Dysplasia from Oesophagus to Anus

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Why talk about dysplasia

- Recognised area of diagnostic difficulty
- Misdiagnosis (both under and over calling) has management implications
- Emerging concepts around non-conventional dysplasia (conventional = adenoma-like intestinal, non-conventional = everything else)

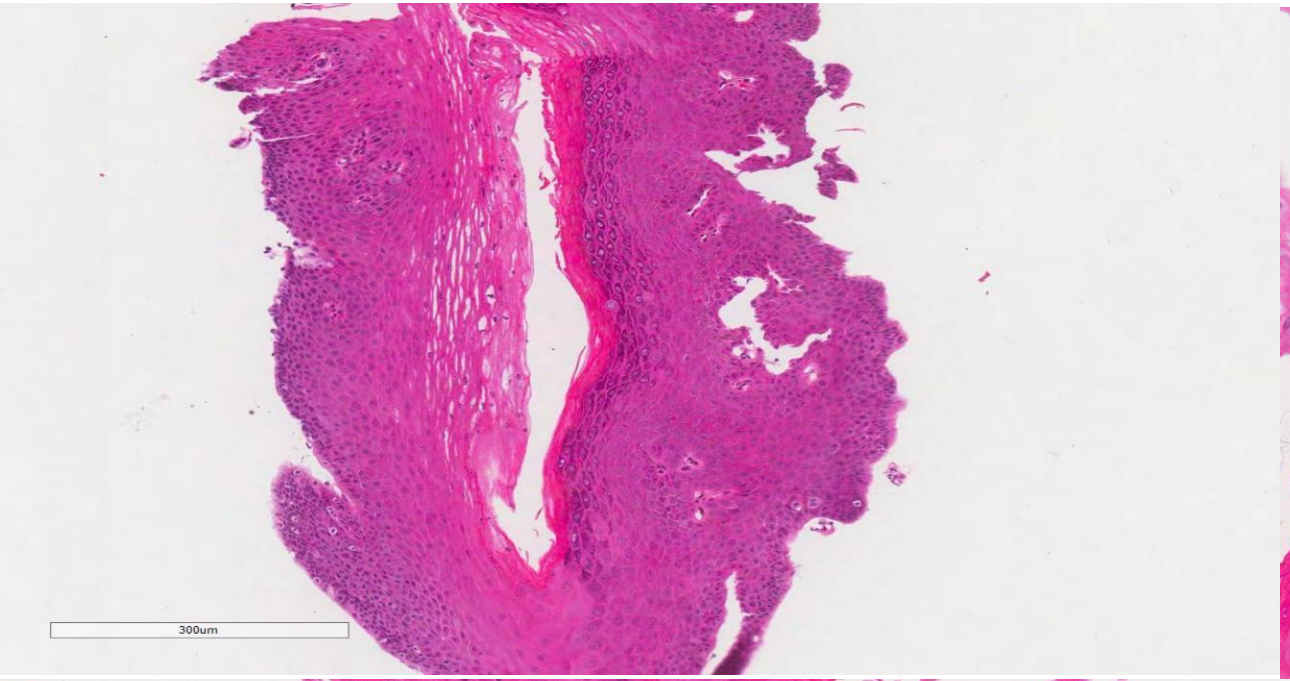
General comments

- All sites in the GI tract use a two tier (low vs high) grade with the exception of anal canal (AIN I-III still in common clinical use)
- Morphology coupled with clinical context is the key – sharp cut-offs; inflammation (diffuse = reactive; focal = reacting to the dysplasia)
- Role for immunohistochemistry – p53, MLH-1, p16
- Double reporting is good practice for everything except ‘adenomas’

Outline

- **Oesophagus**
  - White patches, basal layer dysplasia, poorly differentiated tumours, p53 in Barrett's
- **Stomach**
  - Reactive vs dysplastic, FCGP with dysplasia, native gastric adenomas
- **Colorectum**
  - Non-conventional dysplasia in IBD, dysplastic SSLs
- **Anal canal**
  - LSIL/HSIL & p16

Oesophagus 1 - White plaques don’t always mean candida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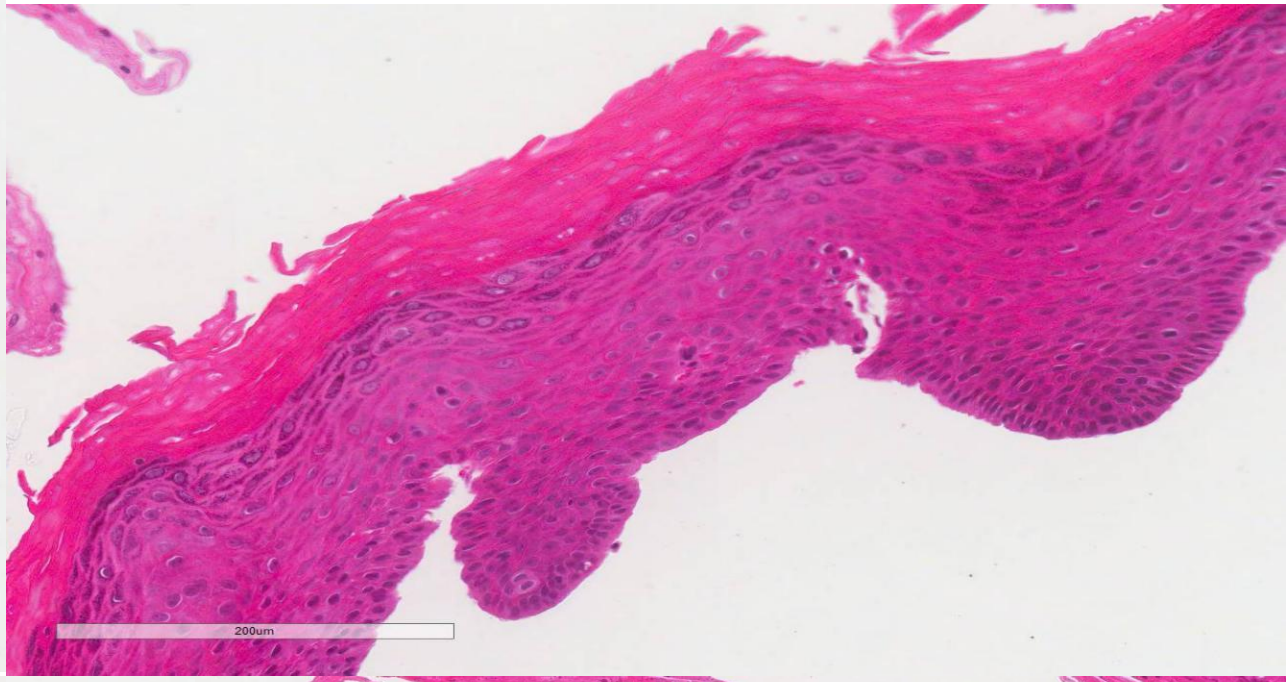
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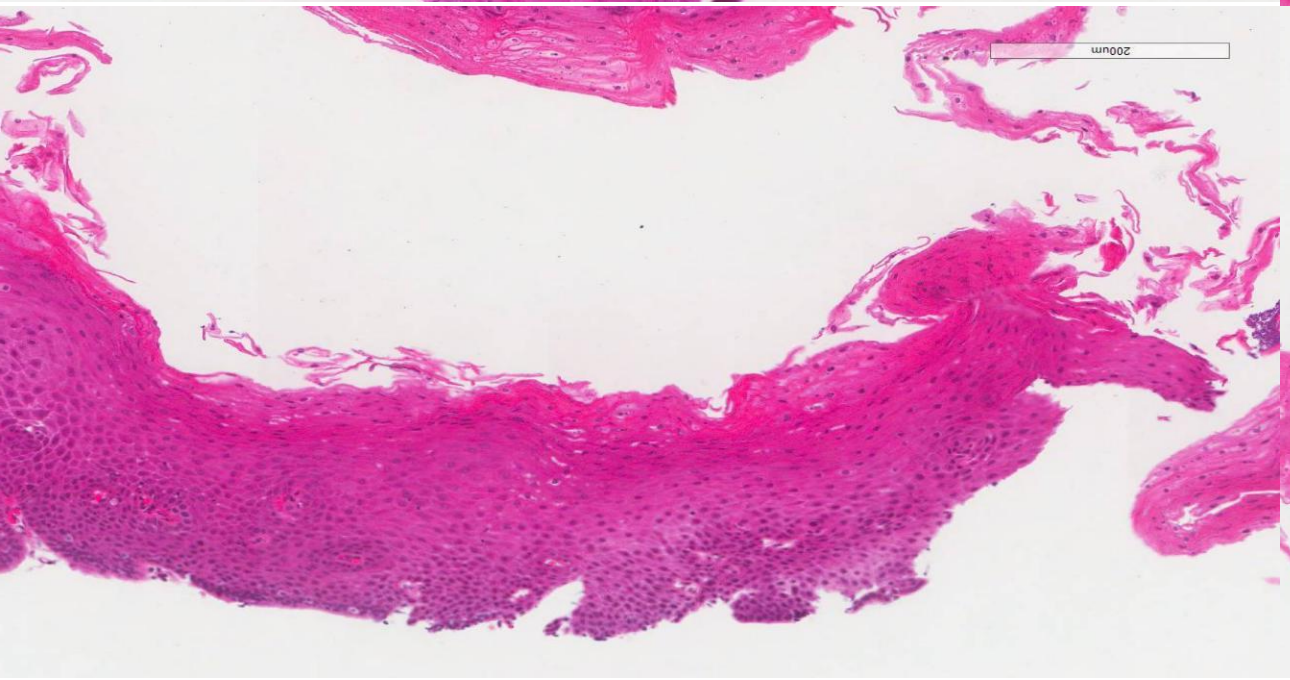
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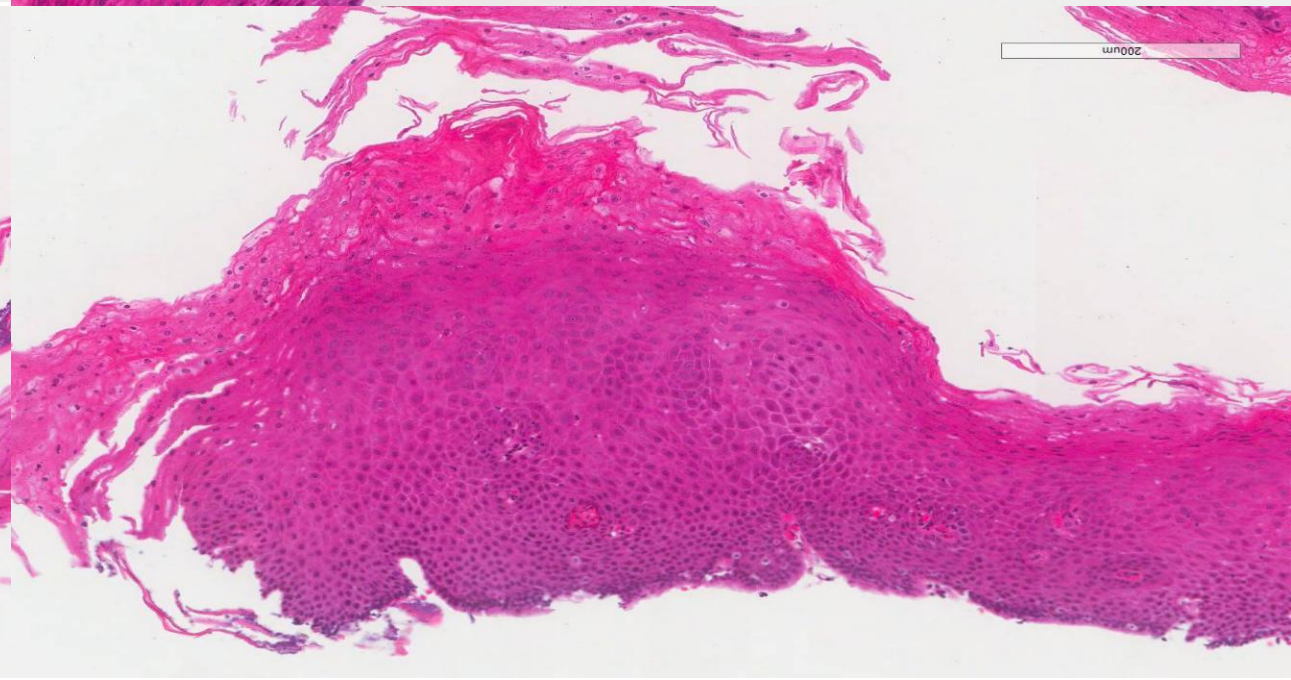
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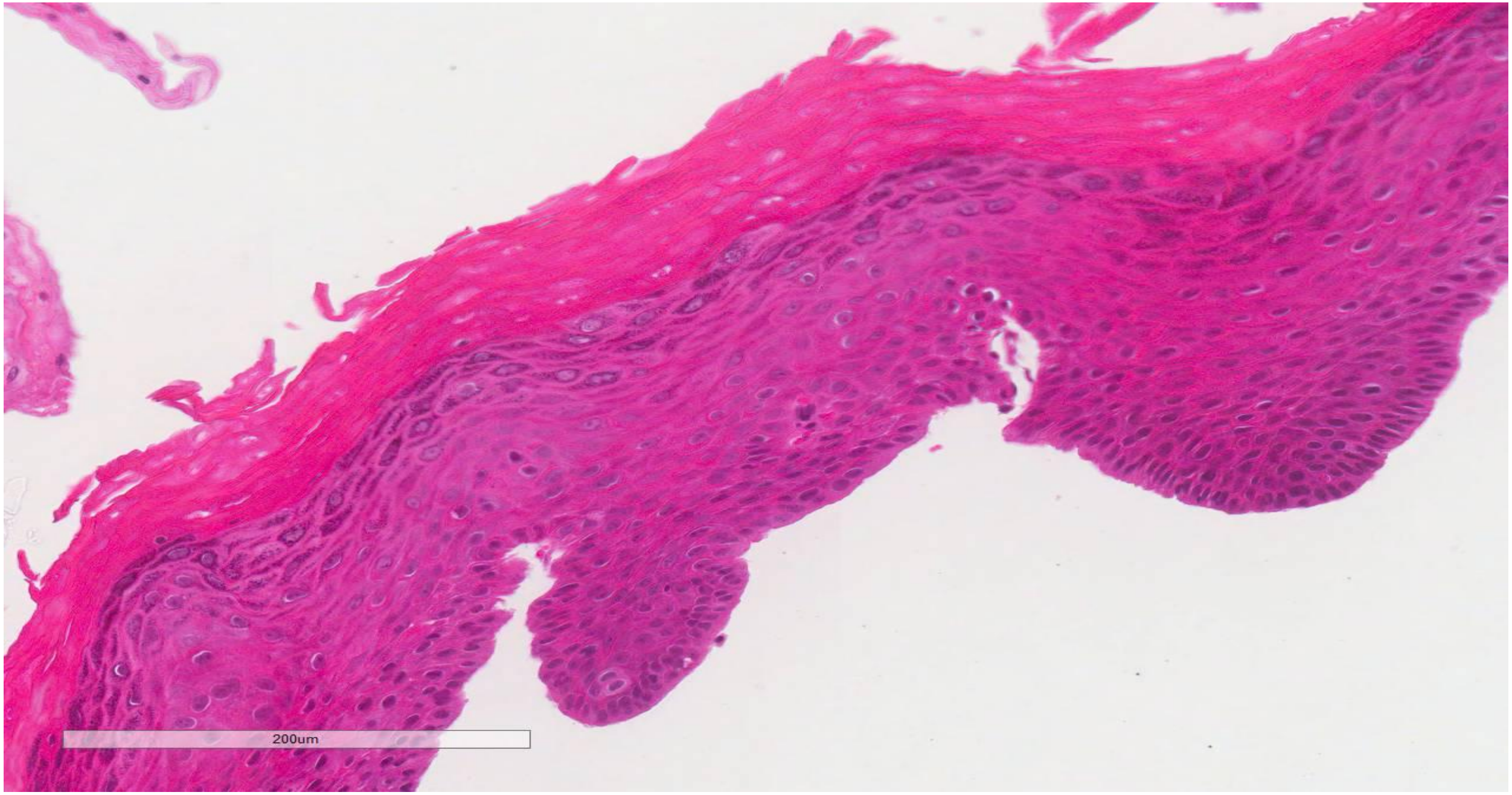
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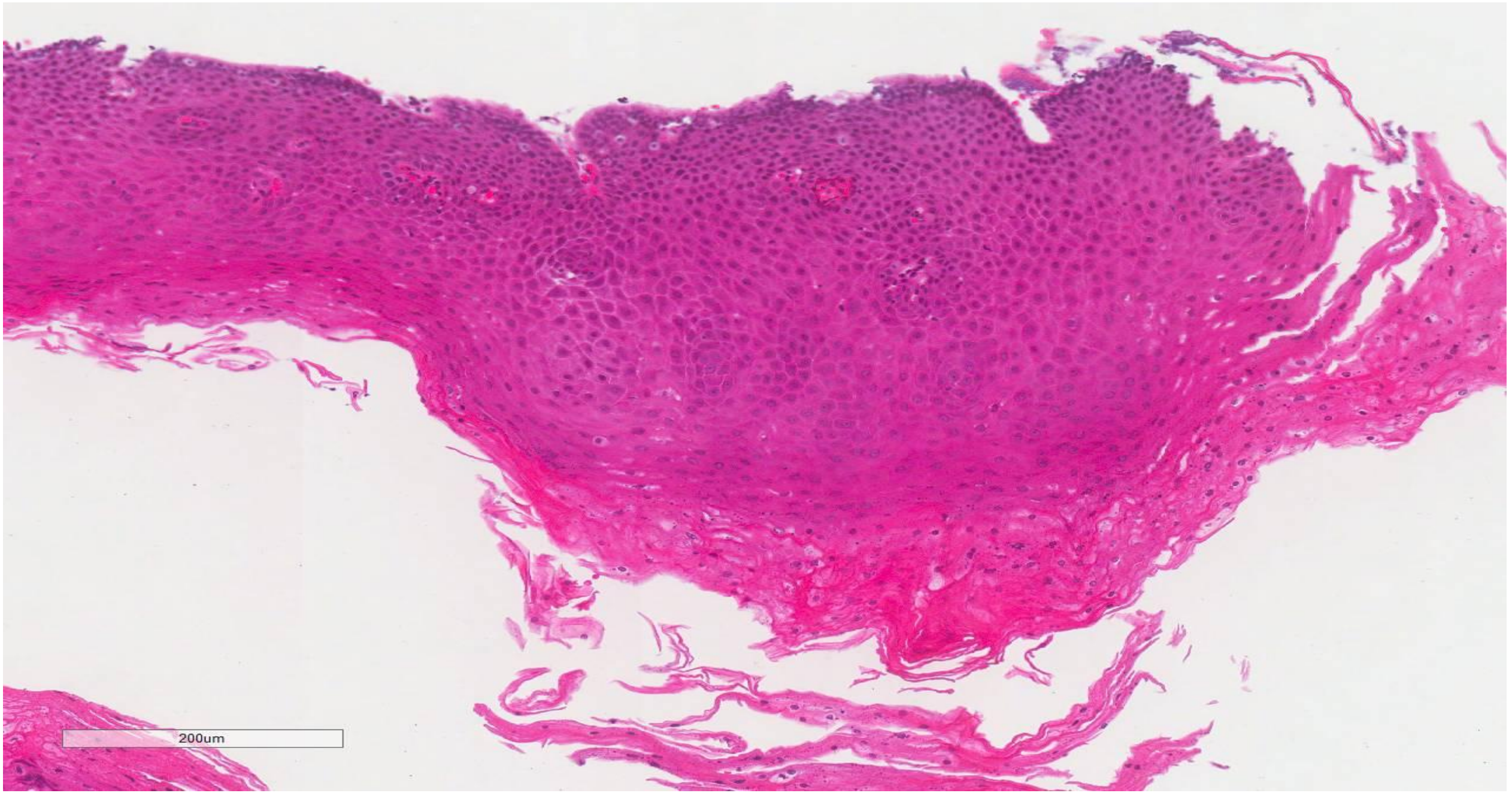
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Microscopic Features Identified

