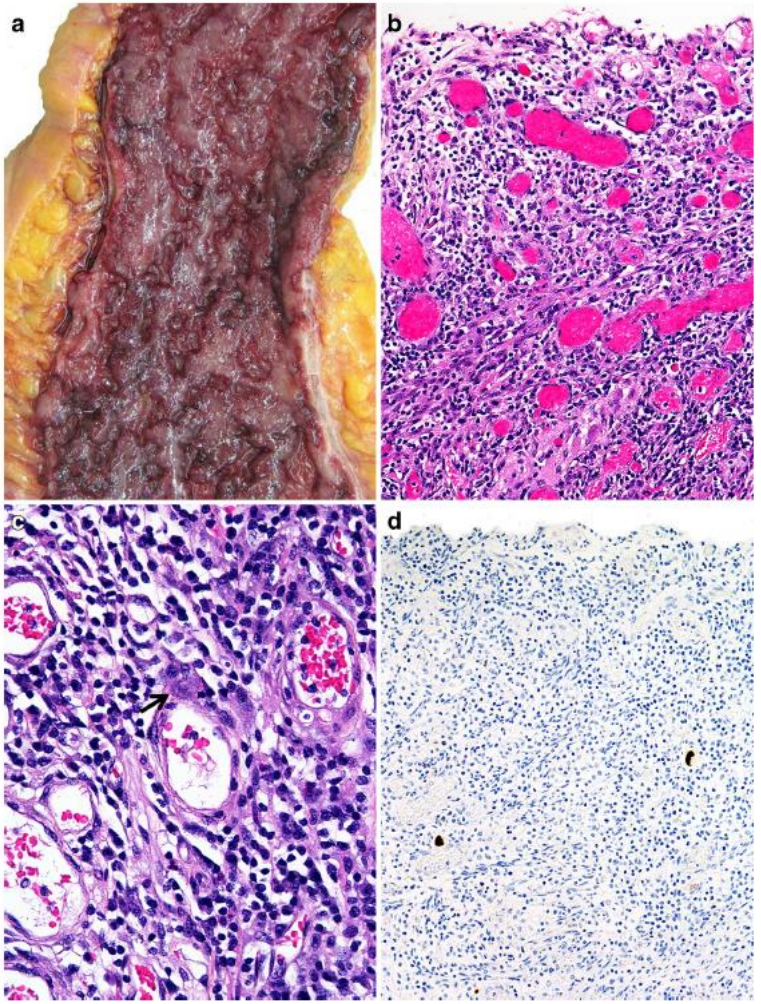
ORIGINAL ARTICLE

Medizinische Universität Graz

Diagnosing cytomegalovirus in patients with inflammatory bowel disease—by immunohistochemistry or polymerase chain reaction?

Nina Zidar · Ivan Ferkolj · Katja Tepeš · Borut Štabuc · Nika Kojc · Tina Uršič · Miroslav Petrovec

Immunohistochemistry (positive cells per mm^2)			Real-time polymerase chain reaction (number of viral copies per mg)		
Base of ulcer	Edge of ulcer	Uninvolved mucosa	Base of ulcer	Edge of ulcer	Uninvolved mucosa
0.37	0.32	0	10	128	3
0.47	0.25	0	2670	802	1
0	0.1	0	0	172	0
0.35	0.1	0	1404	35	0
0.08	0.06	0	3809	1049	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0



Obtain material from mucosal defects (granulation tissue): immunohistochemistry and PCR render comparable results.
Please note: the number of positive cells is small (→ many biopsy specimens and many levels).

Zidar et al. Virchows Arch 2015

Medizinische Universität Graz

European consensus on the histopathology of inflammatory bowel disease☆

F. Magro[a,*,1], C. Langner[b,1], A. Driessen[c], A. Ensari[d], K. Geboes[e], G.J. Mantzaris[f], V. Villanacci[g], G. Becheanu[h], P. Borralho Nunes[i], G. Cathomas[j], W. Fries[k], A. Jouret-Mourin[l], C. Mescoli[m], G. de Petris[n], C.A. Rubio[o], N.A. Shepherd[p], M. Vieth[q], R. Eliakim[r] on behalf of the European Society of Pathology (ESP) and the European Crohn's and Colitis Organisation (ECCO)[2]

ECCO-ESP statement 15

Testing for CMV reactivation on colonic biopsy should be performed in all patients with severe colitis refractory to immunosuppressive therapy. In addition, testing should be performed in biopsies with prominent granulation tissue derived from large ulcers [EL2]. Semiquantitative immunohistochemistry, reporting the number of infected cells and/or the number of CMV positive biopsy fragments, may have a predictive value. Testing in other groups should be on a case by case basis [EL5]

Magro et al. J Crohns Colitis 2013

Medizinische Universität Graz

European consensus on the histopathology of inflammatory bowel disease☆

F. Magro[a,*,1], C. Langner[b,1], A. Driessen[c], A. Ensari[d], K. Geboes[e], G.J. Mantzaris[f], V. Villanacci[g], G. Becheanu[h], P. Borralho Nunes[i], G. Cathomas[j], W. Fries[k], A. Jouret-Mourin[l], C. Mescoli[m], G. de Petris[n], C.A. Rubio[o], N.A. Shepherd[p], M. Vieth[q], R. Eliakim[r] on behalf of the European Society of Pathology (ESP) and the European Crohn's and Colitis Organisation (ECCO)[2]

In patients with UC the risk for reactivation of a latent cytomegalovirus (CMV) infection is increased and is significantly higher than in CD (10%–56.7% vs. 0%–29.6%).[75] Reactivated CMV infection increases the severity of disease and is associated with higher rates of morbidity and hospitalization.[76,77] The risk of CMV reactivation depends on the type of immunosuppressive drugs used and is higher in steroid-refractory than in steroid-responding patients (25–30% vs. 0–9.5%).[75,78] CMV reactivation should be routinely sought for in case of flares or unresponsiveness to treatment. Although CMV viral inclusions may be detected on H&E-stained slides, immunohistochemistry or molecular techniques such as quantitative PCR, are more sensitive techniques with a high diagnostic accuracy.[75]

Magro et al. J Crohns Colitis 2013

Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

J.F. Rahier[a,*], F. Magro[b,c,d], C. Abreu[e], A. Armuzzi[f], S. Ben-Horin[g], Y. Chowers[h], M. Cottone[i], L. de Ridder[j], G. Doherty[k], R. Ehehalt[l], M. Esteve[m], K. Katsanos[n], C.W. Lees[o], E. MacMahon[p], T. Moreels[q], W. Reinisch[r,s], H. Tilg[t], L. Tremblay[u], G. Veereman-Wauters[v], N. Viget[w], Y. Yazdanpanah[x], R. Eliakim[y], J.F. Colombel[z], on behalf of the European Crohn's and Colitis Organisation (ECCO)

Medizinische Universität Graz

ECCO statement OI 4A

Screening for CMV infection is not necessary before starting immunomodulator therapy [EL4]. In patients with acute steroid-resistant colitis, CMV should be excluded, preferably by tissue PCR or immunohistochemistry, before increasing immunomodulator therapy [EL3]. In case of severe steroid-resistant colitis with CMV detected in the mucosa during immunomodulator therapy, antiviral therapy should be initiated and discontinuation of immunomodulators considered until colitis symptoms improve [EL5]. In case of systemic CMV disease, immunomodulator therapy must be discontinued [EL2]

Histopathology combined with **immunohistochemistry** (IHC, using monoclonal antibodies against CMV immediate early antigen) are highly specific and sensitive for verifying CMV infection in tissue or biopsies.

The most commonly used technique for diagnosis of CMV infection and disease is detection of CMV DNA through **PCR in tissue biopsies and in the blood**. The advantages of PCR are rapid results, high sensitivity, the potential for qualitative and quantitative testing.

Rahier et al. JCC 2014

Original Article

Cytomegalovirus Infection in Ulcerative Colitis is Related to Severe Inflammation and a High Count of Cytomegalovirus-positive Cells in Biopsy Is a Risk Factor for Colectomy

Edyta Zagórowicz,[a,b] Marek Bugajski,[a,b] Paulina Wieszczy,[b] Anna Pietrzak,[a,b] Agnieszka Magdziak,[c] Andrzej Mróz[b,d]

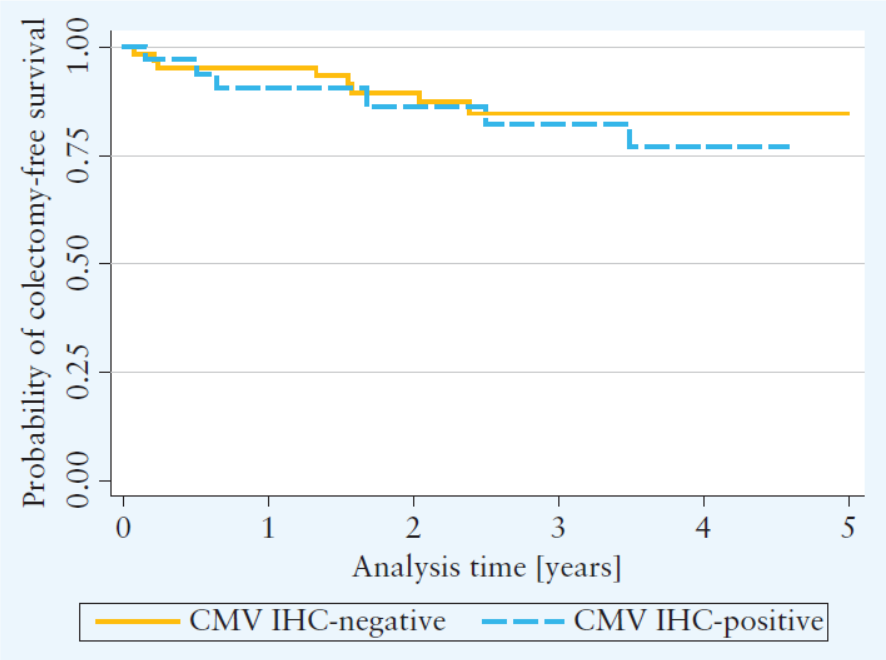


Figure 2. Kaplan-Meier colectomy-free survival estimates in CMV IHC-positive and CMV IHC-negative patients. CMV, cytomegalovirus; IHC, immunohistochemistry.

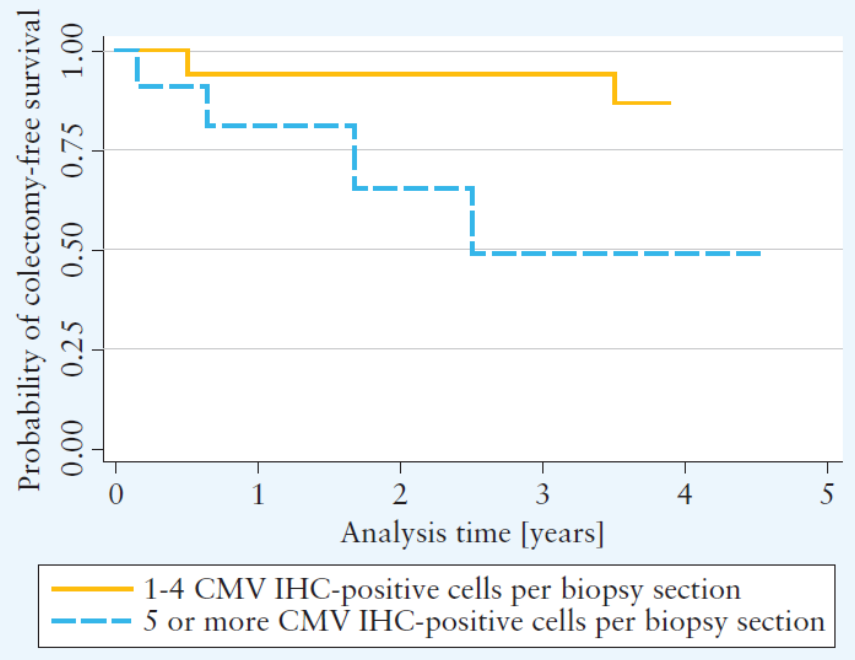


Figure 3. Kaplan-Meier colectomy-free survival estimates in the CMV IHC-positive patients with ≥ 5 and < 1–4 IHC-positive cells per biopsy specimen. CMV, cytomegalovirus; IHC, immunohistochemistry.