- Hyper-ortho and parakeratosis
- Hypergranulosis
- ‘Looks like skin’
- No evidence of inflammation
- No evidence of atypia/invasion
- No candida

Epidermoid Metaplasia Oesophagus

- Epidermoid metaplasia is a rare pattern seen in oesophageal biopsies.
- It is not usually associated with inflammation or typical features of another oesophagitis.
- The aetiology is unclear but in Liverpool it is seen in those in families affected by Tylosis
- It appears to be associated with an (as yet) unquantified risk of squamous neoplasia and if identified warrants follow-up.

Cottreau J et al, Histopath 2016; 68: 998-995

Oesophagus 2 - Is there more to grading squamous dysplasia than 50% thickness?

World Journal of Gastroenterology

World J Gastroenterol. 2015 Feb 7; 21(5): 1663–1665.
Published online 2015 Feb 7. doi: 10.3748/wjg.v21.i5.1663

PMCID: PMC4316110
PMID: 25663787

High-grade dysplasia, restricted to the basal cell layer involving the entire esophagus

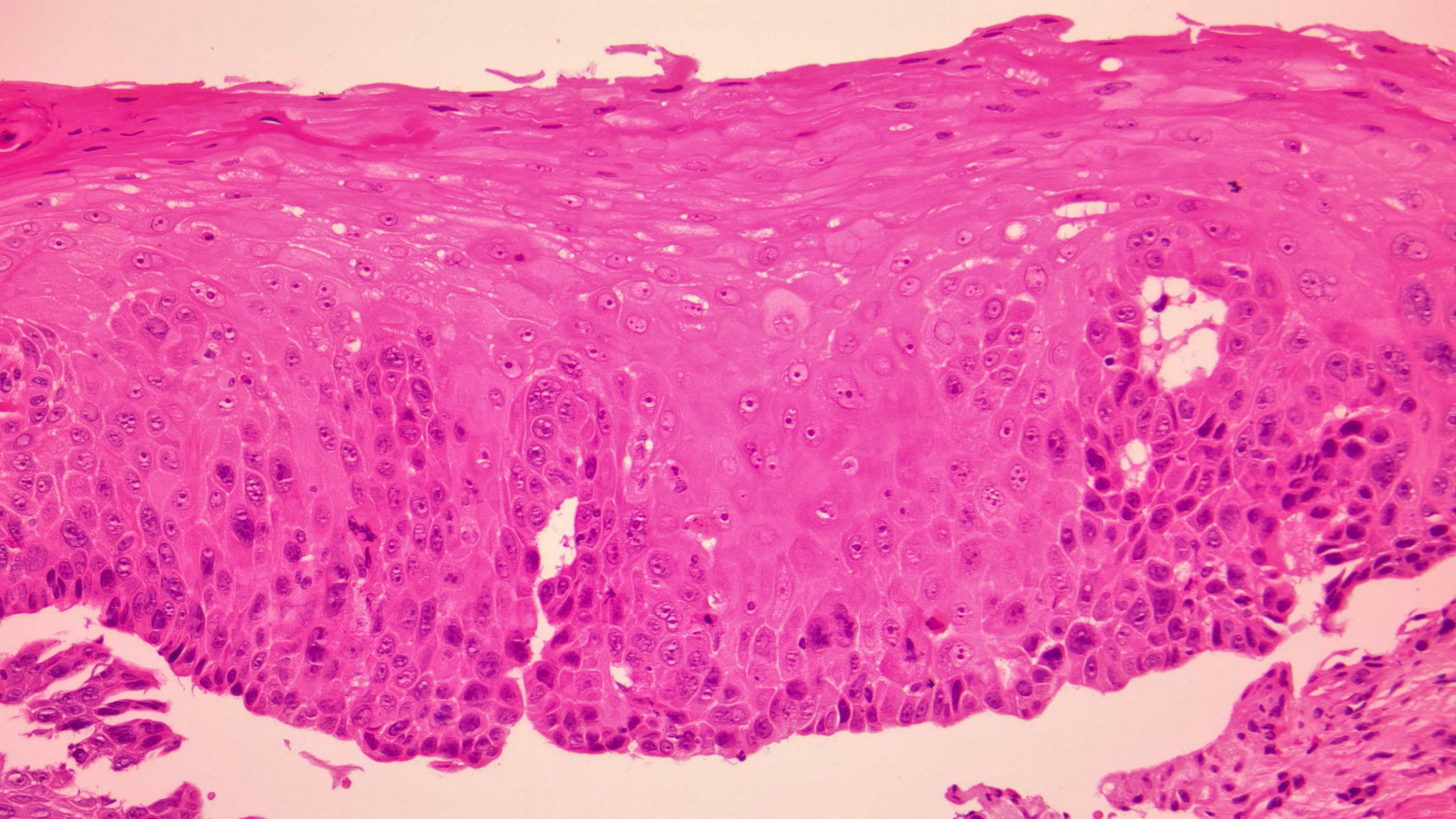
Mario Sarbia, Stefan Wolfer, Diana Karimi, and Albert Eimiller

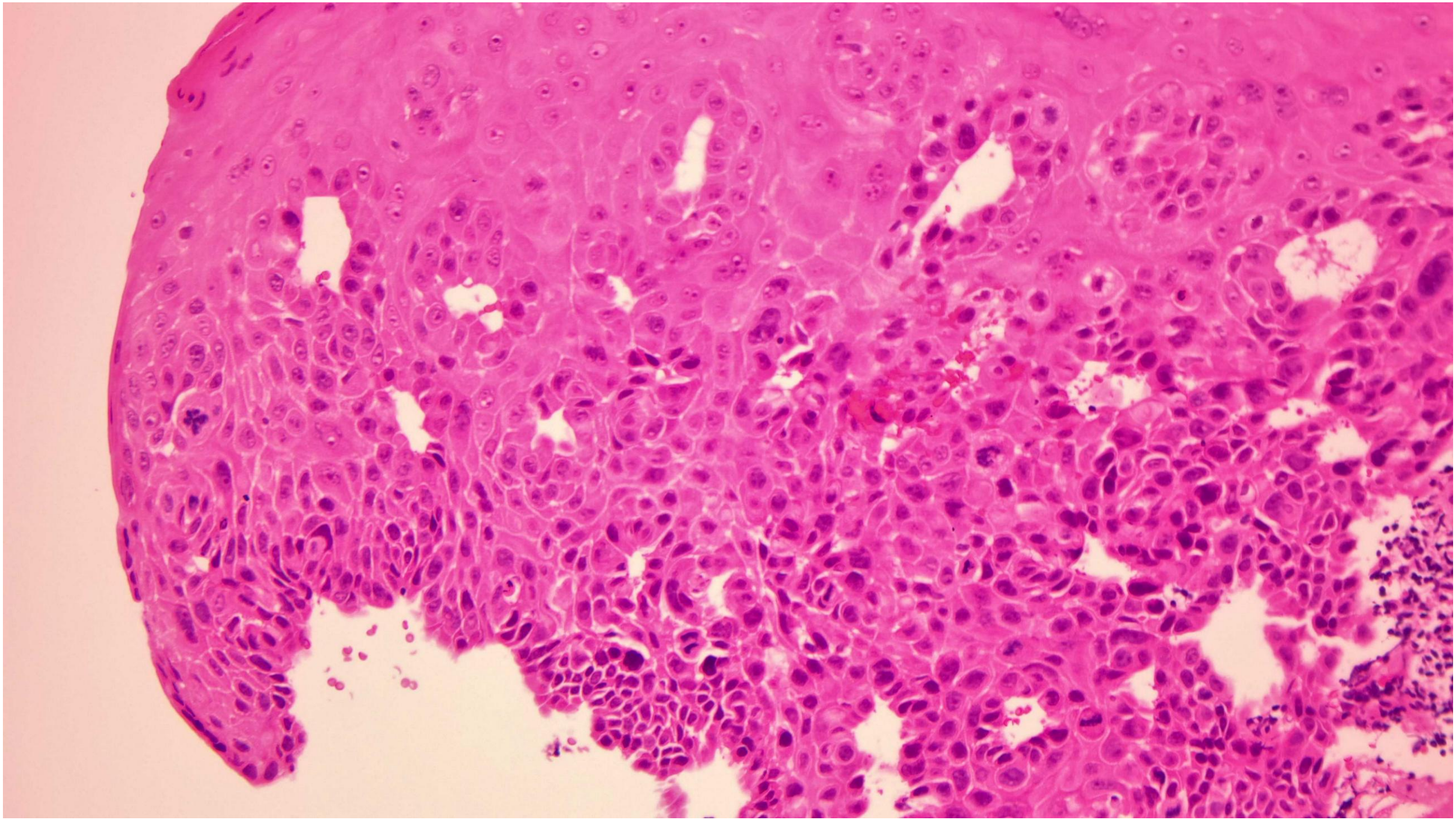
Squamous Neoplasia in the Esophagus

Deepika Savant, MD; Qingzhao Zhang, MD, PhD; Zhaohai Yang, MD, PhD

Arch Pathol Lab Med (2021) 145 (5): 554–561.

https://doi.org/10.5858/arpa.2020-0058-RA **Article history**





Oesophagus 3 - Molecular testing and poorly differentiated tumours

- The molecular test depends on the tumour type and location
  - SCC - PD-L1
  - Adenocarcinoma or undifferentiated (inc reaching GOJ) - MMR, PD-L1, Her-2

- Requires at least intramucosal carcinoma and more than 100 tumour cells

- **Pitfall** - correct subtyping of poorly differentiated carcinoma
  - consider - p40, CDX2, synapto/chromo, Ki-67
- **Pitfall** - external infiltration
  - complete clinical history/consider TTF1

Oesophagus 4 - Should you do p53 immunohistochemistry on every Barrett's biopsy?

Guideline

Thieme

Diagnosis and management of Barrett esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

Authors

Bas L. A. M. Weusten[1,2], Raf Bisschops[3], Mario Dinis-Ribeiro[4], Massimiliano di Pietro[5], Oliver Pech[6], Manon C. W. Spaander[7], Francisco Baldaque-Silva[8,9], Maximilien Barret[10], Emmanuel Coron[11,12], Glòria Fernández-Esparrach[13], Rebecca C. Fitzgerald[5], Marnix Jansen[14], Manol Jovani[15], Ines Marques-de-Sa[4], Arti Rattan[16], W. Keith Tan[5], Eva P. D. Verheij[17], Pauline A. Zellenrath[7], Konstantinos Triantafyllou[18], Roos E. Pouw[17]

Endoscopy 2023; 55: 1124-1146

NICE National Institute for Health and Care Excellence

NICE guideline

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma: monitoring and management

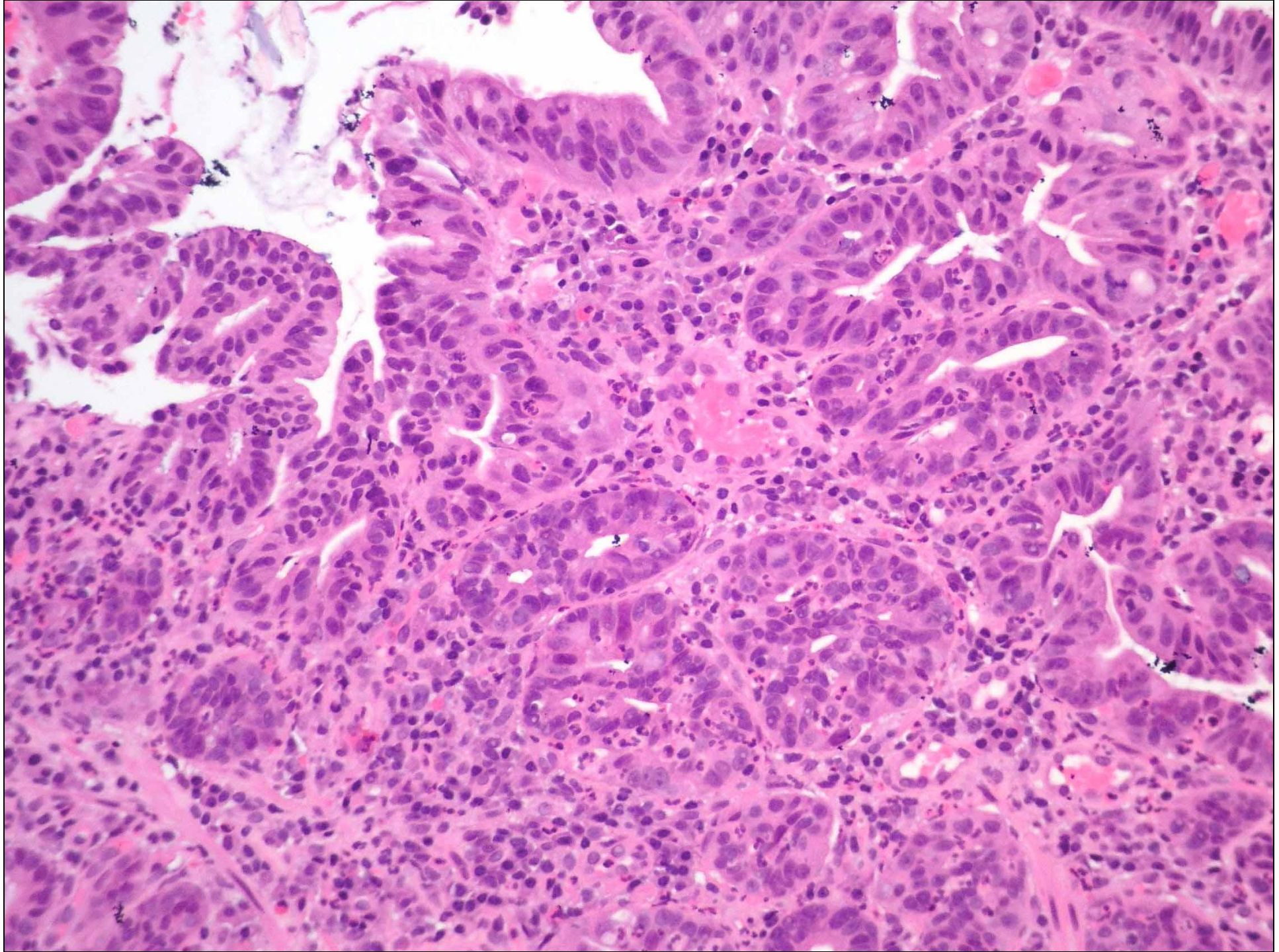
NICE guideline
Published: 8 February 2023