Zagorowicz et al. JCC 2016

Differential Diagnosis

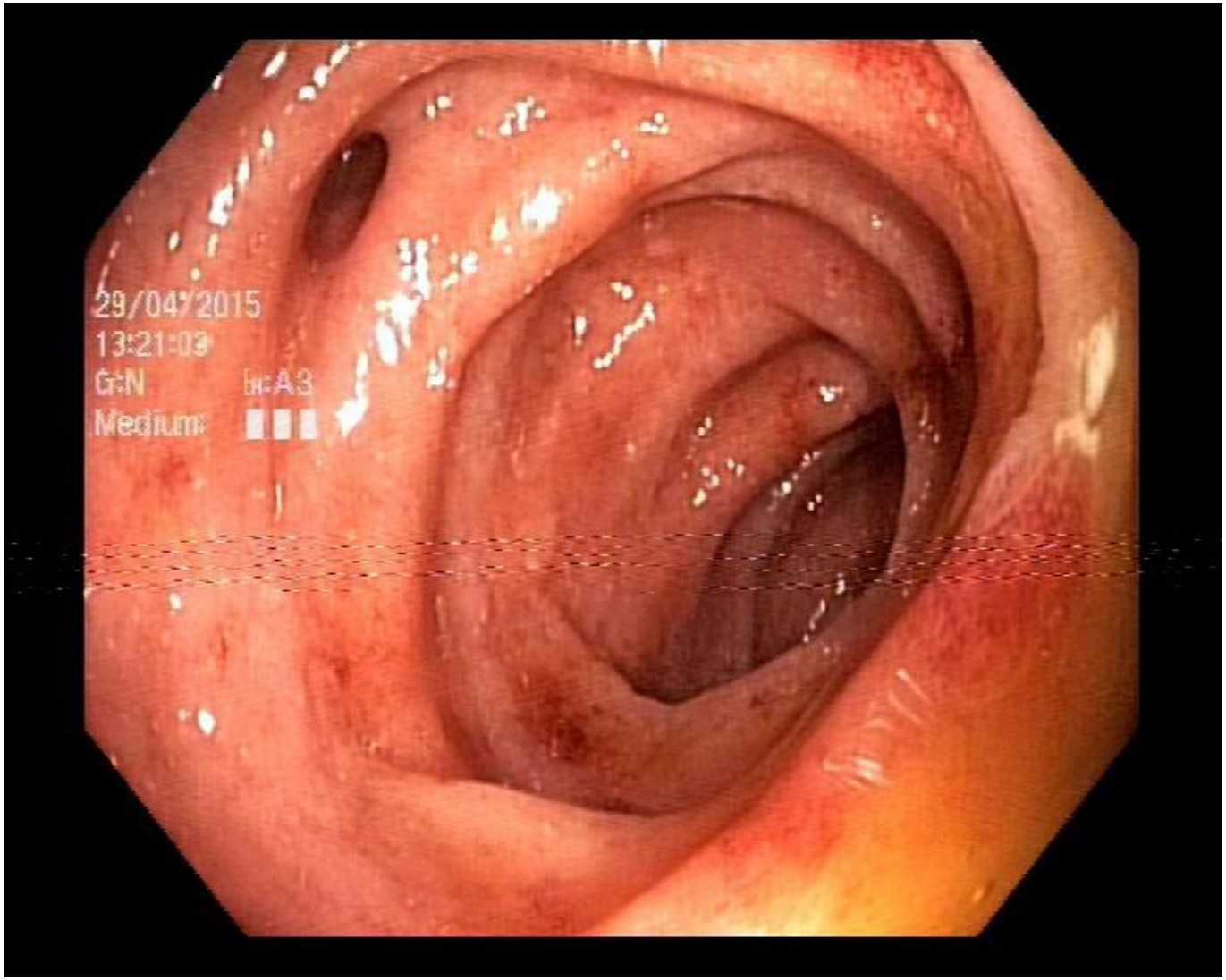
- **Prolonged infection**

  In early-onset IBD (2-6 weeks after the first symptoms), the classical histological features may not be fully established yet

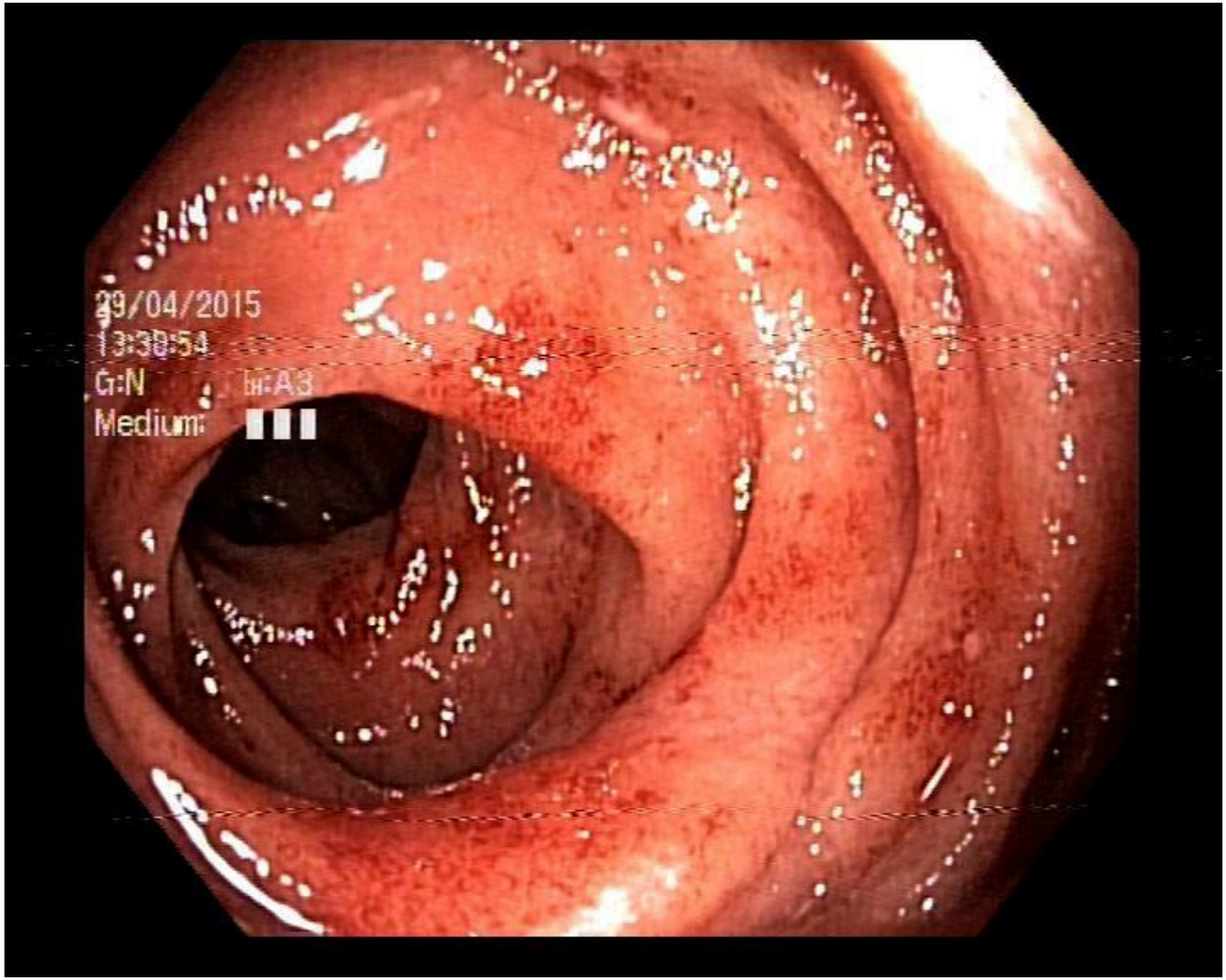
- **Superinfection in established IBD**
  - Bacterial infection
  - Virus infection, particularly CMV

- **Diverticular colitis (segmental colitis associated with diverticulosis/diverticulitis; SCAD)**
  - Chronic colitis with crypt architectural abnormalities, mixed inflammatory infiltrate, cryptitis and crypt abscess formation as well as basal plasmacytosis and occasional Paneth cell metaplasia in the interdiverticular luminal mucosa
  - Biopsies proximal and distal to the involved segment should be normal (in 10% extension into non-diverticular mucosa)

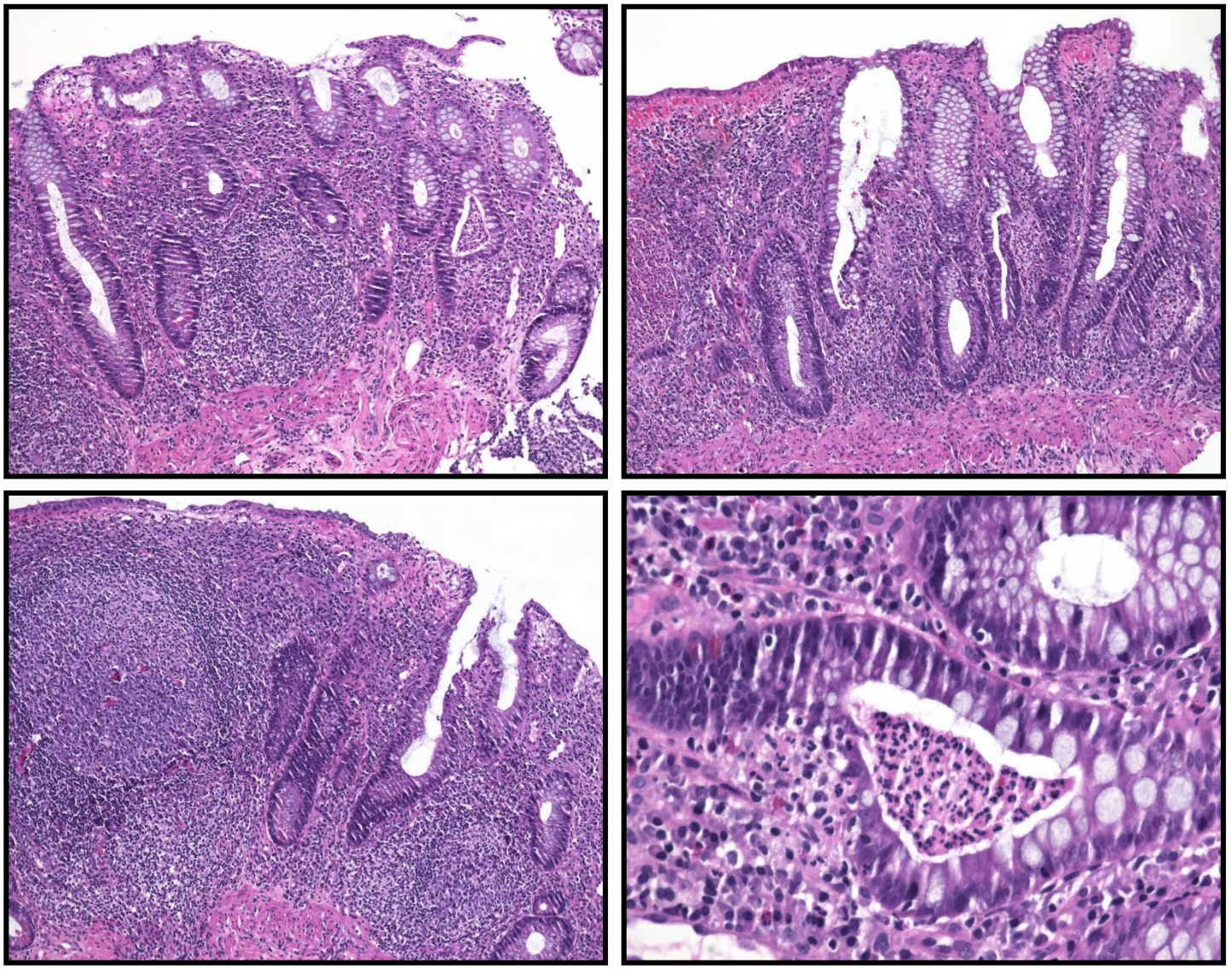
Segmental Colitis Associated with Diverticulosis (SCAD)



Segmental Colitis Associated with Diverticulosis (SCAD)



Segmental Colitis Associated with Diverticulosis (SCAD)



Segmental Colitis Associated with Diverticulosis (SCAD)

Medizinische Universität Graz

Histopathological feature	No. of patients (%)
Mononuclear cell increase in lamina propria	23 (100)
Cryptitis	23 (100)
With crypt abscesses	14 (61)
Basal lymphoid aggregates	23 (100)
Distortion of crypt architecture	20 (87)
Basal plasmacytosis	14 (61)
Surface epithelial sloughing	14 (61)
Paneth cell metaplasia	11 (48)
Granulomatous cryptitis	6 (26)
Villiform configuration of mucosa	2 (9)
Pattern of inflammation	
Diffuse	18 (78)
Focal	5 (22)

TABLE 1. *Histopathological features of 23 cases of diverticular disease-associated colitis*

Makapugay & Dean. Am J Surg Pathol 1996

Iatrogenic pathology of the intestines

Aoife J McCarthy,[1] Gregory Y Lauwers[2] & Kieran Sheahan[1]
[1]*Department of Histopathology, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland, and* [2]*Department of Pathology, Massachusetts General Hospital, Boston, MA, USA*

Medizinische Universität Graz

Table 1. Patterns of injury and drugs most commonly associated with them

Pattern of injury	Drug
Focal active colitis	Ipilimumab, NSAIDs, sodium phosphate
Chronic colitis	Mycophenolate, ipilimumab, TNF-inhibitors, NSAIDs, rituximab
Apoptosis excess	Ipilimumab, mycophenolate, antimetabolites, TNF-inhibitors, colchicine, taxane, NSAIDs, sodium phosphate enema
Dilated damaged crypts and apoptosis	Mycophenolate, sodium phosphate enema, 5-FU
Small intestinal villous atrophy (coeliac disease-like)	Olmesartan, mycophenolate, ipilimumab, colchicine, azathioprine, NSAIDs
Microscopic colitis	Olmesartan, ipilimumab, NSAIDs, lansoprazole, ranitidine, ticlopidine, simvastatin, paroxetine, carbamazepine, penicillin, flutamide, cyclo3 fort, sertraline
Increased mitoses	Colchicine, taxane
Erosions/ulcers	NSAIDs, KCl, kayexalate
Diaphragms/stenosis	NSAIDs
Ischaemic colitis	NSAIDs, kayexalate, cocaine, diuretics, sumatriptan, dopamine, methysergide, amphetamines, oestrogens, ergotamine, alostron, digitalis, pseudoephedrine, vasopressin, interferon
Pseudomembranous colitis	Antibiotics, proton pump inhibitors
Crystal deposition	Kayexalate, kalimate, sevelamer, cholestyramine, bisphosphonates
Strictures	KCL, pancreatic enzymes
	Laxatives
	Corticosteroids
	NSAIDs, oestrogen-progesterone drugs, plavix
	Corticosteroids
	i.v. cyclosporin

TNF inhibitors: tumour necrosis factor alpha inhibitors; 5-FU: fluorouracil;

Mycophenolate mofetil (MMF)

Immune checkpoint inhibitors (Ipilimumab, Nivolumab, Pembrolizumab etc.)