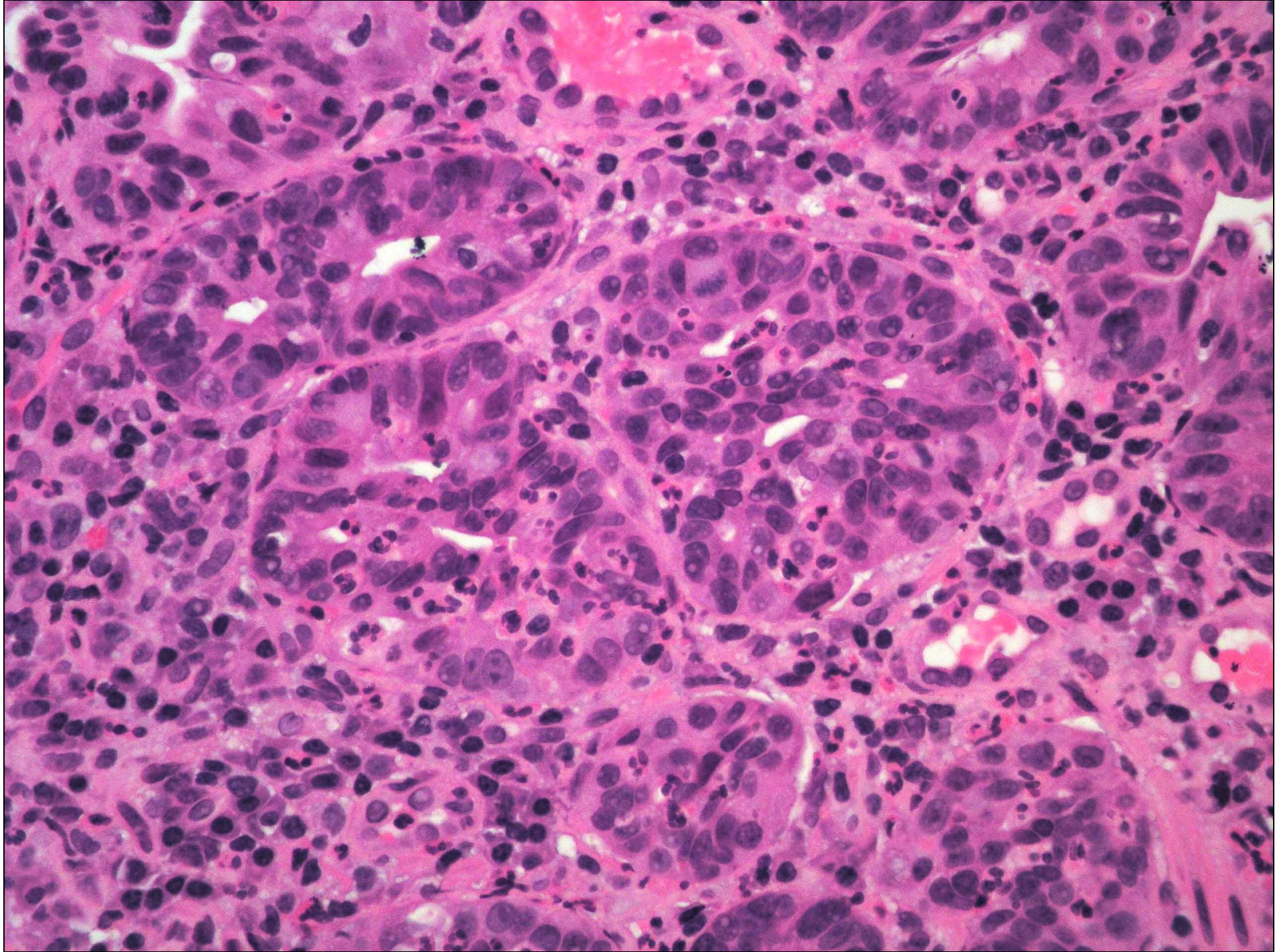
www.nice.org.uk/guidance/ng231

Dysplasia vs Reactive

- Cytology: nuclear enlargement, hyperchromasia, pleomorphism and stratification, nucleoli, mitoses
- Lack of surface maturation
- Abrupt transition with adjacent epithelium
- ?Inflammation

- Crypt & non-intestinal type dysplasia





ORIGINAL ARTICLES

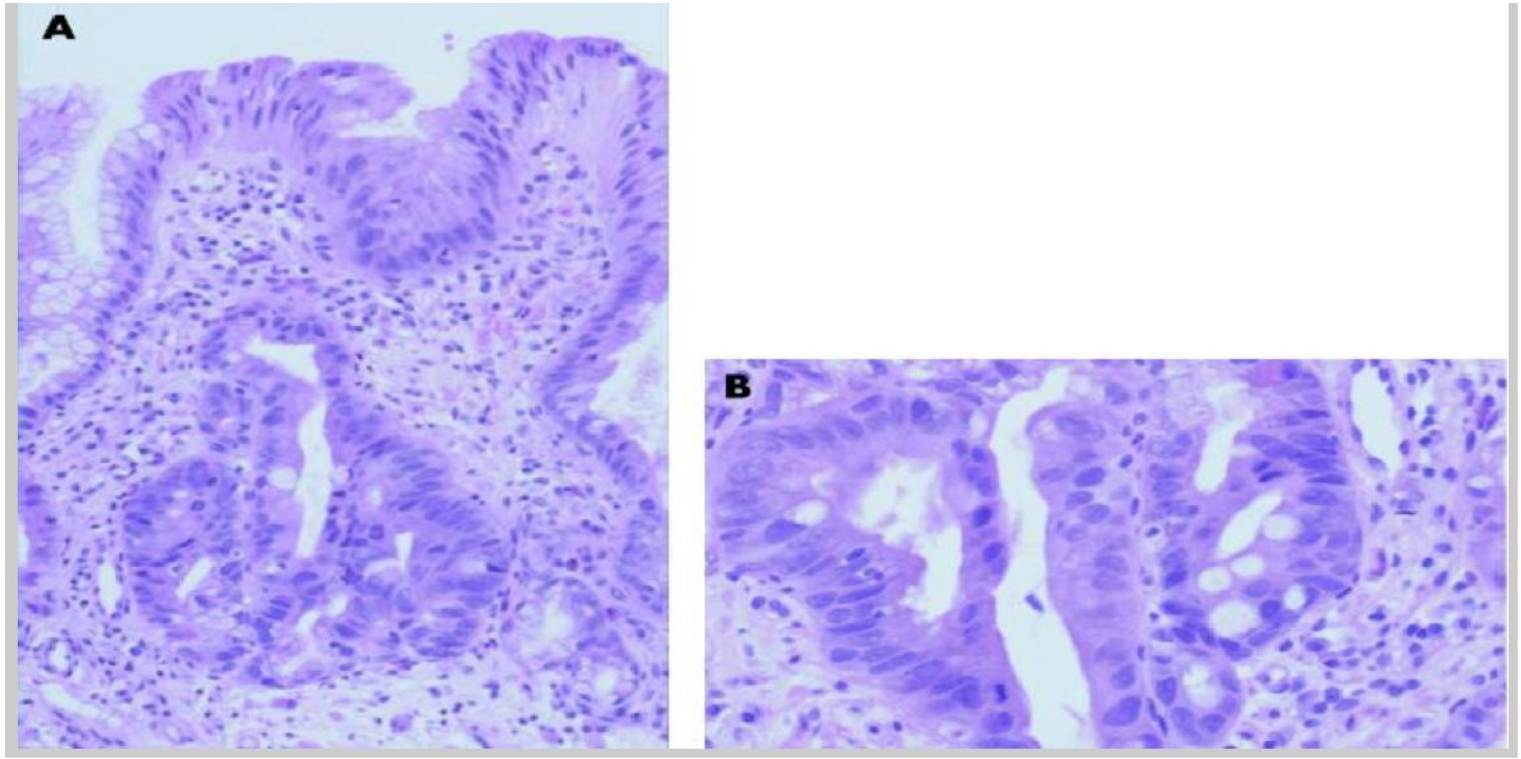
Crypt Dysplasia With Surface Maturation

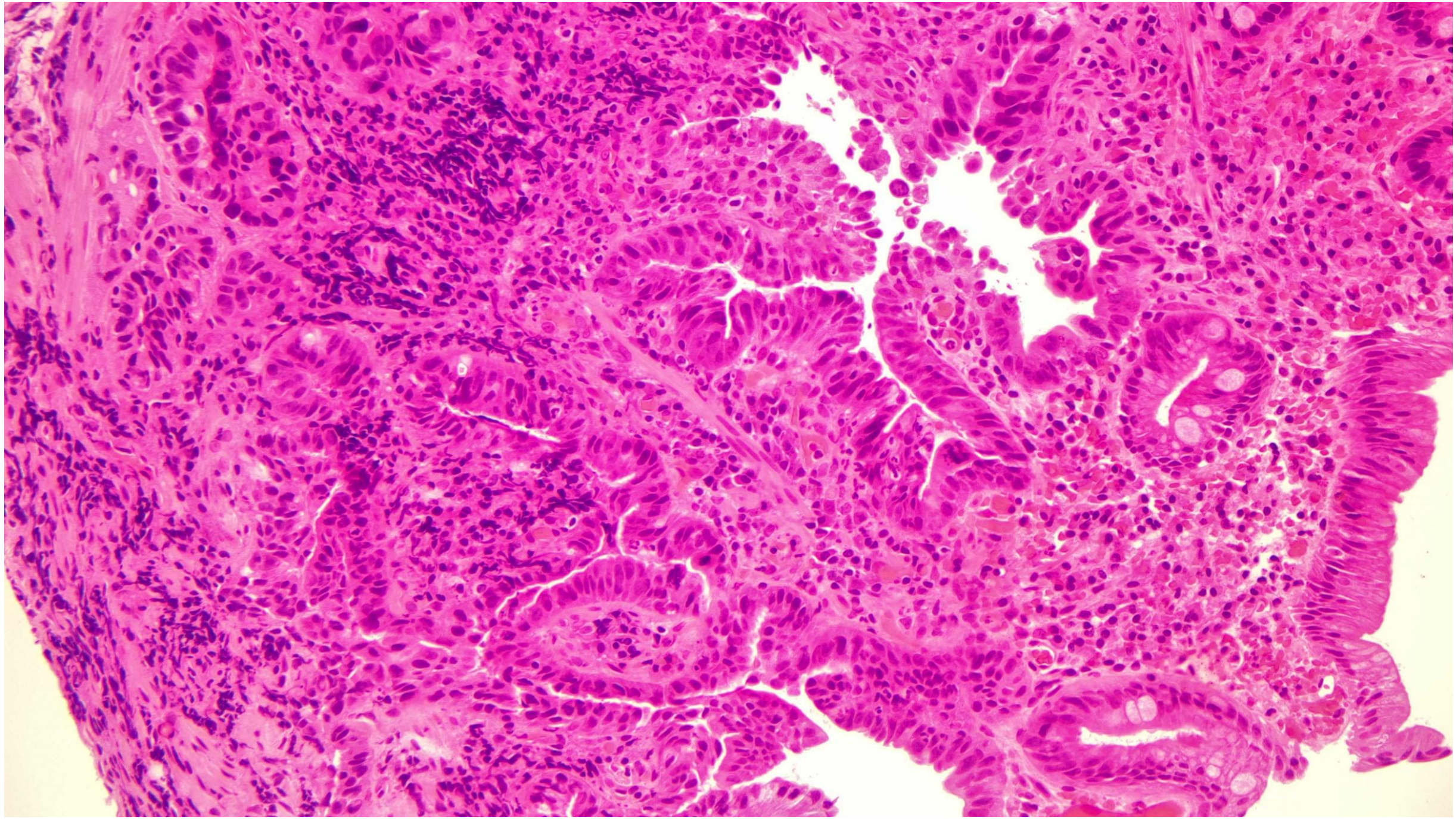
A Clinical, Pathologic, and Molecular Study of a Barrett's Esophagus Cohort

Lomo, Leslie C. MD[*]; Blount, Patricia L. MD[† ‡]; Sanchez, Carissa A. BA[†]; Li, X.[†]; Galipeau, Patricia C. BS[†]; Cowan, David S. BS[†]; Ayub, Kamran MD[§]; Rabinovitch, Peter S. MD, PhD[⊥]; Reid, Brian J. MD, PhD[† ‡ ¶]; Odze, Robert D. MD[*]

Author Information

The American Journal of Surgical Pathology 30(4):p 423-435, April 2006.