McCarthy et al. Histopathology 2015

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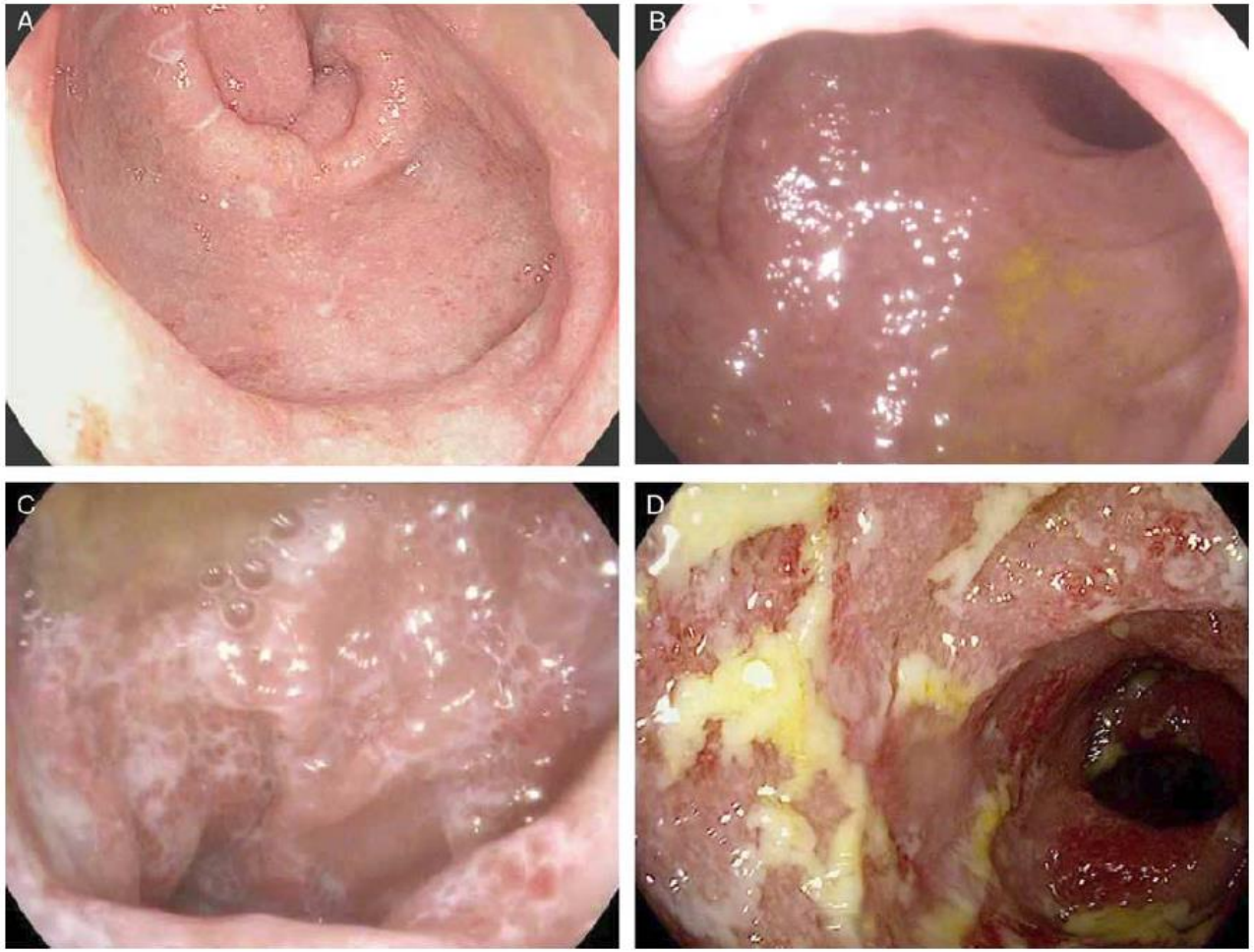
Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies

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



Chen et al. Am J Surg Pathol 2017

Medizinische Universität Graz

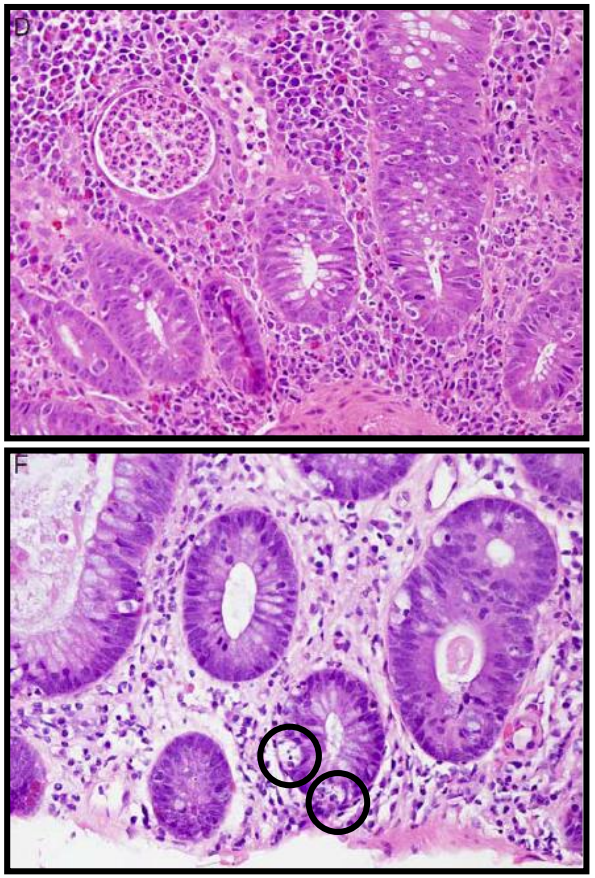
Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies

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

TABLE 2. Histopathologic Features of Anti-PD-1 Colitis

Patient	1	2	3	4	5
Pattern	**Active Colitis With Apoptosis**				
Colon sites involved	Right, left	Distal transverse	Right, left	Transverse, sigmoid	Rectum
Colon sites uninvolved				Rectum	
Extent of involvement	Diffuse	Patchy	Diffuse	Diffuse	Diffuse
Neutrophilic cryptitis	Y	Y	Y	Y	Y
Neutrophilic microabscesses	Y	Y	Y	Y	Y
Expansion of lamina propria	N	N	N	N	N
Basal lymphoplasmacytosis	N	N	N	N	N
Architectural changes	N	N	N	N	N
Paneth cell metaplasia	N	N	N	N	N
Increased crypt epithelial apoptosis	Y	Y	Y	Y	Y
Crypt atrophy/dropout	Y	Y	Y	Y	Y
Increased intraepithelial lymphocytes	N	N	N	N	N
Surface epithelial injury	N	N	Y	N	N
Thickened subepithelial collagen table	N	N	N	N	N

NA indicates not available; N, no; Y, yes.



Chen et al. Am J Surg Pathol 2017

JIM Original Article

doi: 10.1111/joim.12744

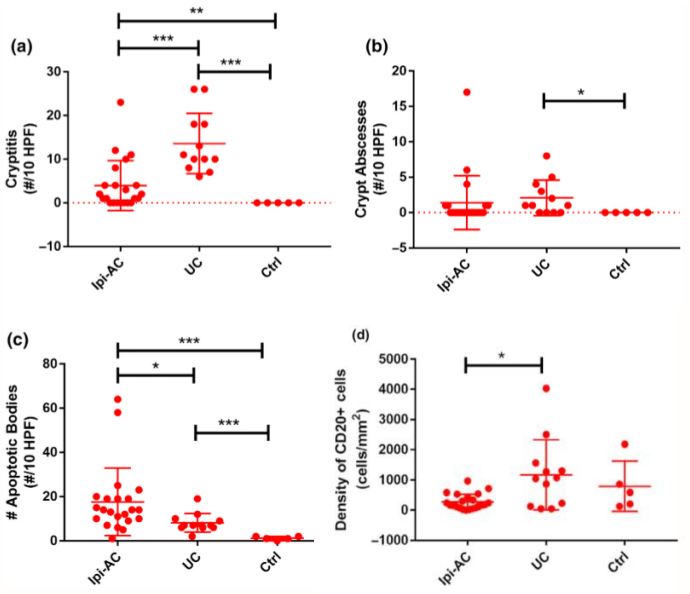
Histopathological and immunophenotypic features of ipilimumab-associated colitis compared to ulcerative colitis

B. L. Adler[1,#], M. K. Pezhouh[2,#], A. Kim[3], L. Luan[2], Q. Zhu[2], F. Gani[4], M. Yarchoan[5], J. Chen[6], L. Voltaggio[2], A. Parian[3], M. Lazarev[3], G. Y. Lauwers[6], T. M. Pawlik[7], E. A. Montgomery[2], E. Jaffee[5,8], D. T. Le[5], J. M. Taube[2,8] & R. A. Anders[2,8]

From the Departments of [1]Rheumatology; [2]Pathology; [3]Gastroenterology; [4]Surgery; [5]Medical Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [6]Department of Pathology, H. Lee Moffitt Cancer and Research Institute, Tampa, FL; [7]Department of Surgery, Ohio State University Wexner Medical Center, Columbus, OH; and [8]The Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD, USA

Table 1 *Demographic, clinical characteristics, endoscopic findings and histopathologic findings of ipilimumab-associated colitis (Ipi-AC, n = 22), ulcerative colitis (UC, n = 12) and normal controls (Ctrl, n = 5)*

	Ipi-AC (n = 22)	UC (n = 12)	Ctrl (n = 5)
Age (years)	62 ± 11.7	42 ± 17.8*	49 ± 16.6#
Sex (% female)	7 (32%)	8 (67%)	3 (60%)
Most common clinical symptom	Watery diarrhoea (n = 21, 95%)	Haematochezia (n = 9, 75%)	Watery diarrhoea (100%)
Most common endoscopic findings	Oedematous and erythematous mucosa (n = 8, 36%)	Erythematous, friable and ulcerated mucosa (n = 9, 75%)	Normal (n = 5, 100%)
Sites biopsied [N (%)]			
Left colon	22 (100%)	12 (100%)	5 (100%)
Right colon	11 (50%)	7 (58%)	2 (40%)
Ileum	6 (27%)	3 (25%)	3 (60%)
Presence of mucosal ulceration [N (%)]	10 (45%)	7 (58%)	0 (0%)#
Cryptitis			
Presence [N (%)]	16 (73%)	10 (83%)	0 (0%)##
Quantitative (#/10 HPF)	3.6 ± 5.3	11.6 ± 6.3***	0 ± 0##
Crypt abscesses			
Presence [N (%)]	7 (32%)	8 (67%)*	0 (0%)
Quantitative (#/10 HPF)	1.8 ± 3.8	1.8 ± 2.4	0 ± 0
Presence of basal plasmacytosis [N (%)]	3 (14%)	11 (92%)***	0 (0%)
Crypt distortion [N (%)]			
Presence (any)	5 (23%)	9 (75%)**	0 (0%)
Mild	4 (18%)	3 (25%)	0 (0%)
Moderate	1 (5%)	4 (33%)	0 (0%)
Severe	0 (0%)	2 (17%)	0 (0%)
Apoptotic Bodies (per 10 HPF)	16.6 ± 15.6	7.3 ± 4.7*	0.8 ± 0.4###



In conclusion, Ipi-AC has many overlapping features with ulcerative colitis but is a distinct pathologic entity with notable clinical and histopathological differences.

Adler et al. J Intern Med 2018

Virchows Arch
https://doi.org/10.1007/s00428-017-2267-z

CrossMark

INVITED ANNUAL REVIEW ISSUE

Medizinische Universität Graz

Immune checkpoint inhibitor colitis: the flip side of the wonder drugs

Naziheh Assarzadegan[1] · Elizabeth Montgomery[2] · Robert A. Anders[2]

CTLA4 inhibitors (ipilimumab)	*Autoimmune-like* enterocolopathy: – Lymphoplasmocytic expansion of lamina propria – Increased apoptosis and intraepithelial lymphocytes – Cryptitis and crypt elongation – Lack of basal plasmocytosis
PD1 inhibitors (pembrolizumab and nivolumab)	– *Active colitis pattern* with increased apoptosis – *Lymphocytic colitis pattern* – Features of chronicity in recurrent cases – Ruptured granuloma
PI3Kδ isoform inhibitor (idelalisib)	"*Triad*" of: – Intraepithelial lymphocytosis – Epithelial cell apoptosis – Neutrophilic cryptitis

Assarzadegan et al. Virchows Arch 2018

Agenda

Medizinische Universität Graz

- Normal Histology
- Basic Principles of IBD Diagnosis
  - Ulcerative Colitis
  - Crohn's Disease
- Difficulties in IBD Diagnosis and Differential Diagnosis
- **Grading of Activity**
- Dysplasia and Cancer
- Take Home Messages

Clinicopathological Correlation

- **Clinical significance**
  - Risk of relapse
  - Risk of dysplasia / carcinoma
- **Clinical remission does not imply endoscopic remission (endoscopic mucosal healing)**
- **Endoscopic remission does not imply histological remission (histological mucosal healing)**
- **Which is the aim of therapy?**
- **The problem of Crohn‘s disease (=discontinuous inflammation affects accuracy of diagnosis)**

Table 1 Histological Scoring Systems in Inflammatory Bowel Disease.

IBD	Author, year	Key features of score	Comments
Ulcerative colitis	Truelove & Richards, (1956)[56]	3 grade scale: 1) no inflammation 2) mild to moderate inflammation 3) severe inflammation	Partially validated. Extensive use in clinical trials and RCT's.
	Matts et al. (1961)[63]	5 grade scale: 1) normal to 5) ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all of its layers	No validated. Extensive use in clinical trials and RCT's.
	Watts et al. (1966)[65]	4 grade scale: 0) normal to 3) severe inflammatory change	Not validated
	Korelitz et al. (1976)[54]	Mucosal cell counting in addition to histologic features	Not validated Cell counting labor intensive
	Powell-Tuck et al. (1982)[55]	3 grade scale: 1) no inflammation 2) mild inflammation 3) moderate/severe inflammation	Not validated
	Keren et al. (1984)[62]	Dichotomized: active versus inactive inflammation	Not validated
	Friedman et al. (1986)[61]	4 grade scale: 0) normal 1) lamina propria inflammation 2) crypt injury 3) ulceration	Not validated. Subsequent use in clinical trials.
	Gomes et al. (1986)[51]	5 grade scale 0) normal, to 4) severe inflammation and active ulceration	Not validated Subsequent use in clinical trials
	Saverymutti et al. (1986)[60]	4 histological features: 1) enterocyte damage 2) crypt abnormalities 3) lamina propria involvement 4) acute inflammatory infiltrate in the lamina propria. Each graded from 0) normal to 3) severe.	Not validated Extensive clinical trials and RCT's.
	Floren et al. (1987)[49]	5 grade scale: 0) normal, to 5) severe inflammation and ulceration	Not validated. Extensive clinical trials and RCT's.
	Riley et al. (1991)[18]	6 histological features assessed; each graded on a 4 point scale	Partially validated. Prognosticates time to relapse. Extensive clinical trials and RCTs.
	Hanauer et al. (1993)[52]	4 grade scale: 0) normal colonic mucosa to 3) high grade active inflammatory bowel disease (combines histologic and endoscopic appearances)	Not validated. Central reference pathologist
	Sandborn et al. (1993)[64]	4 grade scale: 0) inactive chronic colitis to 3) severely active chronic colitis	Not validated.
	Geboes et al. (2000)[50]	7 histological features graded Scoring from 0 to 5.4	Partially validated. Subsequent clinical studies.
	Harpaz Score Fiel et al. (2003)[67]	Harpaz Score: 4 grade scale: 0) no cryptitis, 1) cryptitis < 50% crypts, 2) cryptitis > 50% crypts 4) ulcerations or erosions.	Partially validated. Subsequent clinical studies.
	Rutter et al. (2004)[27]	5 grade scale: 0) normal to 4) severe active inflammation	Not validated.
	Rubin et al. (2007)[26]	6 grade scale: 0) normal to 5) crypt abscesses in > 50% of crypts or erosion/ulceration	Not validated. Case control prospective grading by two pathologists to validate internally
	Baars et al. (2012)[66]	4 grade scale: 0) no active disease to 4) severe inflammation (numerous crypt abscesses)	Not validated.
Crohn's Disease	D'Haens et al. (1998)[57]	16 point grading system 8 histological and distribution features	Subsequently called the CGHAS and IGHAS in clinical trials^
	Nicholls et al. (1994)[59]	4 grades: 1) worse 2) no change, 3) improvement, 4) resolution of inflammation	Subjective. Not validated.
	Breese et al. (1995)[48]	5 histological features (ulceration, acute and chronic inflammation, crypt distortion, goblet cell depletion and villous atrophy). 4 grades: 0) normal to 3) severely inflamed.	Not validated.
	Baars et al. (2012)[66]	4 grade scale: 0) no active disease to 4) severe inflammation (numerous crypt abscesses)	Not validated.