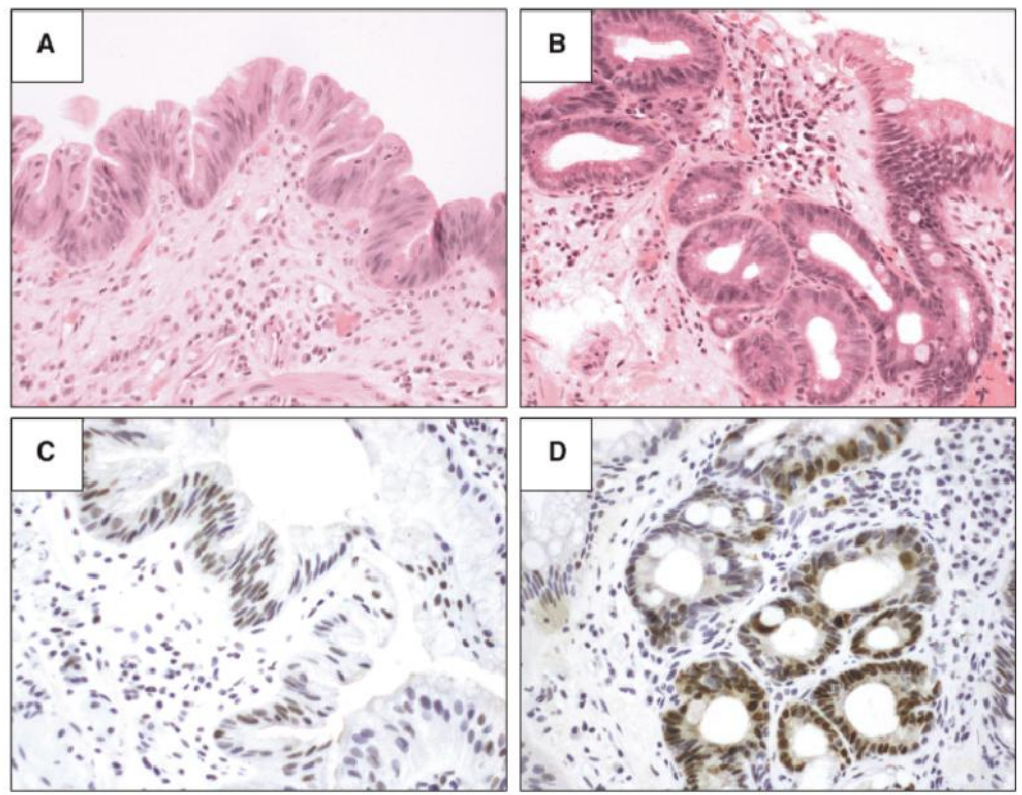


Histopathology

Histopathology 2022, **80**, 1081–1090. DOI: 10.1111/his.14642

The utility of P53 immunohistochemistry in the diagnosis of Barrett's oesophagus with indefinite for dysplasia

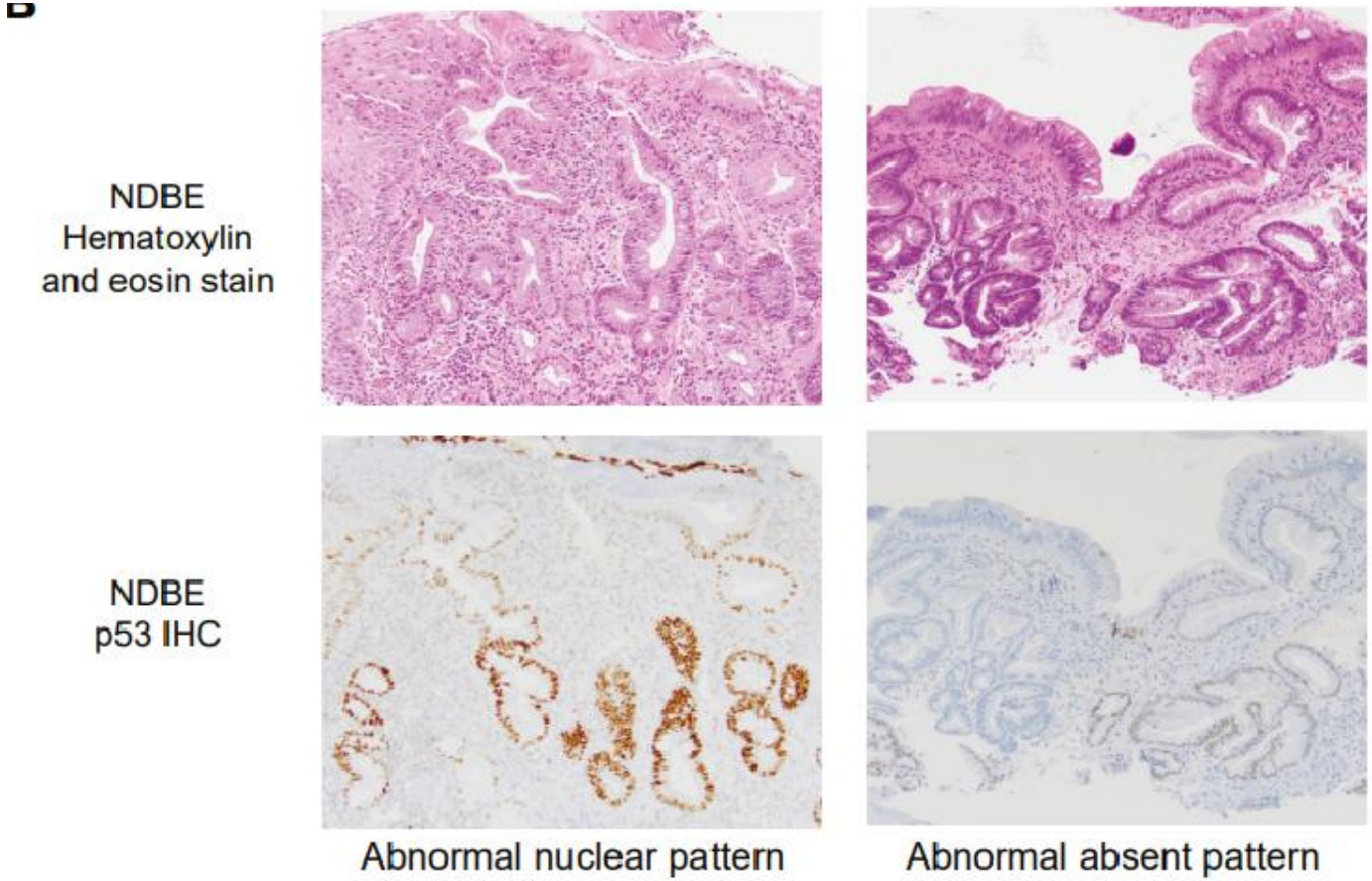
Wladyslaw Januszewicz,[1,2] Nastazja D Pilonis,[1] Tarek Sawas,[3] Richard Phillips,[1] Maria O'Donovan,[4] Ahmad Miremadi,[4] Shalini Malhotra,[4] Monika Tripathi,[4]



Gastroenterology 2022;162:468–481

Abnormal *TP53* Predicts Risk of Progression in Patients With Barrett's Esophagus Regardless of a Diagnosis of Dysplasia

Mark Redston,[1] Amy Noffsinger,[2] Anthony Kim,[3] Fahire G. Akarca,[3] Marianne Rara,[4] Diane Stapleton,[2] Laurel Nowden,[2] Richard Lash,[5] Adam J. Bass,[3,6] and Matthew D. Stachler[4]

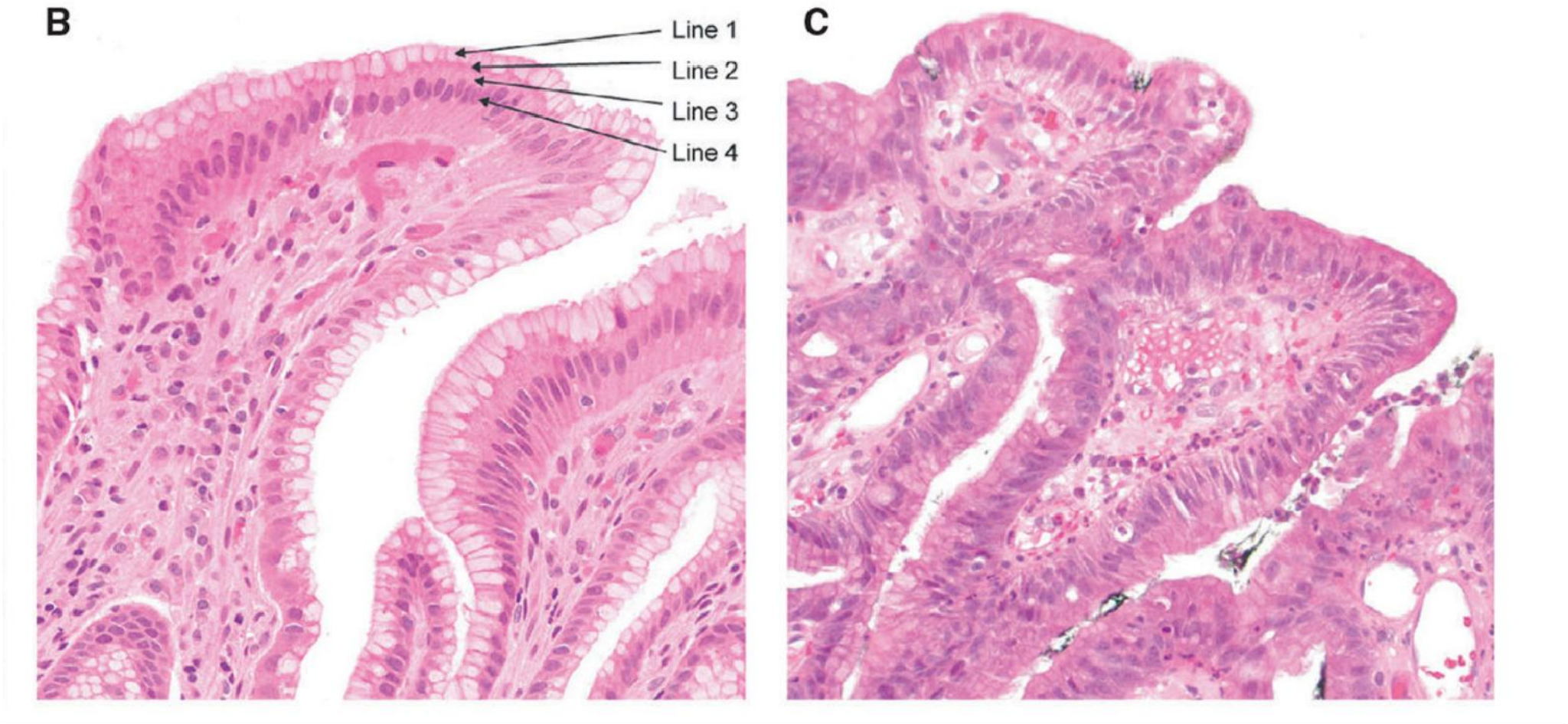


Stomach 1 - Reactive vs Dysplastic

Potential mimics of dysplasia

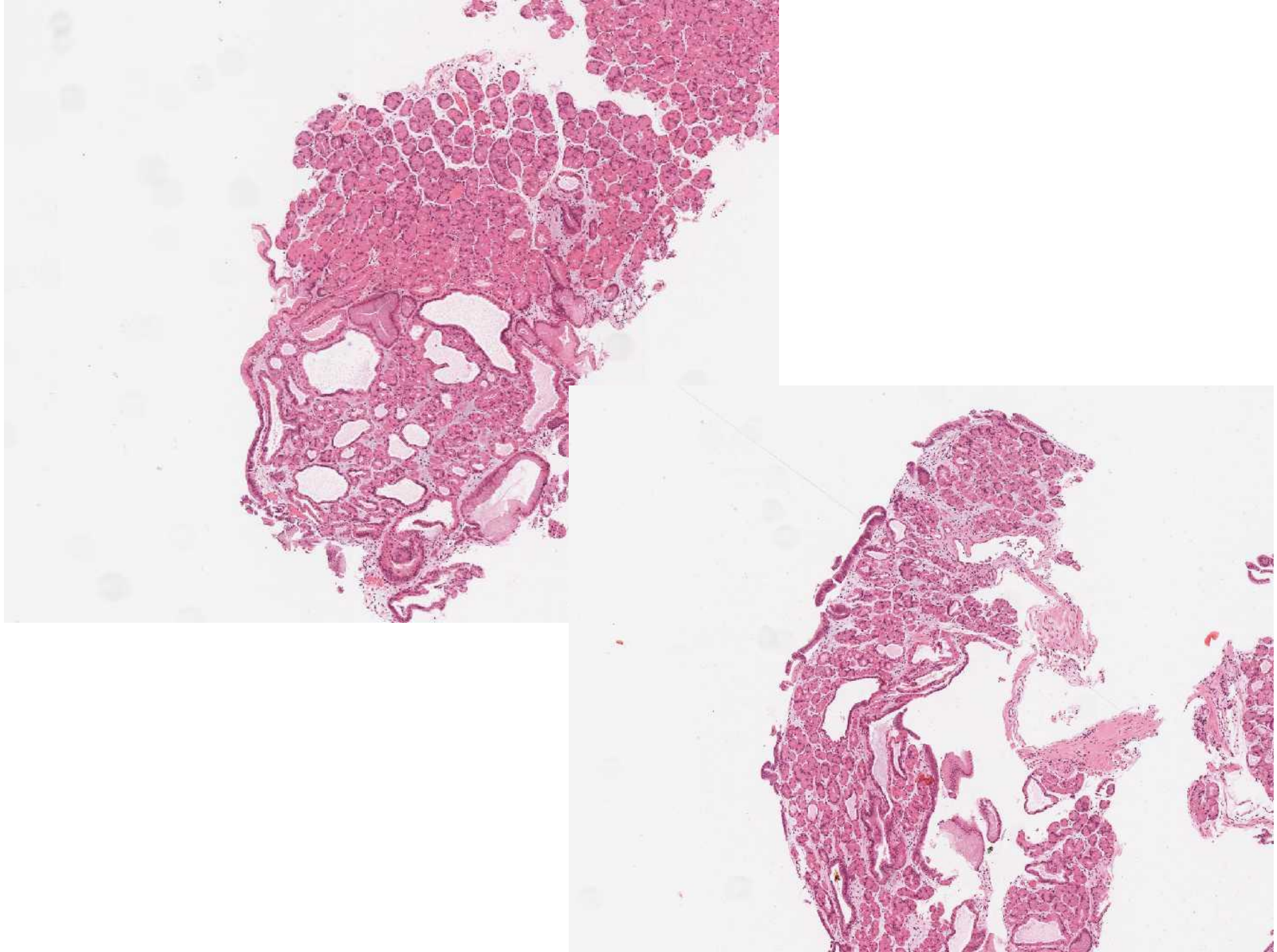
- Florid reactive gastritis
- Ulcer edge/erosion
- Medication associated
  - Iron pill, mycophenolate
- Ischaemic gastritis
- Radiation associated changes

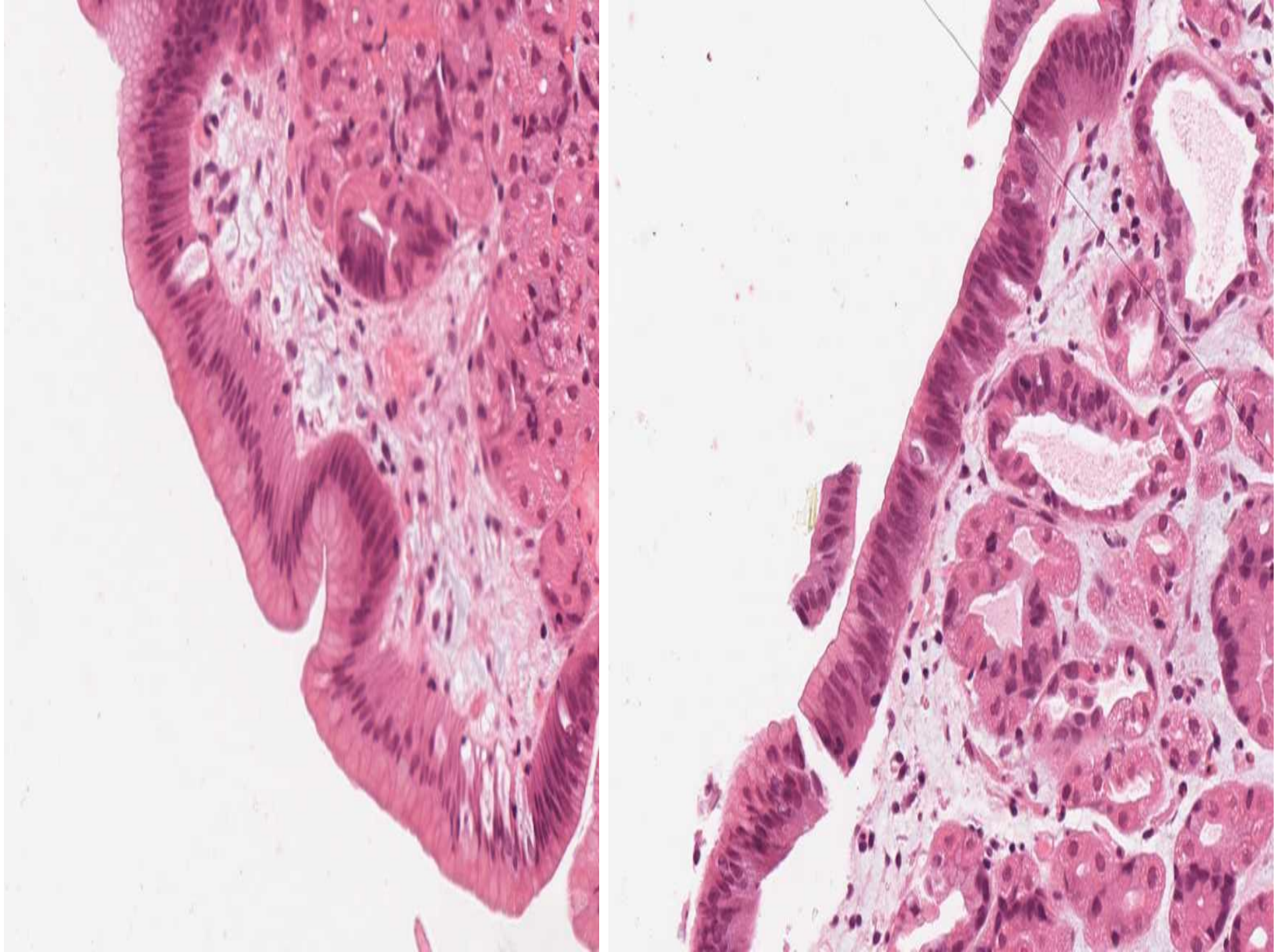
- **Clinical history & endoscopic impression**



from Waters KM et al Histopath 2021; 78: 453-458

Stomach 2 - Fudic cystic gland polyps with dysplasia





Histopathology

Histopathology 2022, **80**, 314–321. DOI: 10.1111/his.14549

High interobserver variability and frequent overdiagnosis of dysplasia in fundic gland polyps can be improved by detecting atypia on the surface epithelium and an abrupt transition to non-neoplastic cells

Christine E Orr,[1] Debra Beneck,[1] Jose Jessurun,[1] Lihui Qin,[1] Kathrin Tyryshkin,[2] Rhonda K Yantiss[1] & Yao-Tseng Chen[1]

[1]*Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, USA, and* [2]*Department of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada*

Characteristics evaluated:

Atypical cells in surface epithelium

Abrupt transition between atypical and non-lesional populations

Nuclear pseudostratification

Mitotic figures in superficial glands

Apoptotic epithelial cells

Loss of apical mucin

Histopathology

Histopathology 2018, **72**, 1172–1179. DOI: 10.1111/his.13485

Comparison of dysplastic fundic gland polyps in patients with and without familial adenomatous polyposis

Shana F Straub,[1] Michael G Drage[2] & Raul S Gonzalez[2]

[1]*Office of the Chief Medical Examiner of New York City, New York, NY, USA, and* [2]*Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA*

Histologically they look the same

Clinically different - in FAP

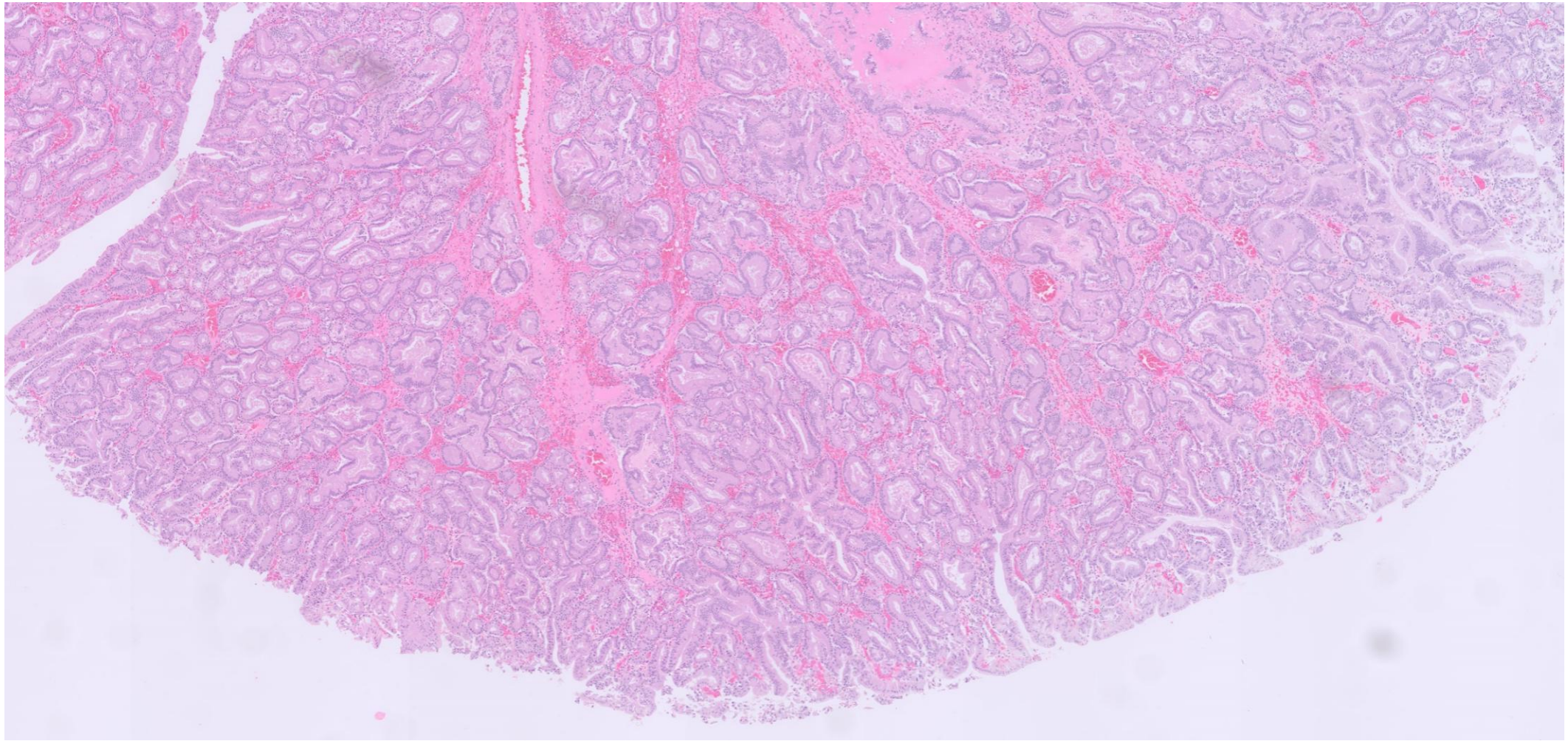
- Younger at presentation
- Less likely to be on PPI
- More likely to get another dysplastic FCGP
- May have duodenal polyps
- Both subsets get non-gastric cancer at similar rates

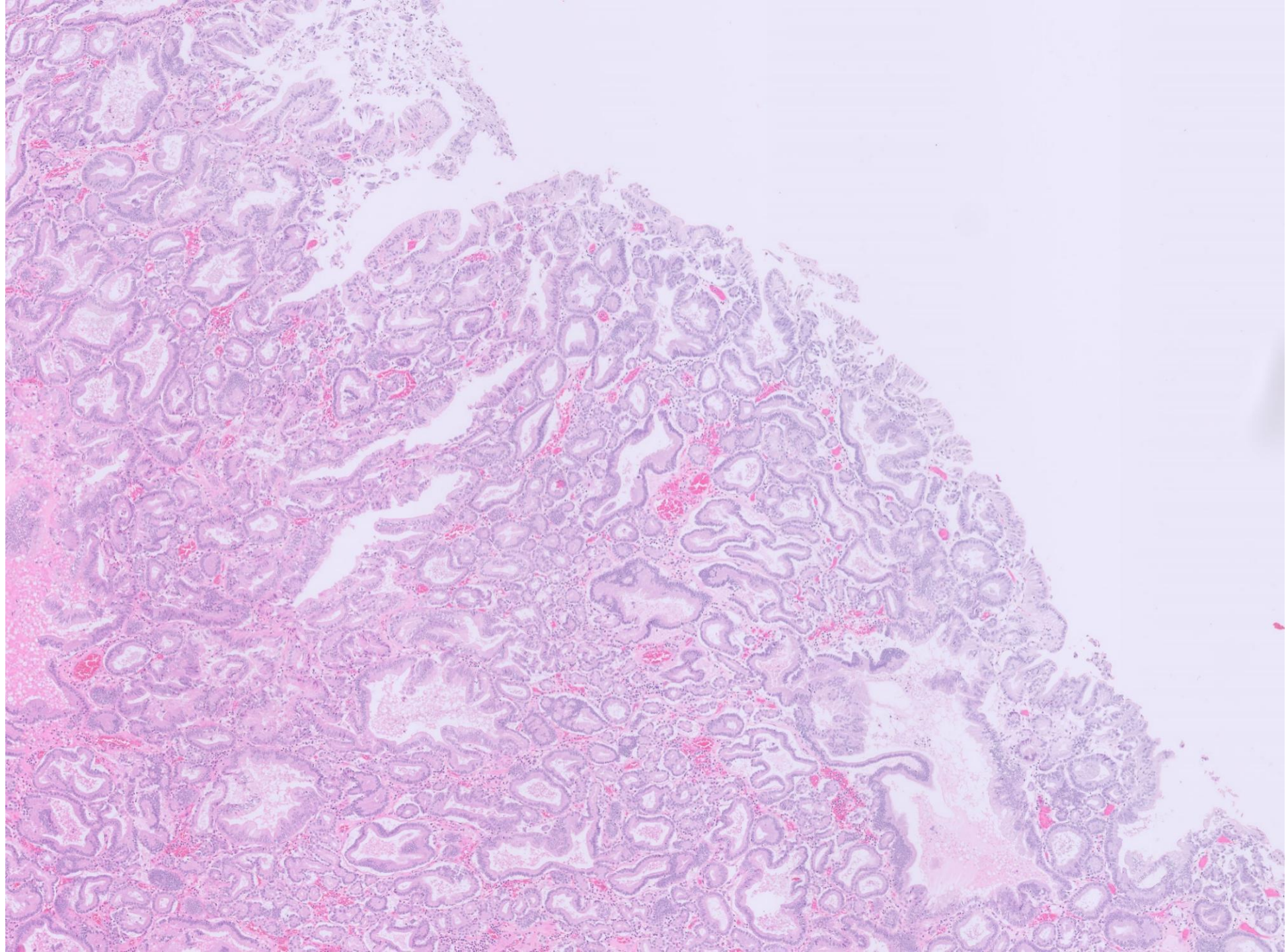
Stomach 3 - Non-conventional dysplasia

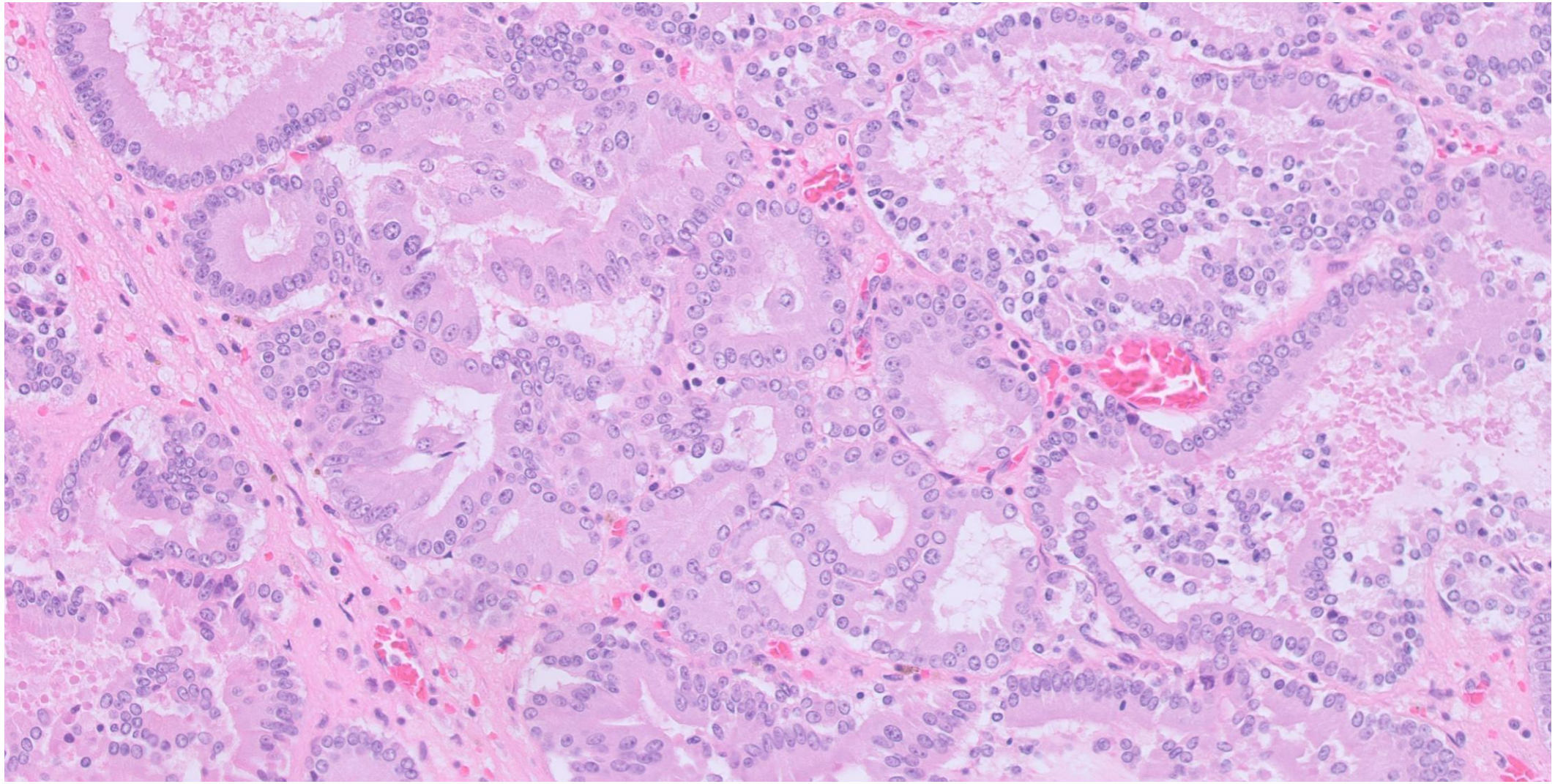
- Arise from surface (intestinal, foveolar) or glands (pyloric, oxyntic)
- May be flat, raised or polypoid lesions
- **Unconventional intestinal**
  - Serrated adenoma
  - Basal crypt/pit dysplasia
- **Non-intestinal**
  - Foveolar dysplasia/adenoma
  - Pyloric gland adenoma
  - Oxyntic gland adenoma

Case

73 year old male, resection of gastric polyp, ?nature.







Pyloric gland adenoma, low grade dysplasia

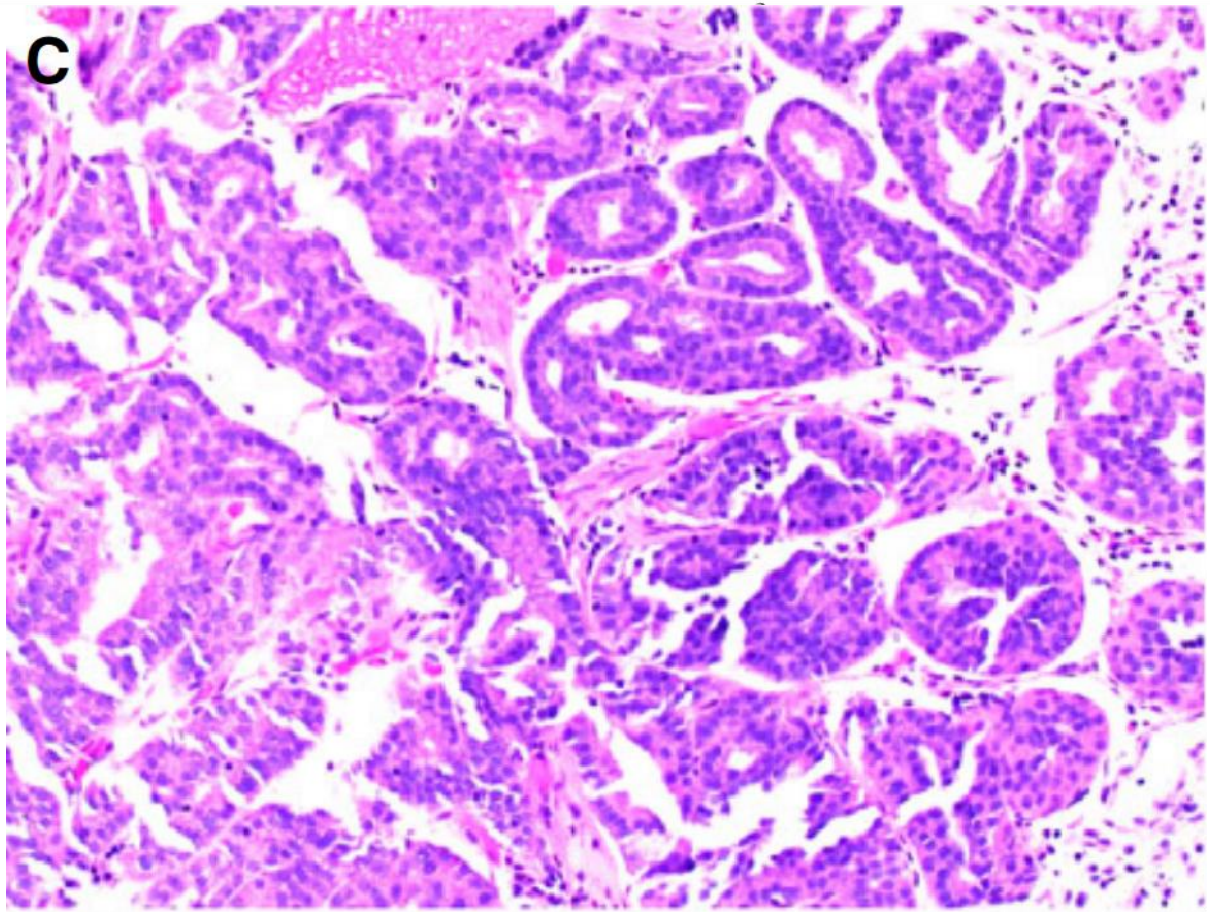
- Typically composed of tightly packed pyloric type glands
- May show low or high grade dysplasia or intramucosal adenocarcinoma
- Express both MUC-6 and MUC-5AC
- Other ‘native gastric adenomas’ include foveolar and oxyntic gland type
- May be associated with FAP
- GNAS/KRAS/APC mutations
- Similar lesion seen in the hepatobiliary tract (gallbladder)