Key: RCT, randomized controlled trial; CGHAS, Colonic Global Histologic Disease Activity Score; IGHAS, Ileal Global Histologic Disease Activity Score.

Bryant et al. J Crohns Colitis 2014

Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study

Talia Zenlea, MD[1], Eric U. Yee, MD[2], Laura Rosenberg, MD[1], Marie Boyle, MD[1], Kavinderjit S. Nanda, MD[1], Jacqueline L. Wolf, MD[1], Kenneth R. Falchuk, MD[1], Adam S. Cheifetz, MD[1], Jeffrey D. Goldsmith, MD[2] and Alan C. Moss, MD, FACG, AGAF[1]

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Table 3. Univariate analysis of factors associated with clinical relapse

Dichotomous variables	OR	95% CI	*P* value
Male gender	0.9	0.4–1.8	0.8
Remission >6 months	0.6	0.2–1.4	0.2
Steroids within 12 months	0.8	0.2–2.1	0.3
Current thiopurine	0.8	0.3–2.2	0.7
Current mesalamine	0.5	0.2–1.1	0.08
Non-smoker	3.8	0.2–62	0.4
NSAID use	1.6	0.6–4	0.3
Extraintestinal features	0.8	0.2–3.4	0.9
Endoscopy score >0	**2.8**	**1.6–4.9**	**0.0002**
Histology score >3	**3.5**	**1.6–6.4**	**0.0001**
Continuous variables			
Age			0.9
White cell count			0.06
Hct			0.7
ESR			0.4
CRP			0.3
Histology score (0–22)			**0.0001**

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

Bold values are statistically significant.

Association of histology scores with relapse

A multivariate model (nominal logistic) that included mesalamine use, white cell count, endoscopy score, and histology grade was generated to determine independent associations with the primary outcome.

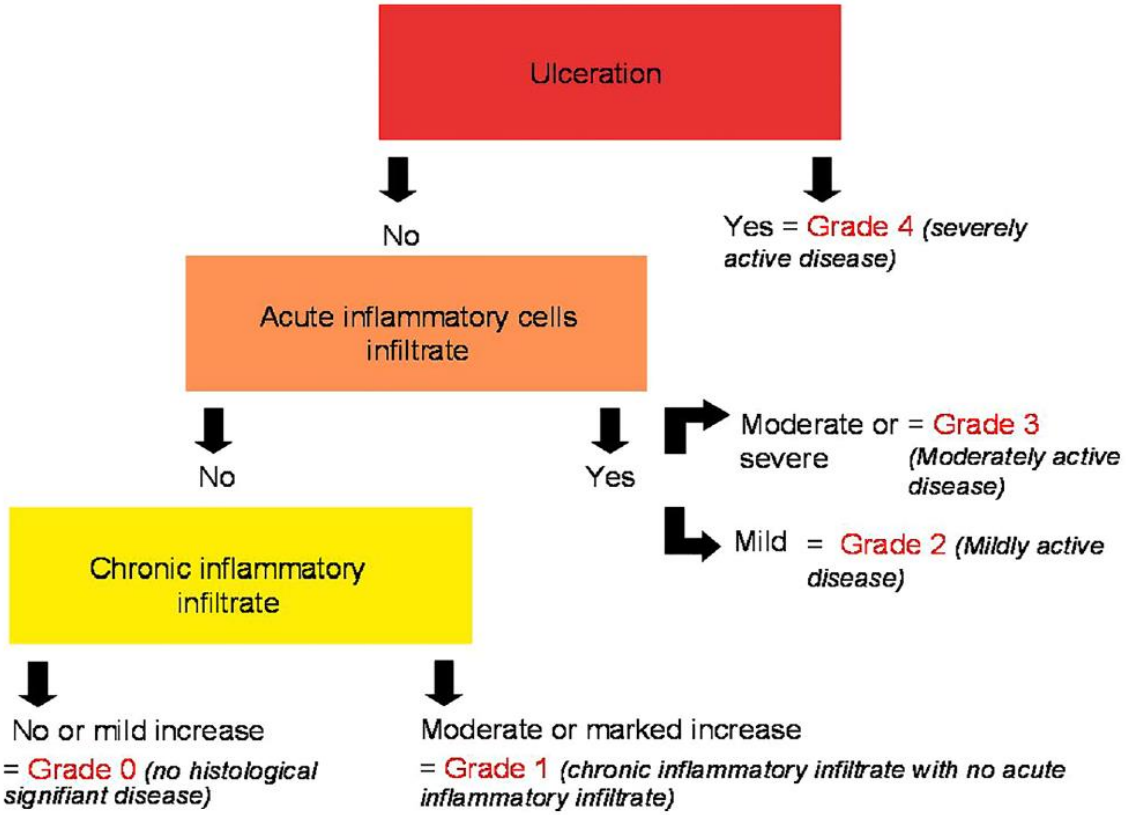
Of these, only the histology grade remained significantly associated with clinical relapse within 12 months (*P* =0.006).

Zenlea et al. Am J Gastroenterol 2016

ORIGINAL ARTICLE

Development and validation of the Nancy histological index for UC

Aude Marchal-Bressenot,[1,2] Julia Salleron,[3] Camille Boulagnon-Rombi,[1] Claire Bastien,[4] Virginie Cahn,[5] Guillaume Cadiot,[6] Marie-Danièle Diebold,[1] Silvio Danese,[7] Walter Reinisch,[8] Stefan Schreiber,[9] Simon Travis,[10] Laurent Peyrin-Biroulet[2,11]



Marchal-Bressenot et al. Gut 2017]

A practical guide to assess the Nancy histological index for UC

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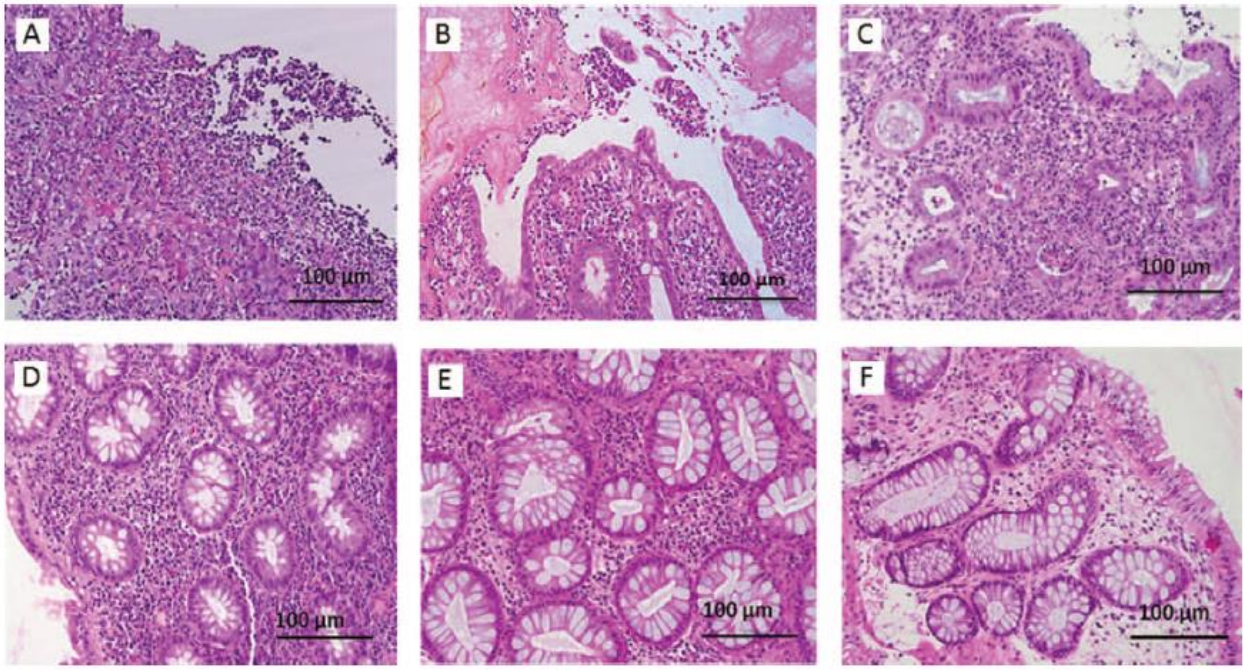

Figure 1 (A) Ulceration of colonic mucosa with inflamed granulation tissue corresponding to *grade 4* of the Nancy index (HES ×200). (B) Ulceration of colonic mucosa with neutrophils in fibrin corresponding to *grade 4* of the Nancy index (HES ×200). (C) Presence of multiple clusters of neutrophils in lamina propria and/or in epithelium that are easily apparent. Acute inflammatory cells infiltrate is moderate to severe, corresponding to *grade 3* of the Nancy index. (HES ×200). (D) Presence of few or rare neutrophils in lamina propria or in the epithelium that are difficult to see. Acute inflammatory cells infiltrate is mild, corresponding to *grade 2* of the Nancy index (HES ×200). (E) Biopsy specimen showing no acute inflammatory cells infiltrate and presence of a moderate-to-severe increase in chronic inflammatory cells number corresponding to *grade 1* of the Nancy index (HES ×200). (F) Biopsy specimen showing a mild increase in chronic inflammatory cell number. In this case, it defines a *grade 0* of the Nancy index (HES ×200). HES, hematoxylin-eosin-saffron.

Marchal-Bressenot et al. Gut 2016

Agenda

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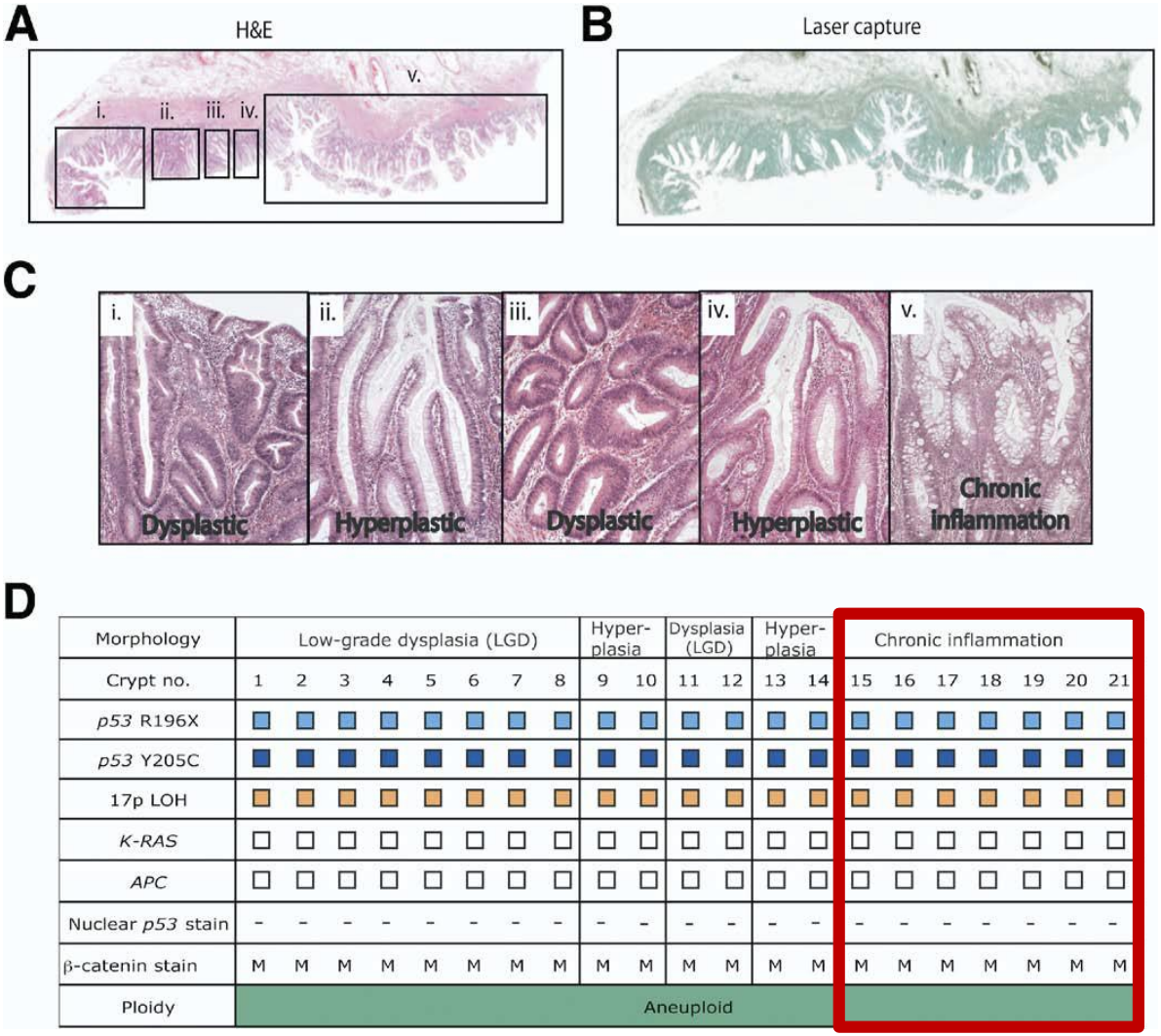
- Normal Histology
- Basic Principles of IBD Diagnosis
  - Ulcerative Colitis
  - Crohn's Disease
- Difficulties in IBD Diagnosis and Differential Diagnosis
- Grading of Activity
- **Dysplasia and Cancer**
- Take Home Messages