Histopathology

Histopathology 2016, **68**, 825–833. DOI: 10.1111/his.12859

Chief cell-predominant gastric polyps: a series of 12 cases with literature review

Karen Chan,[1,2] Ian S Brown,[3] Trevor Kyle,[4] Gregory Y Lauwers[5] & Marian Priyanthi Kumarasinghe[1,6]



Bile duct and gallbladder

- Stones, stents and instrumentation can cause florid reactive changes in biliary biopsies and brushings

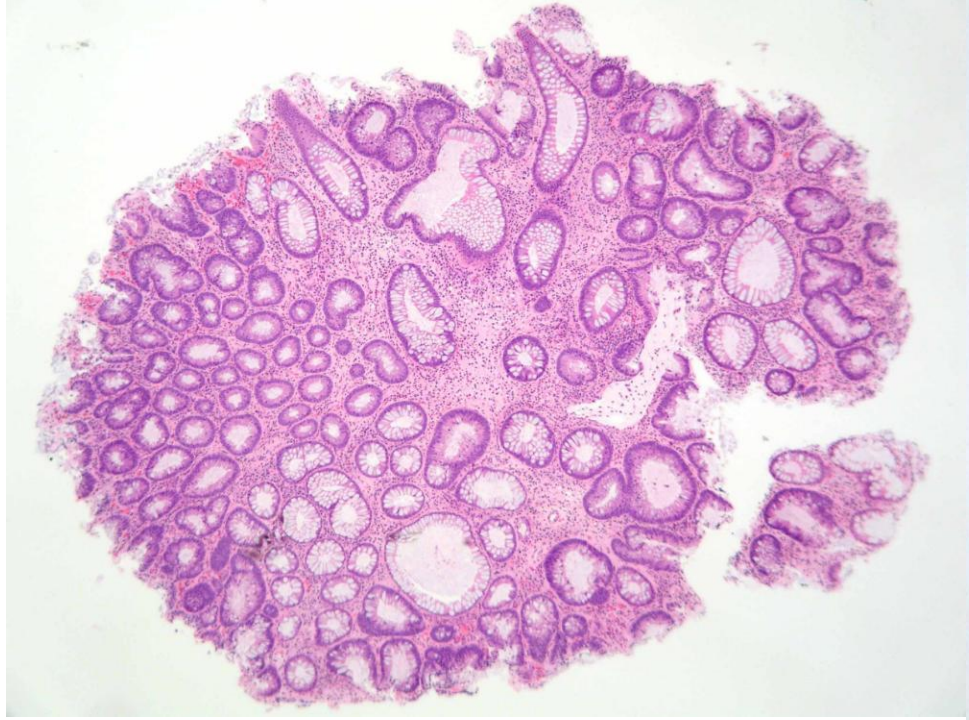
- Dysplasia in gallbladder - LOW - 4 more blocks and confirm cystic duct clear; HIGH - embed the rest

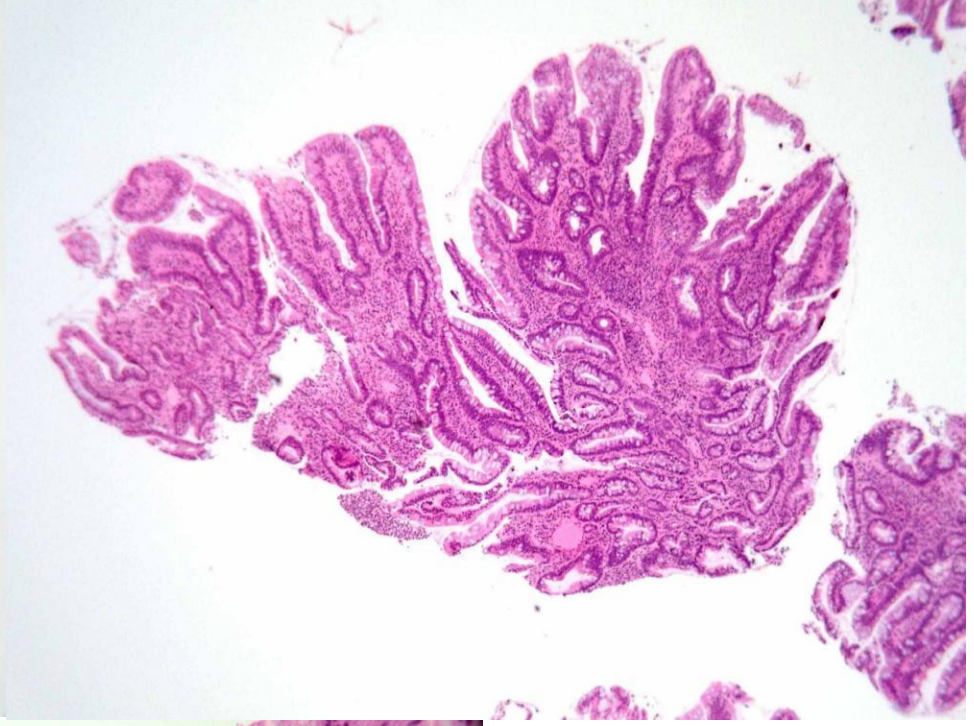
Colon 1 - Dysplasia in IBD

- Endoscopically visible vs detected on random biopsy
- Raised vs flat lesion
- Can it be removed endoscopically
- Low grade dysplasia vs High grade dysplasia vs Adenocarcinoma

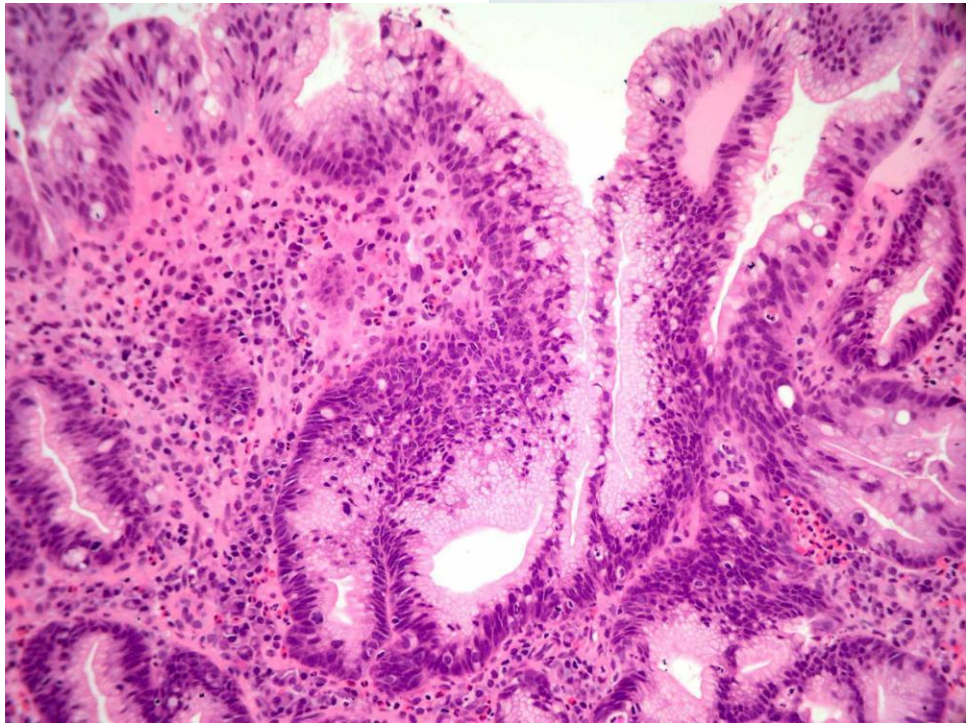
- Confirmed histological diagnosis before undertaking definitive therapy

- p53 may help - strong over-expression & null phenotypes

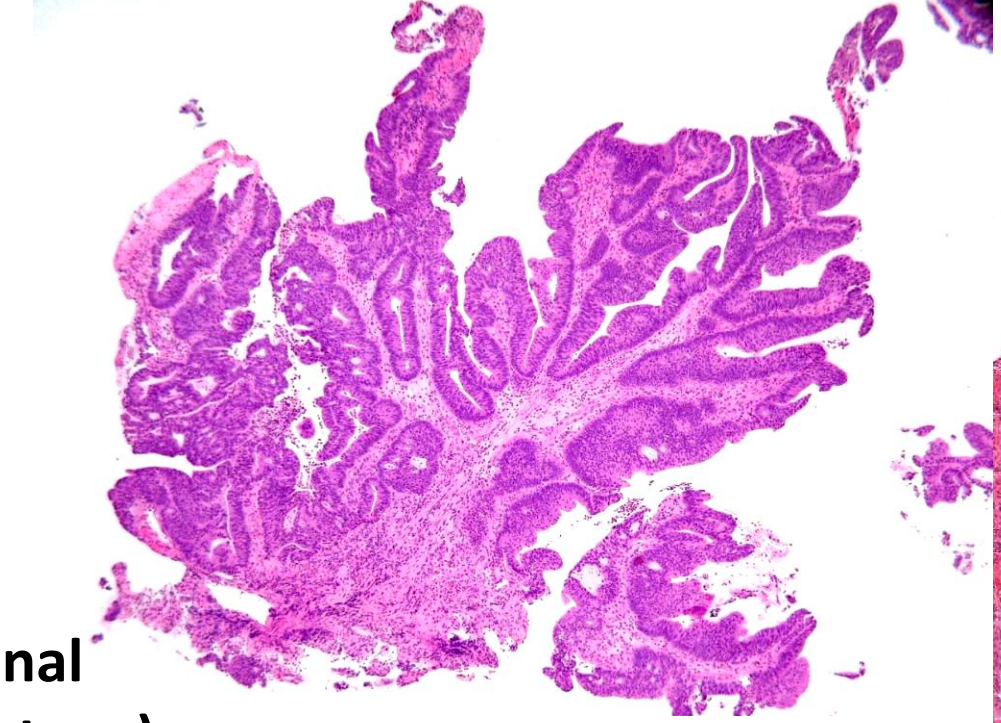


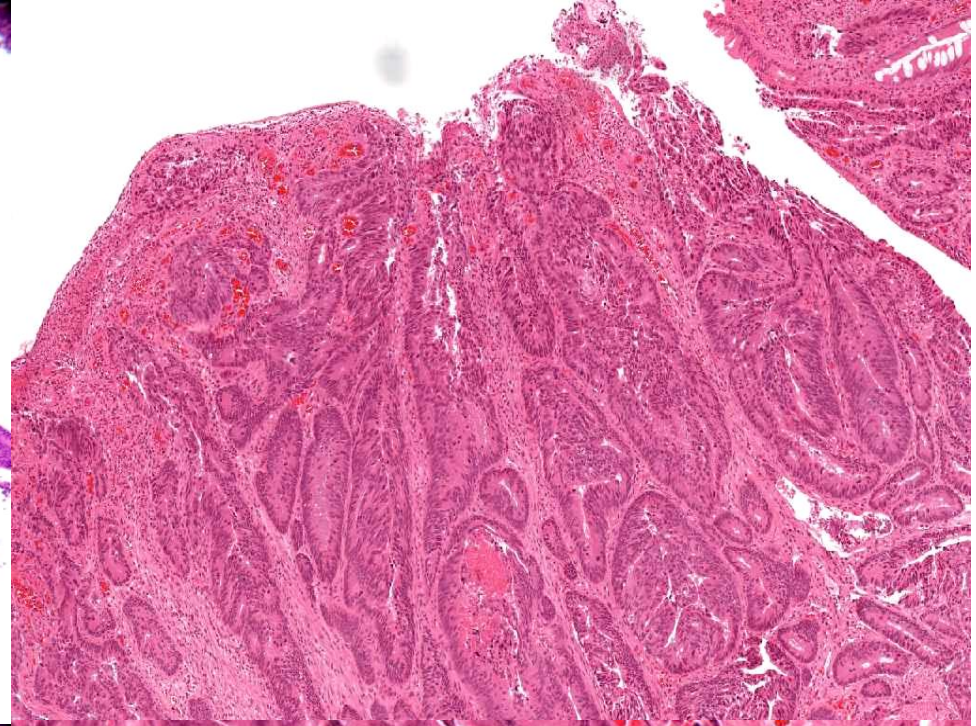


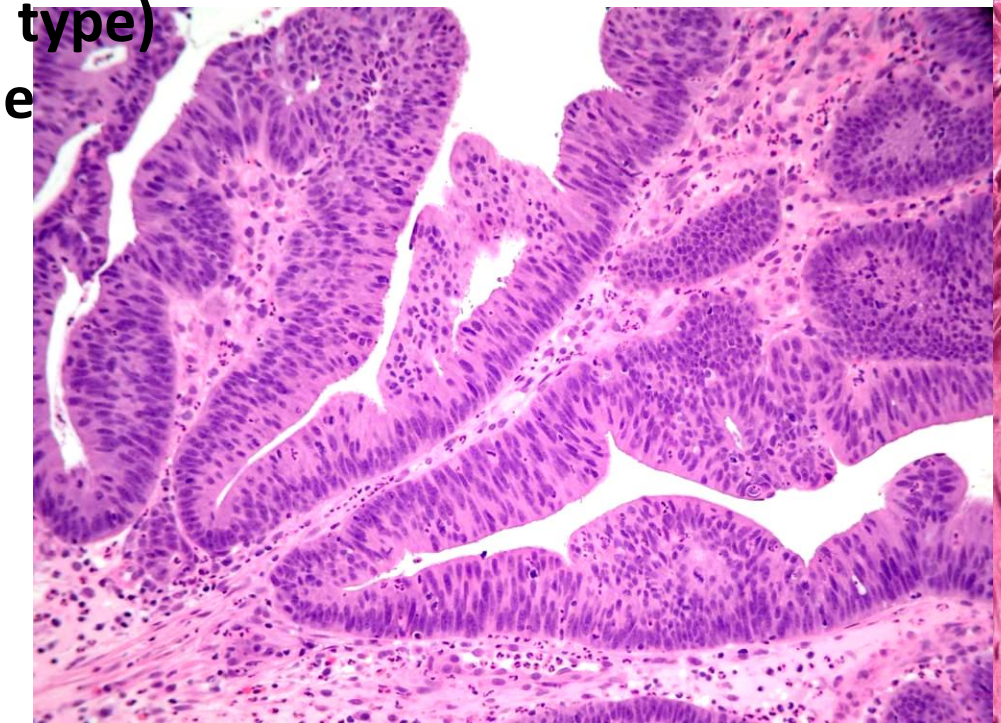
Conventional (adenoma type) low grade dysplasia