Clonality, Founder Mutations, and Field Cancerization in Human Ulcerative Colitis–Associated Neoplasia

SIMON J. LEEDHAM,[*,‡] TREVOR A. GRAHAM,[*] DAHMANE OUKRIF,[§] STUART A. C. MCDONALD,[*,‖] MANUEL RODRIGUEZ–JUSTO,[§] REBECCA F. HARRISON,[#] NEIL A. SHEPHERD,[¶] MARCO R. NOVELLI,[§] JANUSZ A. Z. JANKOWSKI,[‖] and NICHOLAS A. WRIGHT[*]



Morphology	Low-grade dysplasia (LGD)								Hyper-plasia		Dysplasia (LGD)		Hyper-plasia		Chronic inflammation						
Crypt no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
p53 R196X	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
p53 Y205C	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
17p LOH	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
K-RAS	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
APC	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Nuclear *p53* stain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
β-catenin stain	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Ploidy	Aneuploid																				

Leedham et al. Gastroenterology 2009

Dysplastic Lesions in Inflammatory Bowel Disease

Molecular Pathogenesis to Morphology

Kristina A. Matkowskyj, MD, PhD; Zongming E. Chen, MD, PhD; M. Sambasiva Rao, MD; Guang-Yu Yang, MD, PhD

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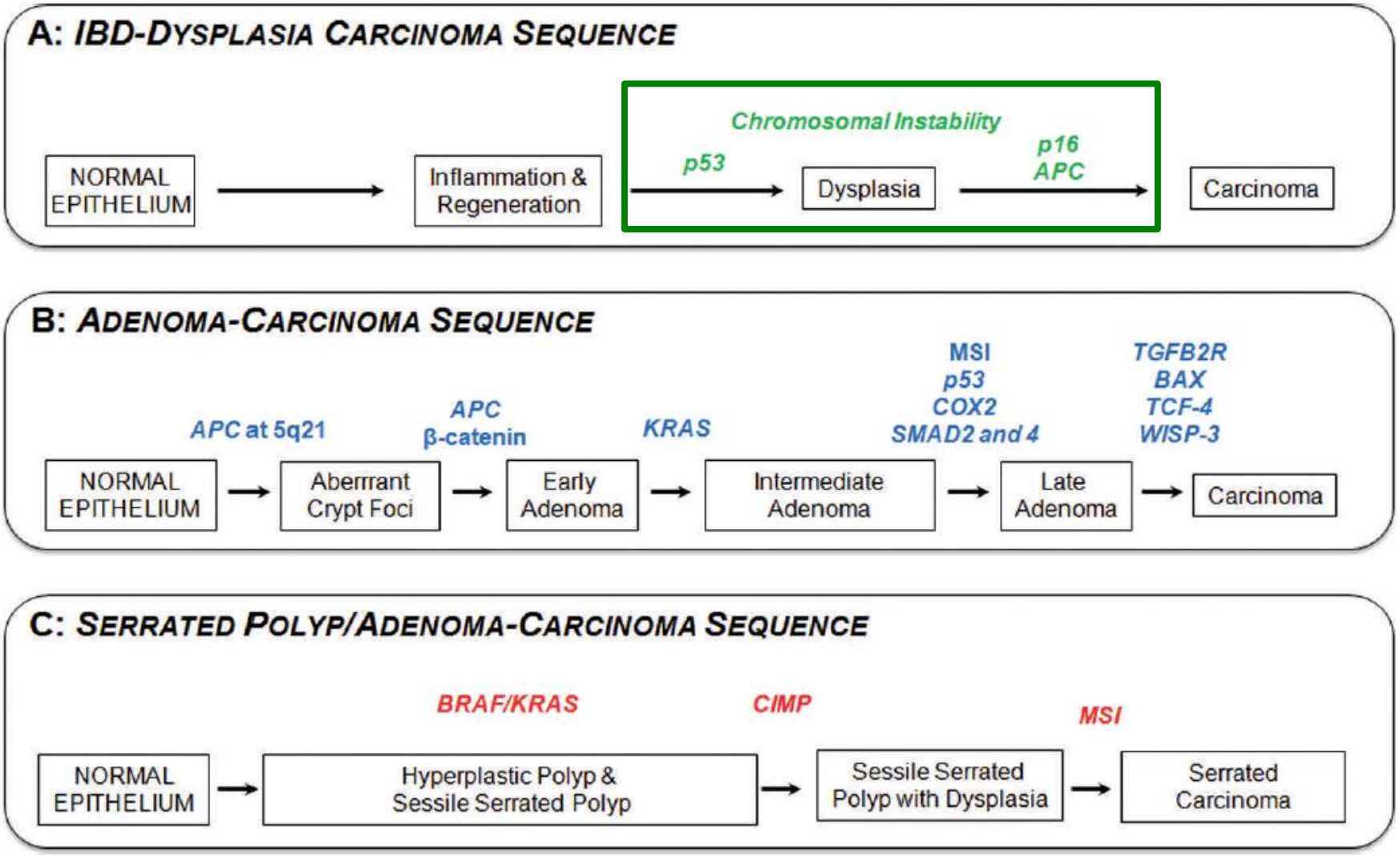

Matkowskyj et al. Arch Pathol Lab Med 2013

Medizinische Universität Graz

European consensus on the histopathology of inflammatory bowel disease☆

F. Magro[a,*,1], C. Langner[b,1], A. Driessen[c], A. Ensari[d], K. Geboes[e], G.J. Mantzaris[f], V. Villanacci[g], G. Becheanu[h], P. Borralho Nunes[i], G. Cathomas[j], W. Fries[k], A. Jouret-Mourin[l], C. Mescoli[m], G. de Petris[n], C.A. Rubio[o], N.A. Shepherd[p], M. Vieth[q], R. Eliakim[r] on behalf of the European Society of Pathology (ESP) and the European Crohn's and Colitis Organisation (ECCO)[2]

ECCO-ESP statement 17

Dysplasia (intrepithelial neoplasia) represents the best and most reliable marker of malignancy risk in patients with ulcerative colitis. Colitis-associated dysplasia develops only in areas with chronic inflammation and can be divided into 4 morphologic categories: negative (regenerating epithelium), indefinite and positive for low-grade dysplasia and high-grade dysplasia [EL 2]. Inter-observer agreement is poor for low-grade and indefinite dysplasia. Confirmation of dysplasia by an independent expert GI pathologist is recommended [EL 2]

Magro et al. J Crohns Colitis 2013

Differential Diagnosis Flat Dysplasia vs. Regenerating Epithelium

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	Colitis-associated dysplasia	Regenerating epithelium
Crypt architecture	Altered (budding, branching, cribriforming, crowding or back-to-back growth)	Preserved
Cytological atypia	Moderate (to marked)	Mild (to moderate)
N/C ratio	Increased	Normal
Nuclei	Enlarged, irregular, hyperchromatic, stratification, loss of polarity	Regular, smooth membrane, no stratification
Nucleoli	Prominent, enlarged (or multiple)	May be prominent, but usually not enlarged
Mitoses	Frequent, pathological mitoses	Frequent, normal looking
Surface maturation	No	Yes
Increased lamina propria inflammation	Variable	Usually present (neutrophils!)

Odze. Gastroenterol Clin North Am 2006

Microscopic Patterns of Dysplasia

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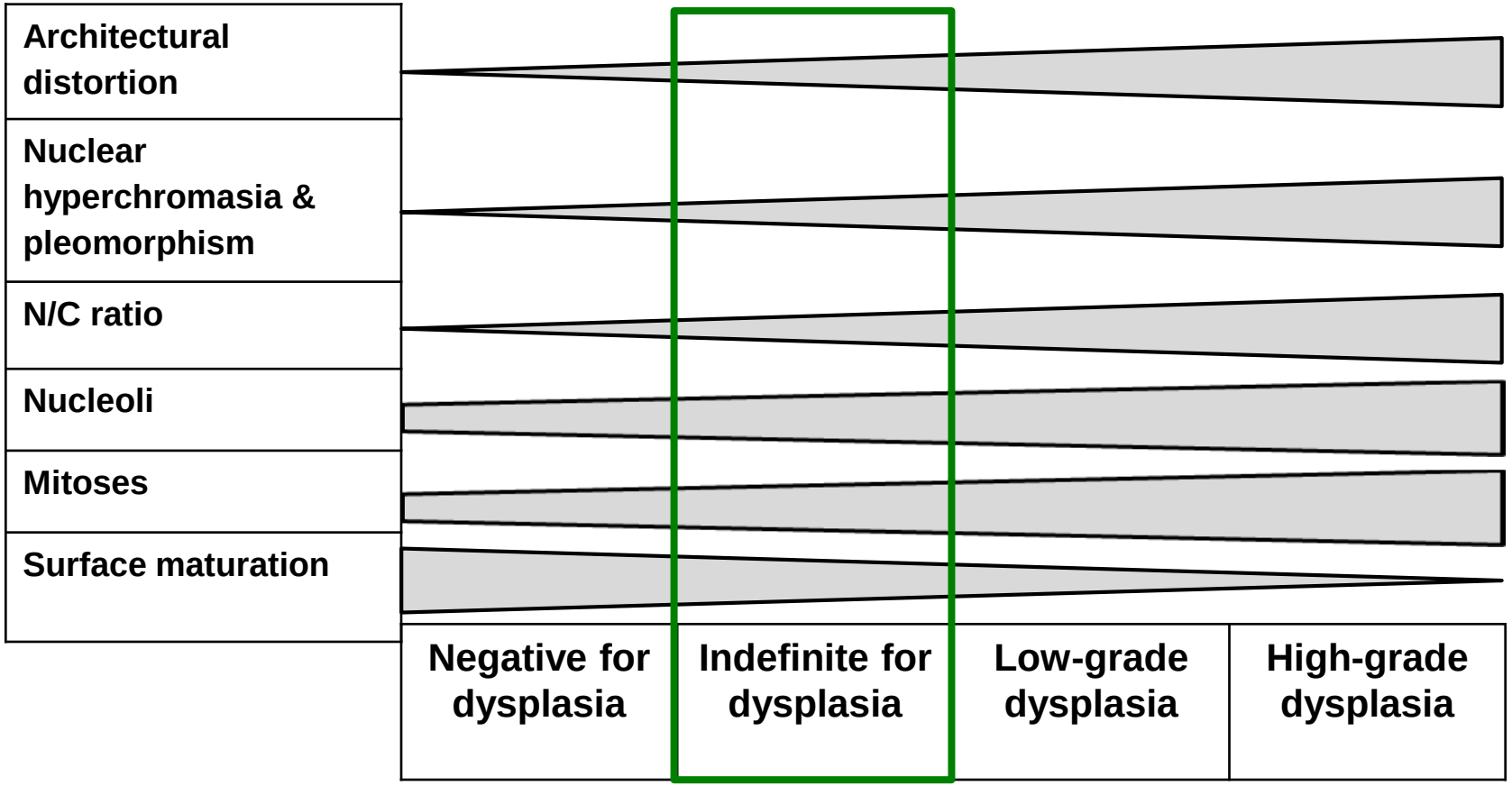

Medizinische Universität Graz

European evidence based consensus for endoscopy in inflammatory bowel disease☆

Vito Annese[a,*,1,2], Marco Daperno[b,2], Matthew D. Rutter[c,d,2], Aurelien Amiot[e], Peter Bossuyt[f], James East[g], Marc Ferrante[h], Martin Götz[i], Konstantinos H. Katsanos[j], Ralf Kießlich[k], Ingrid Ordás[l], Alessandro Repici[m], Bruno Rosa[n], Shaji Sebastian[o], Torsten Kucharzik[p], Rami Eliakim[q,**,1,2] on behalf of ECCO

ECCO Statement 13J

A finding of dysplasia should be confirmed by an independent gastrointestinal specialist pathologist [EL2] [Voting results: 100% agreement].

ECCO Statement 13K

A visible lesion with dysplasia should be completely resected by an experienced endoscopist, irrespective of the grade of dysplasia or the localisation relative to the inflamed mucosal areas. In the absence of dysplasia in the surrounding mucosa, ongoing meticulous colonoscopic surveillance is appropriate [EL1].
If endoscopic resection is not possible or if dysplasia is found in the surrounding flat mucosa, proctocolectomy should be recommended [EL4] [Voting results: 100% agreement].

Annese et al. J Crohns Colitis 2013

Medizinische Universität Graz

European evidence based consensus for endoscopy in inflammatory bowel disease☆

Vito Annese[a,*,1,2], Marco Daperno[b,2], Matthew D. Rutter[c,d,2], Aurelien Amiot[e], Peter Bossuyt[f], James East[g], Marc Ferrante[h], Martin Götz[i], Konstantinos H. Katsanos[j], Ralf Kießlich[k], Ingrid Ordás[l], Alessandro Repici[m], Bruno Rosa[n], Shaji Sebastian[o], Torsten Kucharzik[p], Rami Eliakim[q,**,1,2] on behalf of ECCO

Most dysplasia is visible at colonoscopy,[410–412] even with standard resolution endoscopes. Raised dysplastic lesions on a background of colitis (formerly referred to as DALMs) have until recently been considered an indication for colectomy. In the context of colitis surveillance, the term "flat lesion" has traditionally been used for endoscopically invisible dysplastic lesions diagnosed by random biopsies. Both these terms are confusing and should abandoned, especially as the term "flat" now has an entirely different endoscopic definition (Paris endoscopic classification).[413] It is preferable to use the terms endoscopically visible and non-visible lesions, since it is increasingly recognised that well-circumscribed visible lesions may be amenable to complete endoscopic resection[410,414–418] regardless of their location within or outside areas of documented UC and irrespective of the presence of LGD or HGD. This applies also for sporadic adenomas in the context of colitis.[419]

Annese et al. J Crohns Colitis 2013

GIE®

CONSENSUS STATEMENT

SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease

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TABLE 1. Terminology for reporting findings on colonoscopic surveillance of patients with inflammatory bowel disease (modified from Paris Classification[15])

Term	Definition
Visible dysplasia	Dysplasia identified on targeted biopsies from a lesion visualized at colonoscopy
Polypoid	Lesion protruding from the mucosa into the lumen ≥2.5 mm
Pedunculated	Lesion attached to the mucosa by a stalk
Sessile	Lesion not attached to the mucosa by a stalk: entire base is contiguous with the mucosa
Nonpolypoid	Lesion with little (<2.5 mm) or no protrusion above the mucosa
Superficial elevated	Lesion with protrusion but <2.5 mm above the lumen (less than the height of the closed cup of a biopsy forceps)
Flat	Lesion without protrusion above the mucosa
Depressed	Lesion with at least a portion depressed below the level of the mucosa
General descriptors	
Ulcerated	Ulceration (fibrinous-appearing base with depth) within the lesion
Border	
Distinct border	Lesion's border is discrete and can be distinguished from surrounding mucosa
Indistinct border	Lesion's border is not discrete and cannot be distinguished from surrounding mucosa
Invisible dysplasia	Dysplasia identified on random (non-targeted) biopsies of colon mucosa without a visible lesion

„It was agreed that the terms dysplasia-associated lesion or mass (DALM), adenoma-like, and non-adenoma-like should be abandoned"

Laine et al. Gastrointest Endosc 2015

ECCO Guideline/Consensus Paper

Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders

Fernando Magro,[a,†] Paolo Gionchetti,[b,†] Rami Eliakim,[c,#] Sandro Ardizzone,[d] Alessandro Armuzzi,[e] Manuel Barreiro-de Acosta,[f] Johan Burisch,[g] Krisztina B. Gecse,[h] Ailsa L. Hart,[i] Pieter Hindryckx,[j] Cord Langner,[k] Jimmy K. Limdi,[l] Gianluca Pellino,[m] Edyta Zagórowicz,[n] Tim Raine,[o] Marcus Harbord,[p#] Florian Rieder;[q] for the European Crohn's and Colitis Organisation [ECCO]

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8.5.2. Macroscopic patterns of dysplasia

There is inconsistency in the literature about the definitions used to designate the macroscopic characteristics of dysplastic lesions in UC.[493,536] Terms such as dysplasia-associated lesion or mass [known as 'DALM'], adenoma-like, non-adenoma like, and flat, often cause confusion among endoscopists as they are often used to describe a variety of differently shaped lesions. Thus, in agreement with the SCENIC international consensus, these terms should be abandoned.[541] Dysplasia detected during surveillance procedures should be classified into three categories: polypoid, non-polypoid, and endoscopically invisible.

Magro et al. J Crohns Colitis 2017

Summary of Guideline Statements

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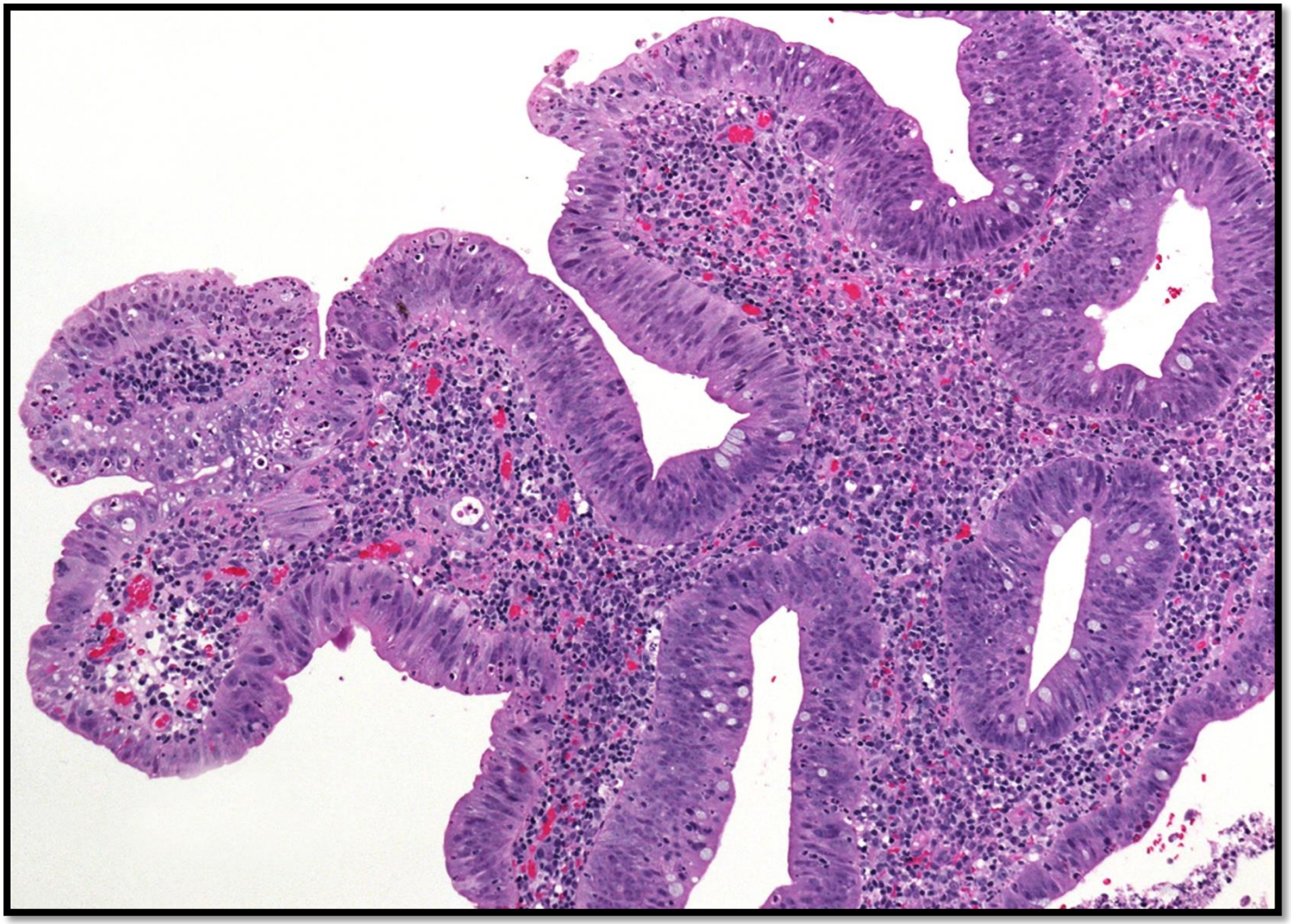
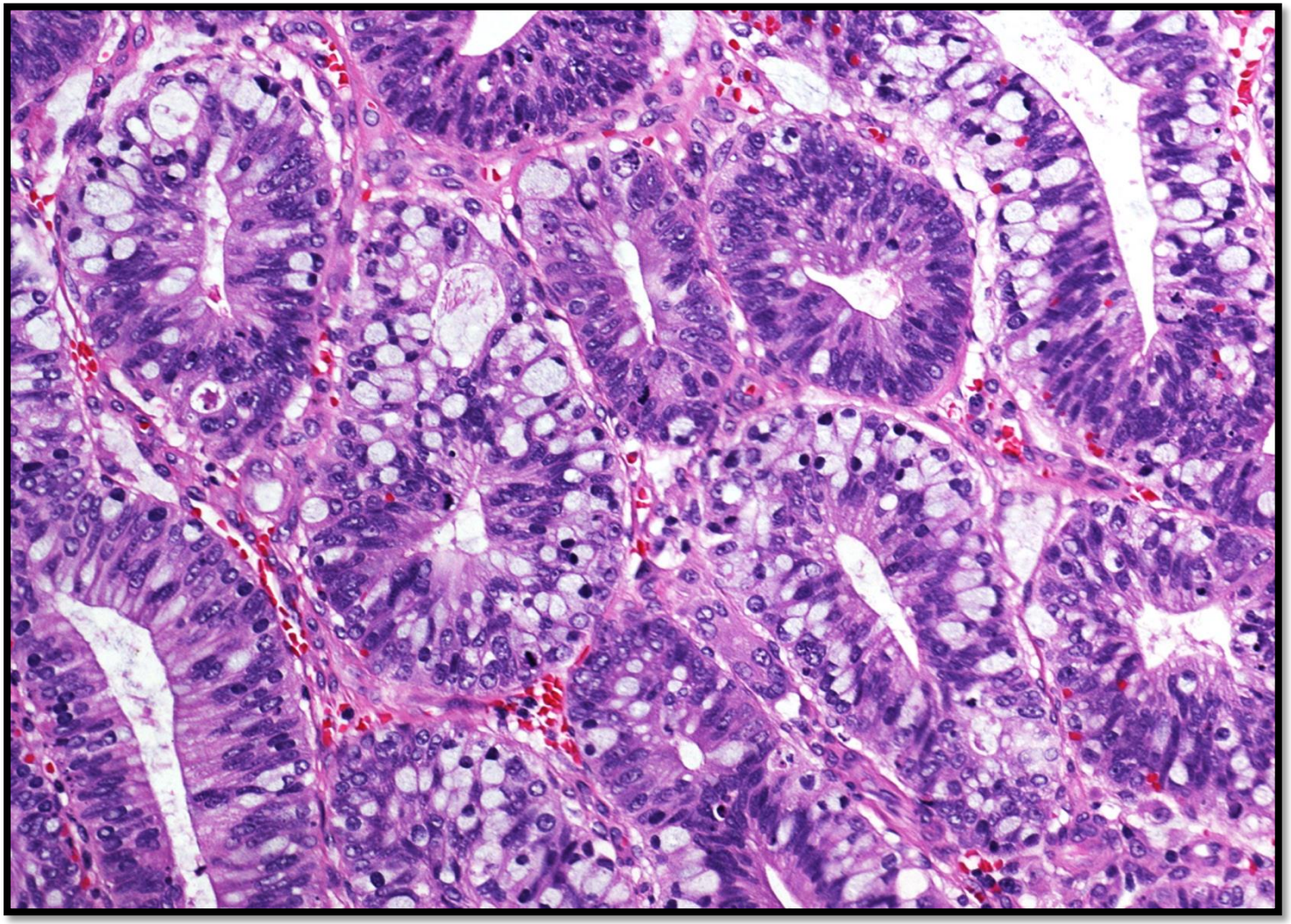
ECCO ESP CED Histology Consensus 2013	ECCO IBD Endoscopy Consensus 2013	SCENIC Consensus Statement 2015	ECCO UC Consensus 2017
Flat and elevated dysplasia (low grade versus high grade), colitis-associated dysplasia vs. colitis-independent dysplasia (adenoma-like lesion, sporadic adenoma)	Visible and invisible dysplasia (low grade versus high grade), no distinction between colitis-associated dysplasia vs. colitis-independent dysplasia (sporadic adenoma)	Visible (polypoid versus non-polypoid) and invisible dysplasia (low grade versus high grade), colitis-associated dysplasia vs. colitis-independent dysplasia (sporadic adenoma)	Polypoid, non-polypoid and endoscopically invisible dysplasia (low grade vs. high grade), adenomas only in non-inflamed mucosa (proximal in UC)

Differential diagnosis dysplasia vs. regenerating epithelium



Differential diagnosis dysplasia vs. regenerating epithelium



Interobserver Variability

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Interobserver Variability in the Diagnosis of Ulcerative Colitis-Associated Dysplasia by Telepathology

Robert D. Odze, M.D., F.R.C.P.C., John Goldblum, M.D., Amy Noffsinger, M.D., Nada Alsaigh, M.D., Lyndo A. Rybicki, M.S., Franz Fogt, M.D., M.R.C. Path.

TABLE 1. Kappa Indices for Interobserver Agreement among Four Gastrointestinal Pathologists

Category	Kappa	*P*	95% Confidence Interval	Interpretation[a]
Digitalized images				
Negative	0.51	<0.001*	0.38–0.64	Good
Indefinite	0.18	0.008*	0.05–0.31	Poor
LGD	0.36	<0.001*	0.23–0.49	Poor
HGD	0.54	<0.001	0.41–0.67	Good
Overall	0.40	<0.001*	0.32–0.48	Fair
Microscopic s				
Negative				Fair
Indefinite				Poor
LGD				Good
HGD				Fair
Overall				Fair