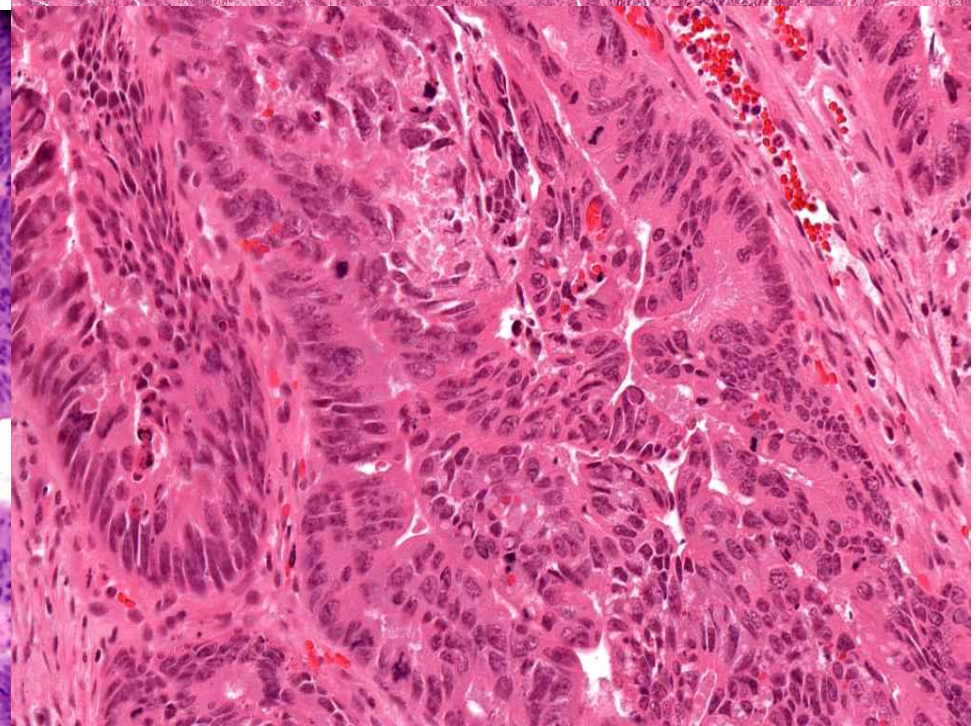


Conventional (adenoma type) HIGH grade dysplasia





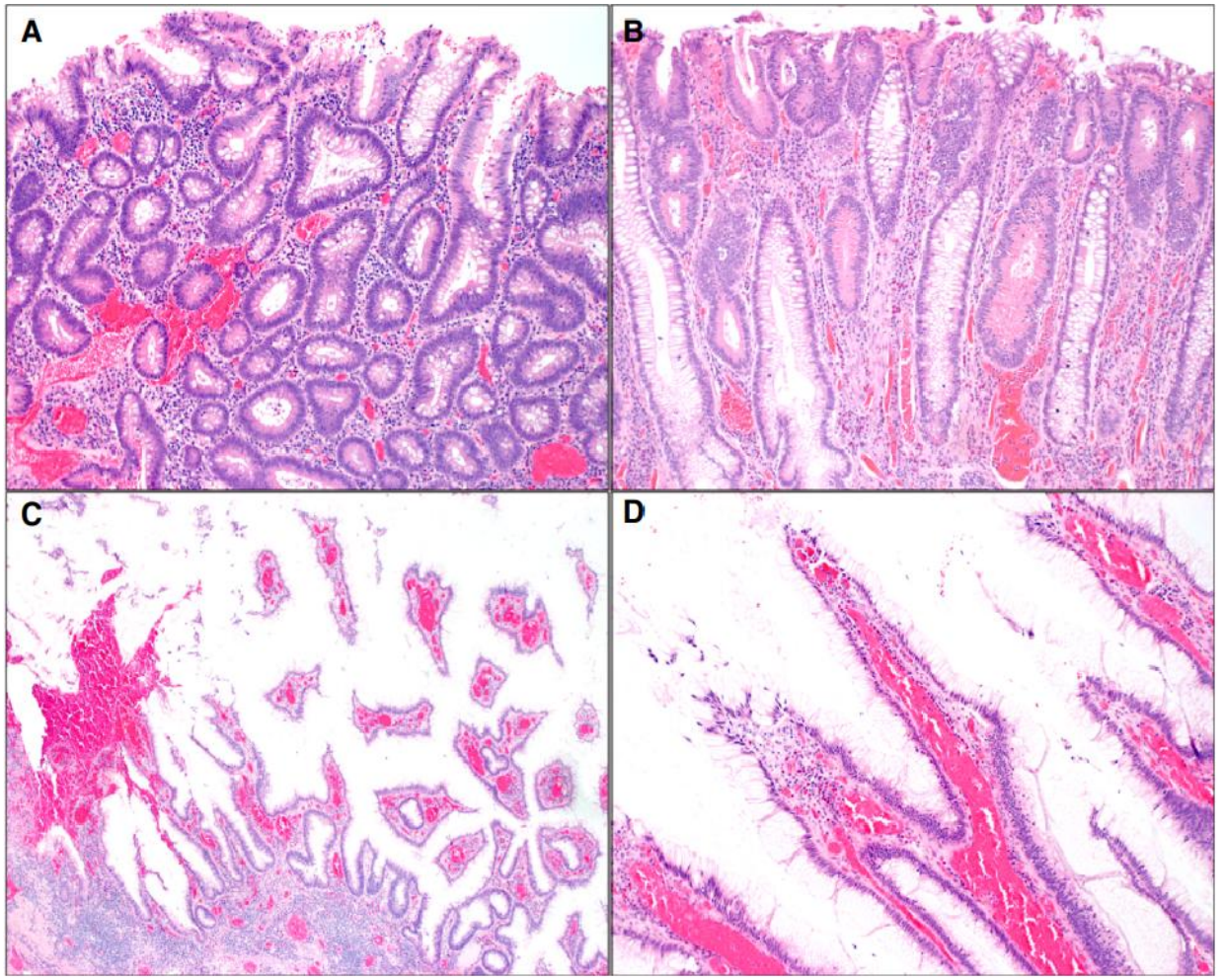




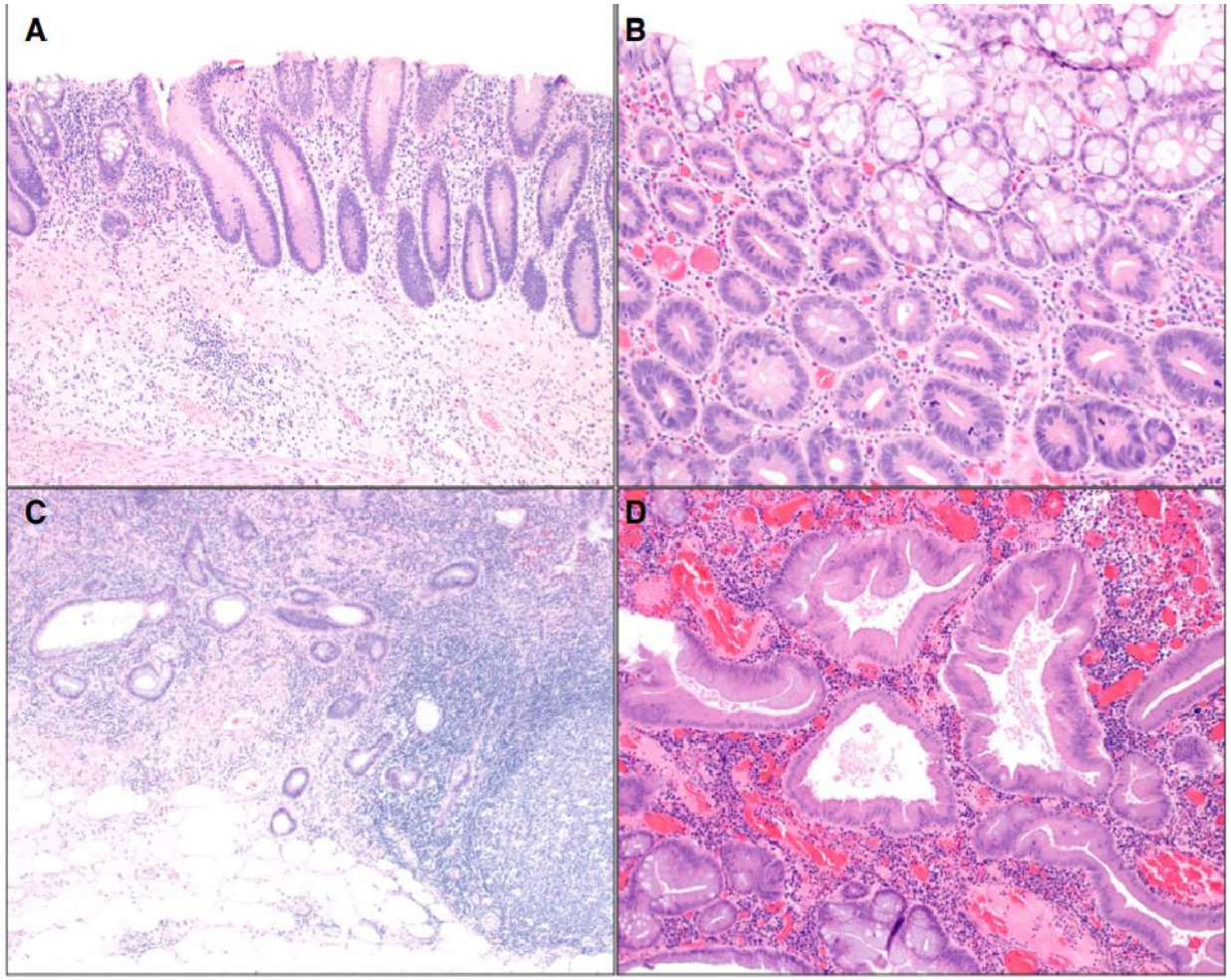
Non-conventional dysplasia

- Dysplasia with increased paneth cell differentiation
- Hypermucinous
- Goblet cell deficient
- Crypt cell dysplasia
- Traditional serrated adenoma-like
- Sessile serrated lesion-like
- Serrated lesion not otherwise specified

- (Serrated epithelial change)



from Bahceci D et al, Histopath 2022; 81: 183-191



from Bahceci D et al, Histopath 2022; 81: 183-191

Understanding is incomplete

- Are these subtypes more likely to be endoscopically invisible?
- Is there conventional dysplasia also present?
- Some of them have high risk genetics - should they be managed aggressively?
- Do we need to lump or split - reproducible classification needed to allow comparison between studies
- Role of p53 - strong overexpression useful in diagnosis

Review

Recently described types of dysplasia associated with IBD: tips and clues for the practising pathologist

Zahra Alipour, Kristen Stashek

ABSTRACT
Longstanding inflammatory bowel disease (especially in patients with severely active disease or primary sclerosing cholangitis) is associated with an increased risk of developing dysplasia and adenocarcinoma.

At the molecular level, colitis-associated carcinomas (CAC) differ remarkably from their sporadic counterparts. Although *APC* mutations occur early in the adenoma-to-carcinoma sequence of many sporadic lesions, CAC often lacks *APC* mutations.[11]

J Clin Pathol 2024; 77: 77-81

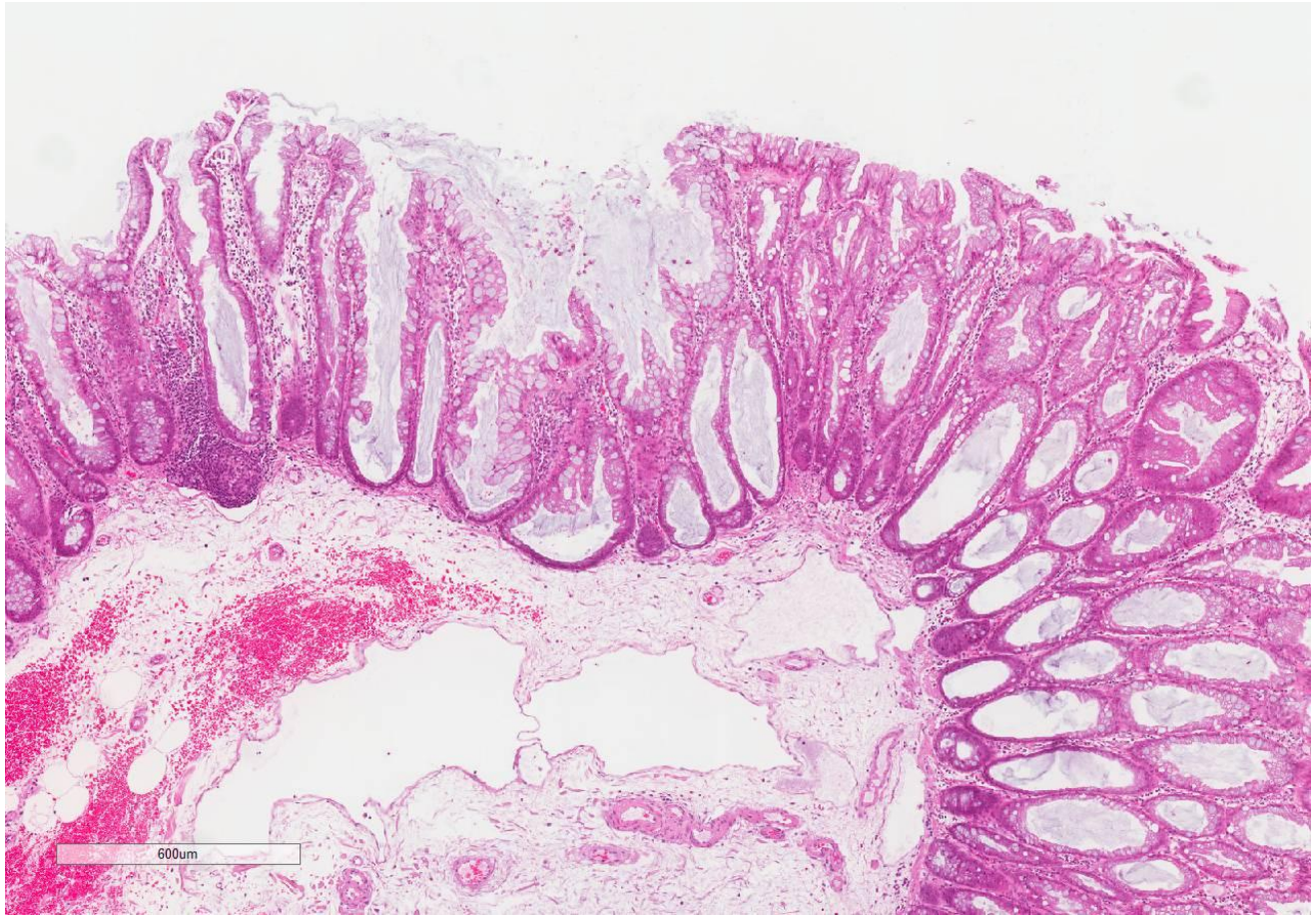
› Hum Pathol. 2023 Aug:138:49-61. doi: 10.1016/j.humpath.2023.05.008. Epub 2023 May 27.

Colorectal dysplasia in chronic inflammatory bowel disease: a contemporary consensus classification and interobserver study

Noam Harpaz [1], John R Goldblum [2], Neil A Shepherd [3], Robert H Riddell [4], Carlos A Rubio [5], Michael Vieth [6], Helen H Wang [7], Robert D Odze [8]

Colon 2 - Sessile serrated lesions

Remember:
Herniation into submucosa



Remember:
Perineuriomatous stroma

J Clin Pathol. 2019 Aug;72(8):562-565. doi: 10.1136/jclinpath-2019-205849. Epub 2019 May 16.