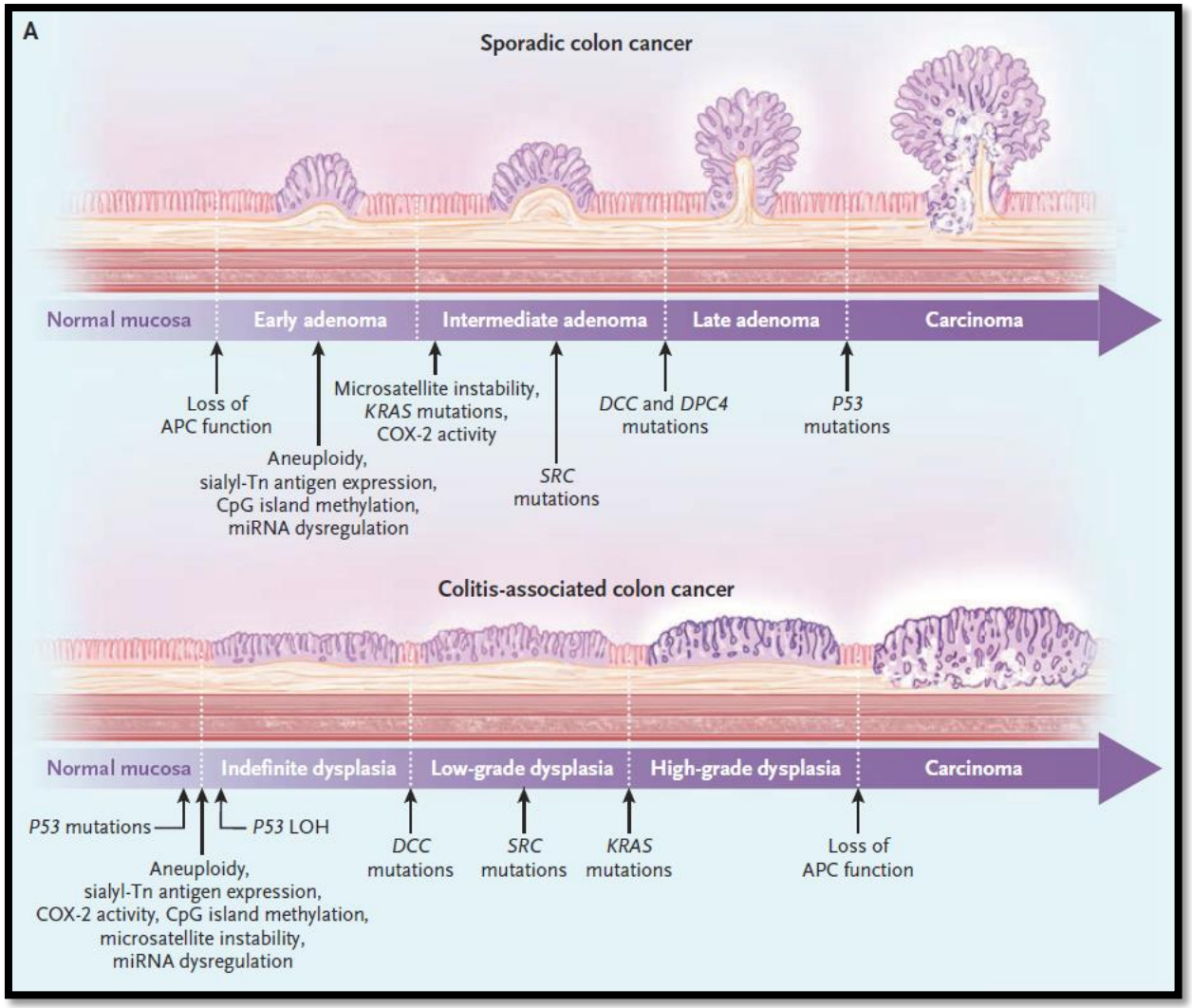
LGD, = low-grade
* Significant agree
[a] Poor: kappa < 0.

Do the data of this study and similar studies convey the need for ancillary techniques, i.e. immunohistochemistry or molecular analysis?

Odze et al. Mod Pathol 2002

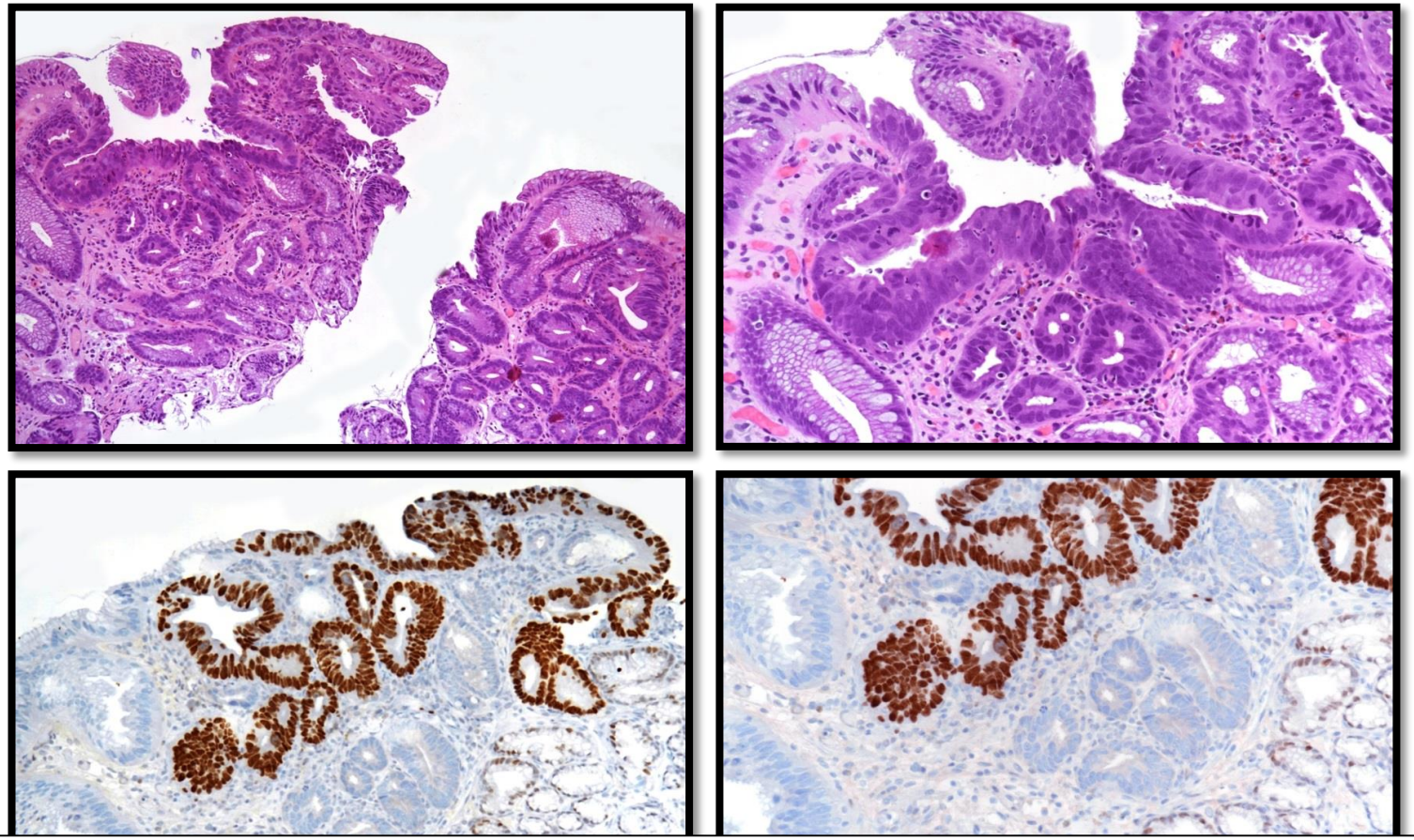
Cancers Complicating Inflammatory Bowel Disease

Laurent Beaugerie, M.D., Ph.D., and Steven H. Itzkowitz, M.D.



Beaugerie & Itzkowitz. N Engl J Med 2015

p53 Immunostaining in Dysplastic Lesions



Two principal patterns of abnormal p53 staining („all or nothing“):

Strongly positive (due to impaired protein degradation)

Completely negative (due to protein truncation, not recognized by the antibody)

Kaye et al. Histopathology 2010

Modern Pathology (2015) 28, 1584–1593

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Serrated colorectal polyps in inflammatory bowel disease

Huaibin M Ko[1,4], Noam Harpaz[1,2,4], Russell B McBride[1,3], Miao Cui[1], Fei Ye[1], David Zhang[1], Thomas A Ullman[2] and Alexandros D Polydorides[1,2]

Table 1 Clinicopathologic features of study patients with serrated polyps

	SP-LGD (N = 25)	*SP-IND (N = 18)*	*SP-NEG (N = 35)*	*HP (N = 28)*	*Reference (N = 1465)*
Mean age ± s.d. (years)	56.4 ± 14.4	55.9 ± 13.0	54.3 ± 14.2	55.6 ± 13.7	37.5 ± 16.9
Sex					
M (%)	16 (64%)	15 (83%)	16 (46%)	17 (61%)	737 (50%)
F (%)	9 (36%)	3 (17%)	19 (54%)*	11 (39%)	728 (50%)
Polyp site					
R (%)	5 (20%)	4 (22%)	20 (57%)#	9 (32%)	
L (%)	20 (80%)	14 (78%)	15 (43%)	19 (68%)	
Mean size ± s.d. (cm)	1.23 ± 0.80	0.66 ± 0.55	0.87 ± 0.45	0.52 ± 0.25+	
IBD type (UC:CD:IC)	18:6:1	16:2:0	22:11:2	19:9:0	1416:49:0
Disease >10 years (%)	84%	89%	86%	89%	60%
Mean surveillance (mo)	101.1	98.7	103.2	113.4	88.0
Mean colonoscopies	9.6	8.8	7.0	7.4	5.8

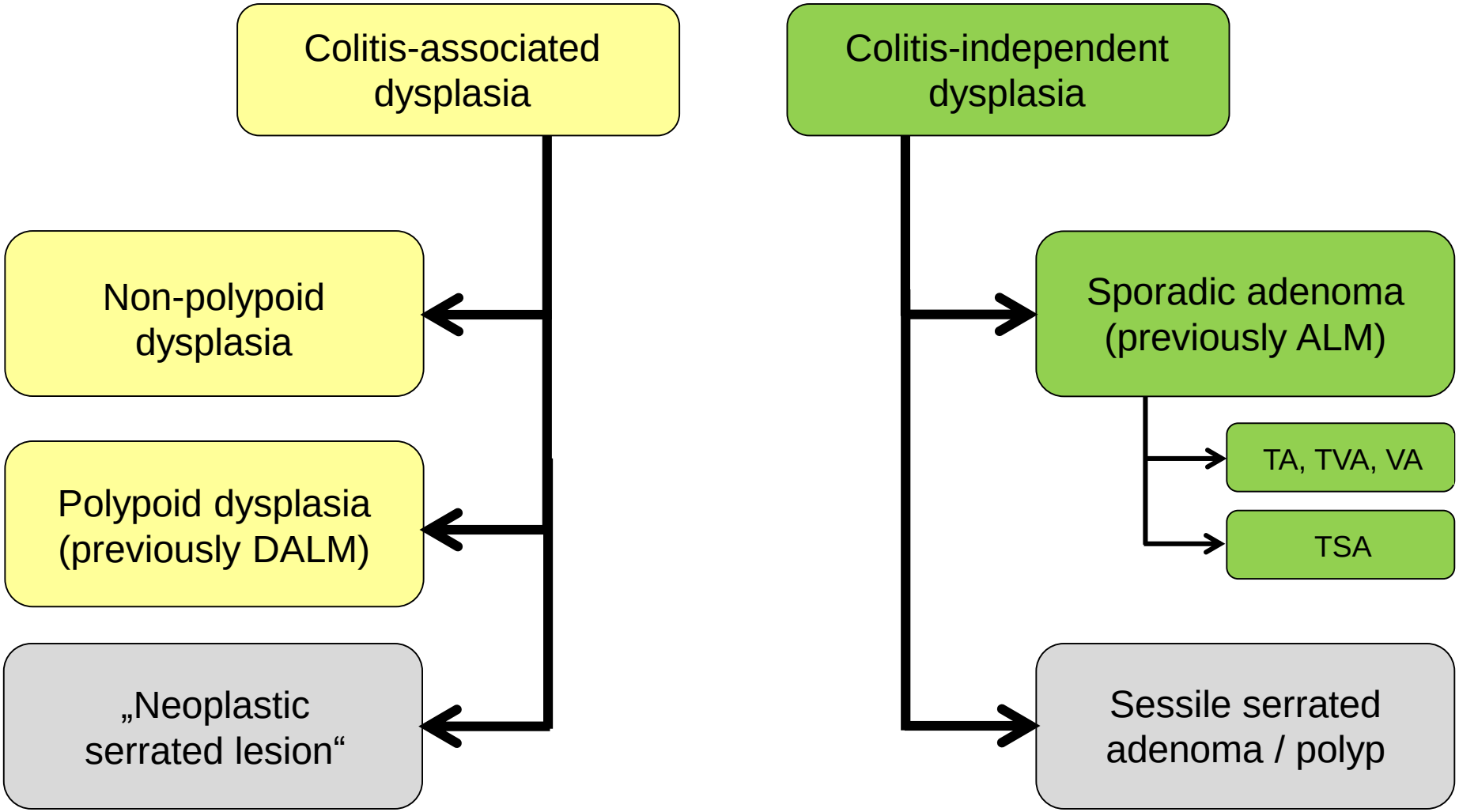
Table 2 Molecular characteristics of serrated polyps

	SP-LGD (N = 11)	*SP-IND (N = 8)*	*SP-NEG (N = 23)*	*Total (N = 42)*
BRAF muta				17 (40%)
KRAS muta				11 (26%)
Wild type f				14 (33%)

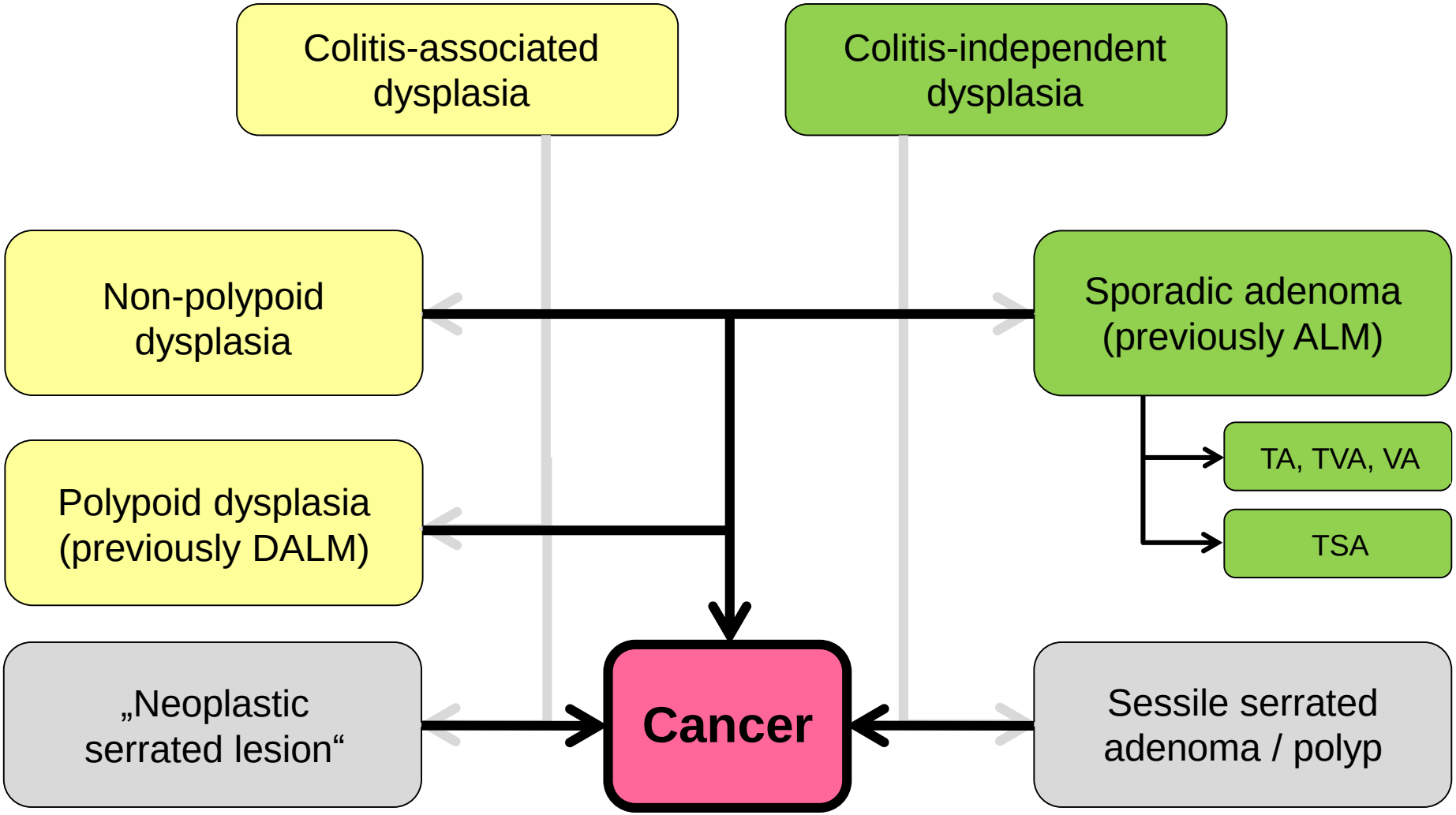
…their clinical significance (IBD-dependent versus IBD-independent serrated lesion) still needs to be defined

Ko et al. Mod Pathol 2015

Conclusion


Colitis-associated dysplasia
Colitis-independent dysplasia
Non-polypoid dysplasia
Polypoid dysplasia (previously DALM)
„Neoplastic serrated lesion“
Sporadic adenoma (previously ALM)
TA, TVA, VA
TSA
Sessile serrated adenoma / polyp

Conclusion


Colitis-associated dysplasia
Colitis-independent dysplasia
Non-polypoid dysplasia
Sporadic adenoma (previously ALM)
TA, TVA, VA
TSA
Polypoid dysplasia (previously DALM)
„Neoplastic serrated lesion“
Cancer
Sessile serrated adenoma / polyp

Take Home Messages I

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- Accurate histological diagnosis of IBD is based upon the analysis of multiple biopsies from different segments of the large bowel (in combination with endoscopic and clinical data)
- **Histological categories of classical IBD (UC and CD)**
  - Alteration in mucosal (crypt) architecture
  - Increased lamina propria cellularity
  - Neutrophil polymorph infiltration
  - Epithelial abnormality: mucosal breaks as marker of (highly) active disease, metaplastic changes as proof of chronic disease
- **Differential diagnosis**
  - Ulcerative colitis vs. Crohn's disease (IBD unclassified, IBD in patients with PSC)
  - Prolonged infection
  - Superinfection in established IBD (in particular CMV)
  - Diverticular colitis (segmental colitis associated with diverticulosis/diverticulitis; SCAD)
  - Adverse drug reactions (primary vs. secondary autoimmune enteropathy)

Take Home Messages II

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- Colitis-associated dysplasia develops in areas with chronic inflammation (colitis-independent dysplasia versus sporadic adenoma → the distinction is no longer clinically relevant)
- It represents the best and most reliable marker of malignancy risk in patients with IBD
- Four morphologic categories need to be distinguished: negative (regenerating epithelium), indefinite and positive for low-grade dysplasia and high-grade dysplasia (the role of serrated lesions needs to be defined in future studies: colitis-dependent versus colitis-independent)
- There is considerable morphological overlap between the categories → the interobserver agreement is low (the interobserver variation high)
- P53 immunostaining may be helpful in difficult cases, but needs knowledge on the possibilities (different expression patterns: “all or nothing”) and limitations (negativity does not necessarily rule out dysplasia) of the method

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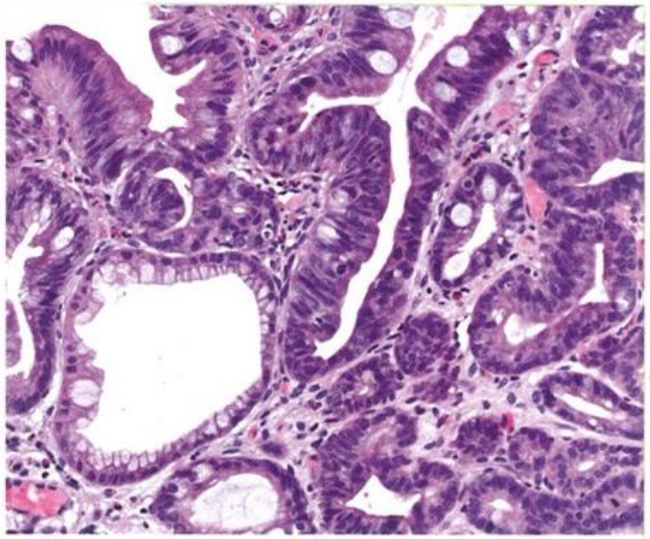
ENGIP



European Network of Gastrointestinal Pathology

www.medunigraz.at/engip

http://www.medunigraz.at/projekte-forschen/engip/

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- Structure
- Upcoming Events
- Research
- WG Digestive Diseases ESP
- Pannonian WG of GI Pathology
- Guidelines
- Case of the Month
- Links

European Society of Pathology

European Network of Gastrointestinal Pathology (ENGIP)

Welcome to the European Network of Gastrointestinal Pathology (ENGIP) which was established in March 2012 by members of the Working Group of Digestive Diseases of the European Society of Pathology (ESP) with the purpose to get a route for dissemination of relevant information such as society information, guidelines, consensus documents, courses, grants etc. in the field of gastrointestinal pathology.

ENGIP is a non-profit organization and works as a network for communication rather than a formal society. Member fees are not taken. To become a member you only need to be a practicing pathologist (M.D.). Non-pathologists with special interest in gastrointestinal pathology are offered affiliate membership.

European Network of Gastrointestinal Pathology

ENGIP

Kontakt

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European Network of Gastrointestinal Pathology

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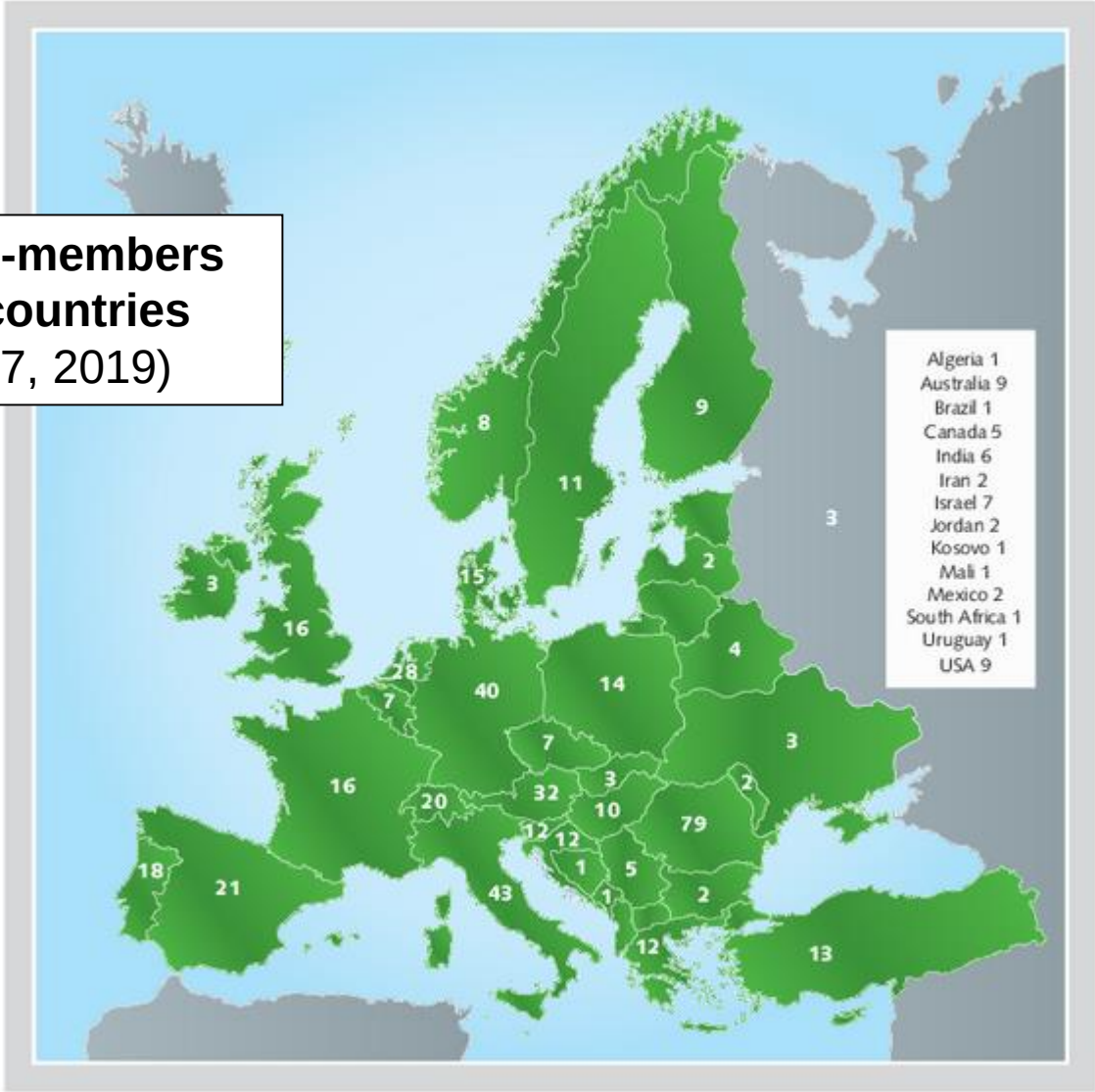
520 ENGIP-members from 47 countries
(March 27, 2019)



Pannonian ENGIP Members (n=75)

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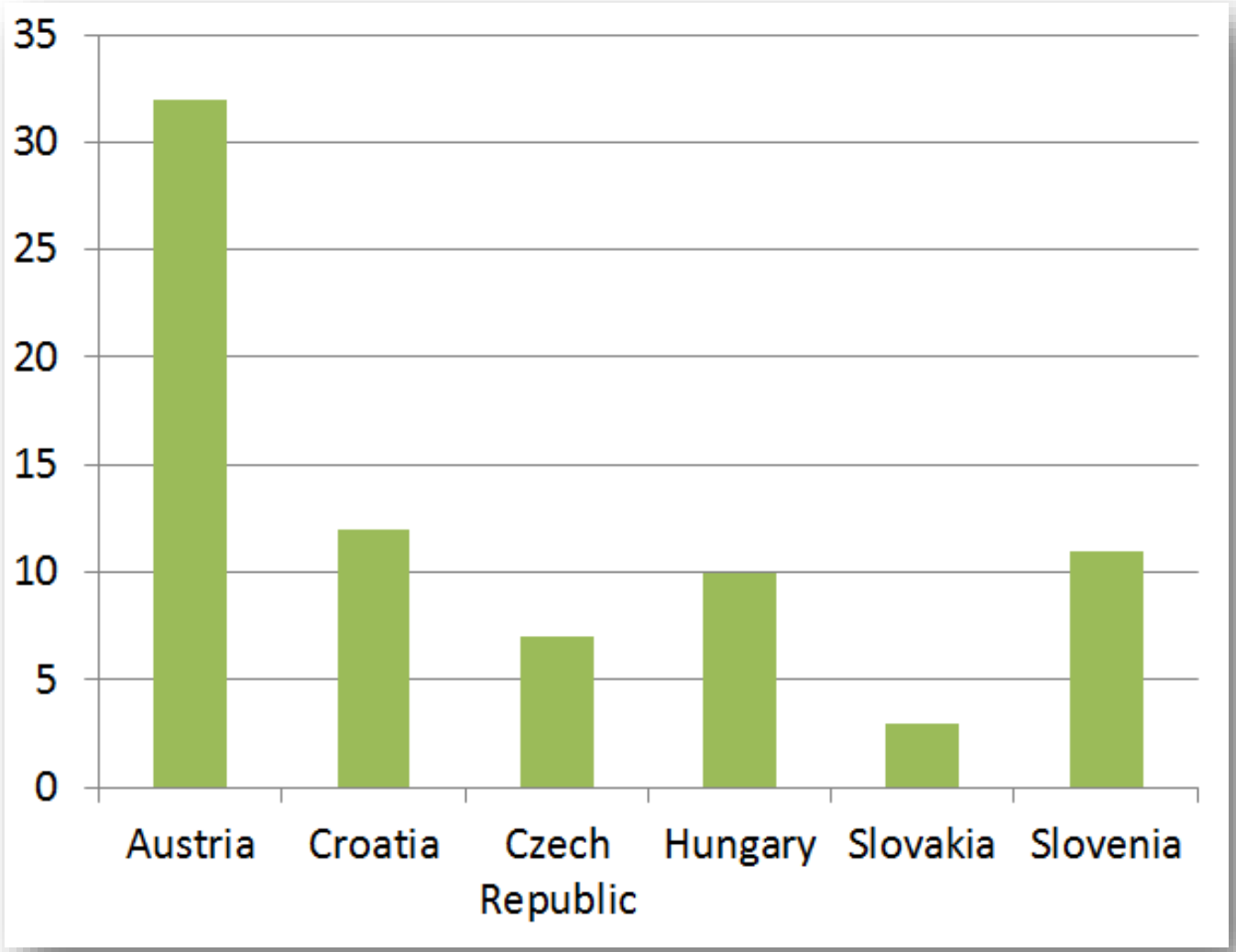

Thank you very much for your kind attention!

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