Intramucosal fat is uncommon in large bowel polyps but raises three differential diagnoses

Newton A C S Wong [1], Orla O'Mahony [2]

- Mucosal perineurioma/serrated polyps with fat among the perineuriomatous stroma
- Extension from a submucosal lipoma
- Intramucosal lipoma (may be associated with Cowden syndrome but more often sporadic)

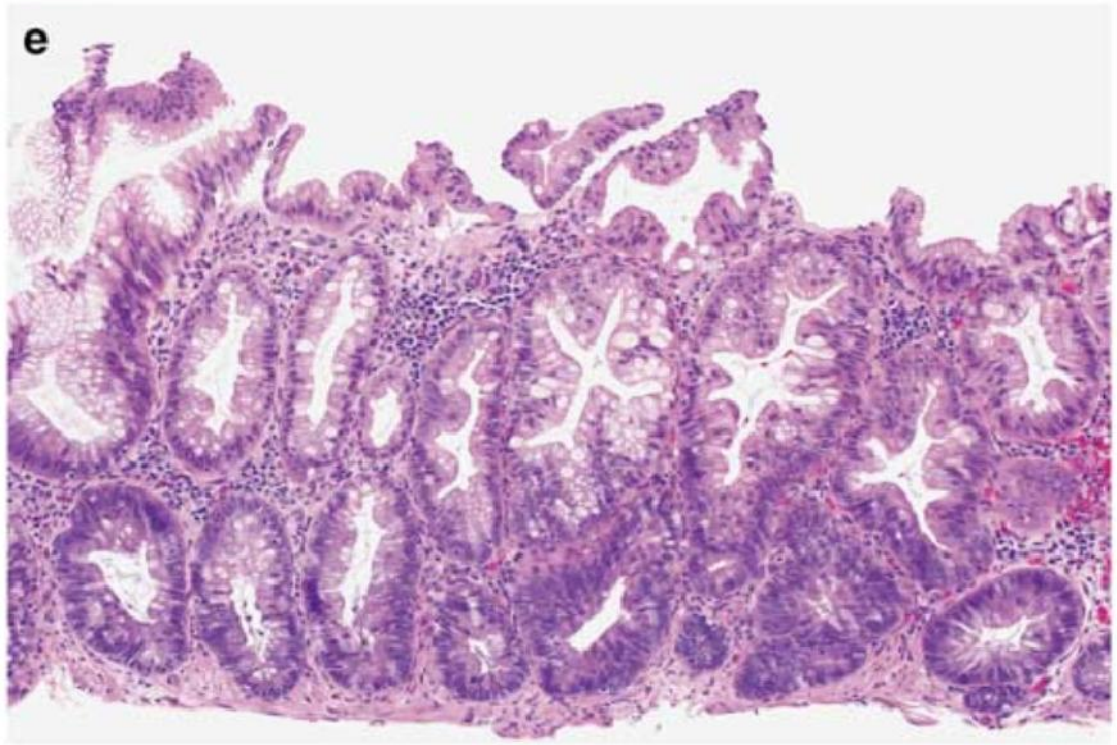
Serrated polyposis

- Either =or>5 serrated lesions proximal to the rectum with all =or>5mm in size and =or>2 being =or>10mm
- Or >20 serrated lesions of any size distributed throughout the large bowel with =or>5 proximal to the rectum
- Any serrated lesion is included in the count
- No single genetic cause clearly identified – should be referred to genetics if suspected

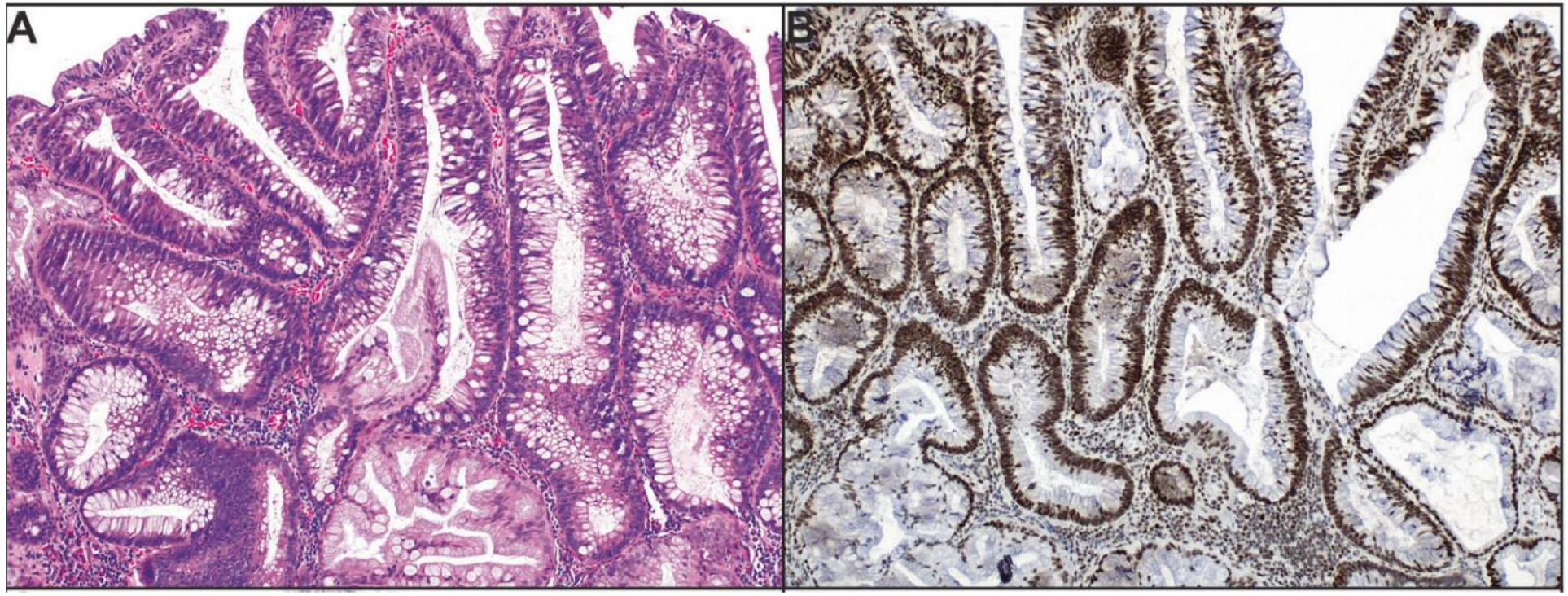
SSL with dysplasia

- Rare lesion
- Important not to overdiagnose
- Consider the possibility of a mixed tubular adenoma/SSL if very discrete cut-off

- Types of dysplasia
  - Adenomatous
  - Serrated
  - Minimal deviation
  - NOS

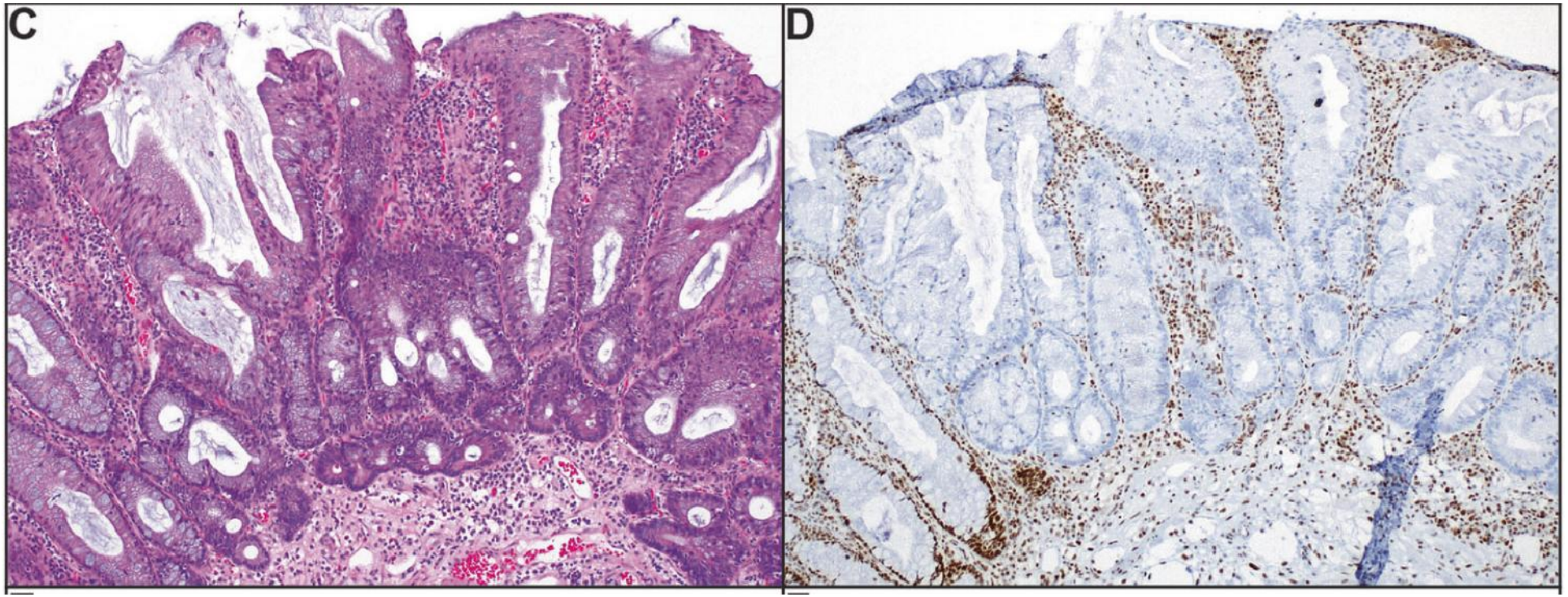


Liu C et al Mod Path 2017 30 1728-1738



SSL with adenomatous dysplasia and retained MLH-1

from Pai RK et al Mod Path 2019; 32 1390 - 1415

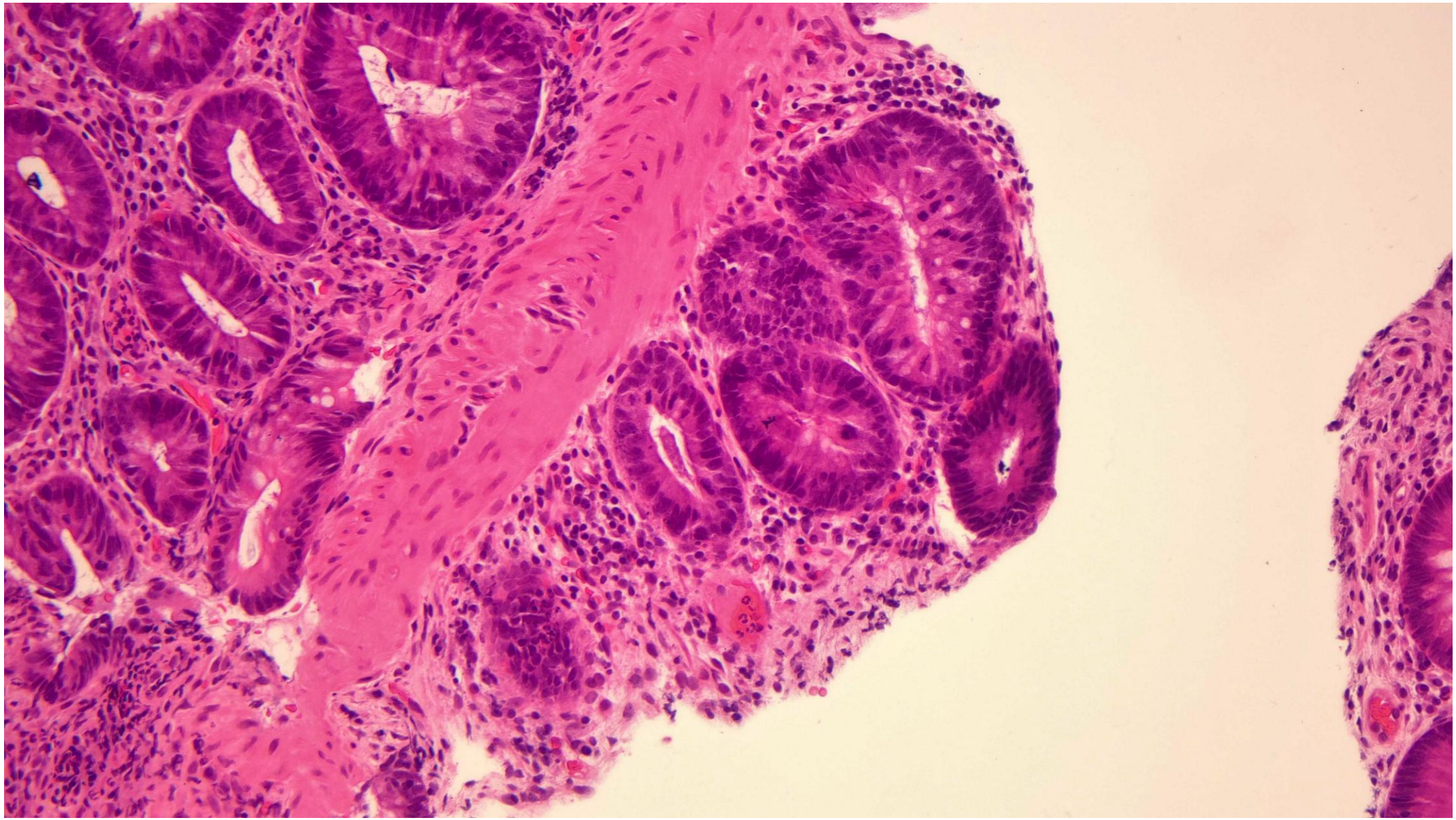


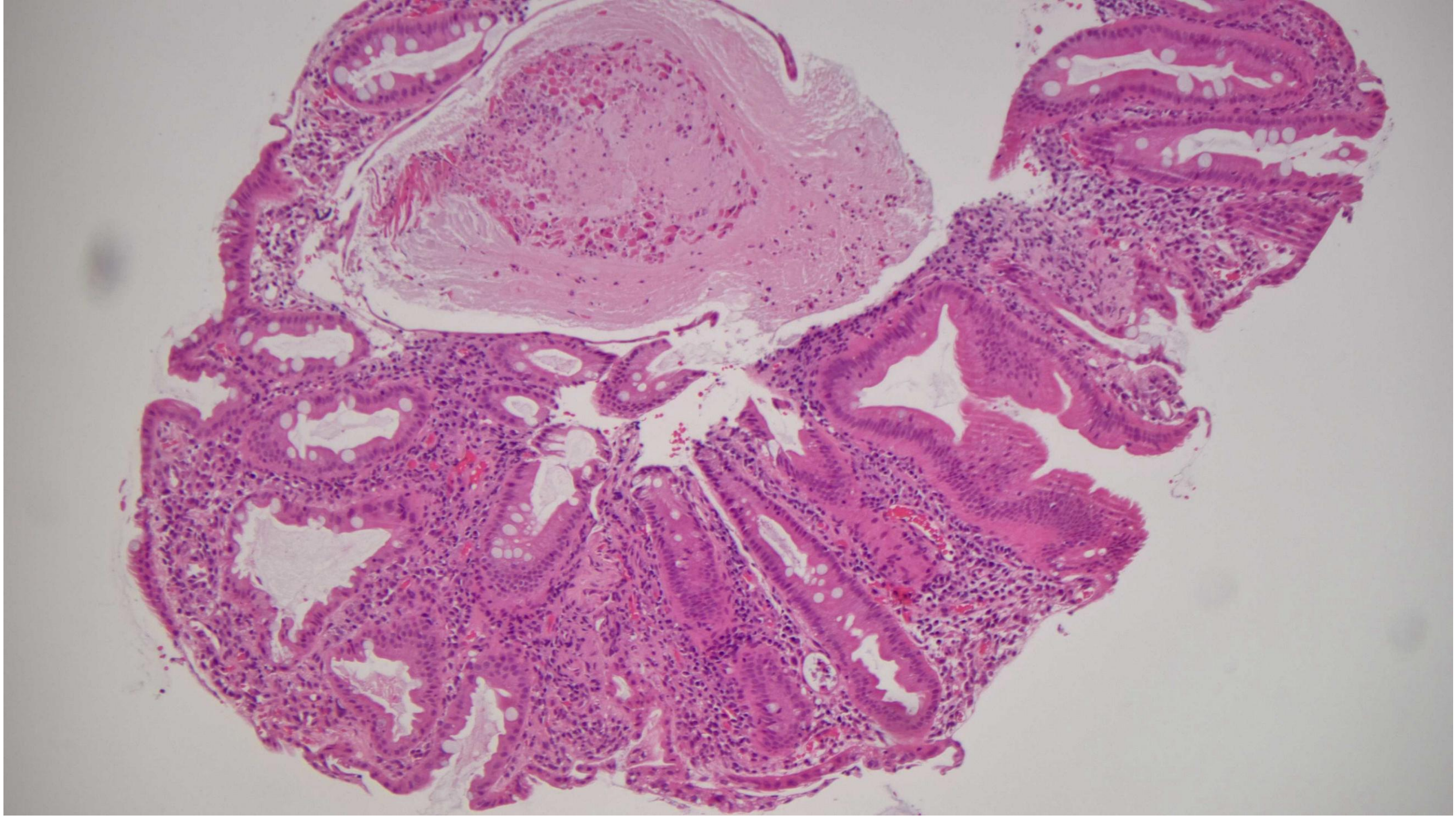
SSL with minimal deviation type dysplasia and loss of MLH-1

from Pai RK et al Mod Path 2019; 32 1390 - 1415

So...should you do an MLH-1 on every SSL?

Context is everything!





And finally - AIN II & p16

- AIN I/II/III vs LSIL/HSIL
- LSIL (AIN I) – lower third, ‘productive’ infection, low risk of transformation
- HSIL (AIN III) – upper 2/3, ‘transforming’ infection, cancer precursor
- AIN II - something in the middle - is it LSIL or HSIL - how to classify - H&E & p16 IHC

- **?p16 positivity is equated to a high grade lesion**
  - p16 is over-expressed in a (small) proportion of benign and low grade lesions
  - p16 is not over-expressed in all high grade lesions
  - there is interobserver variation in the interpretation of p16 IHC

THE BRITISH ASSOCIATION OF GYNAECOLOGICAL PATHOLOGISTS

Interpretation of p16 Immunohistochemistry In Lower Anogenital Tract Neoplasia

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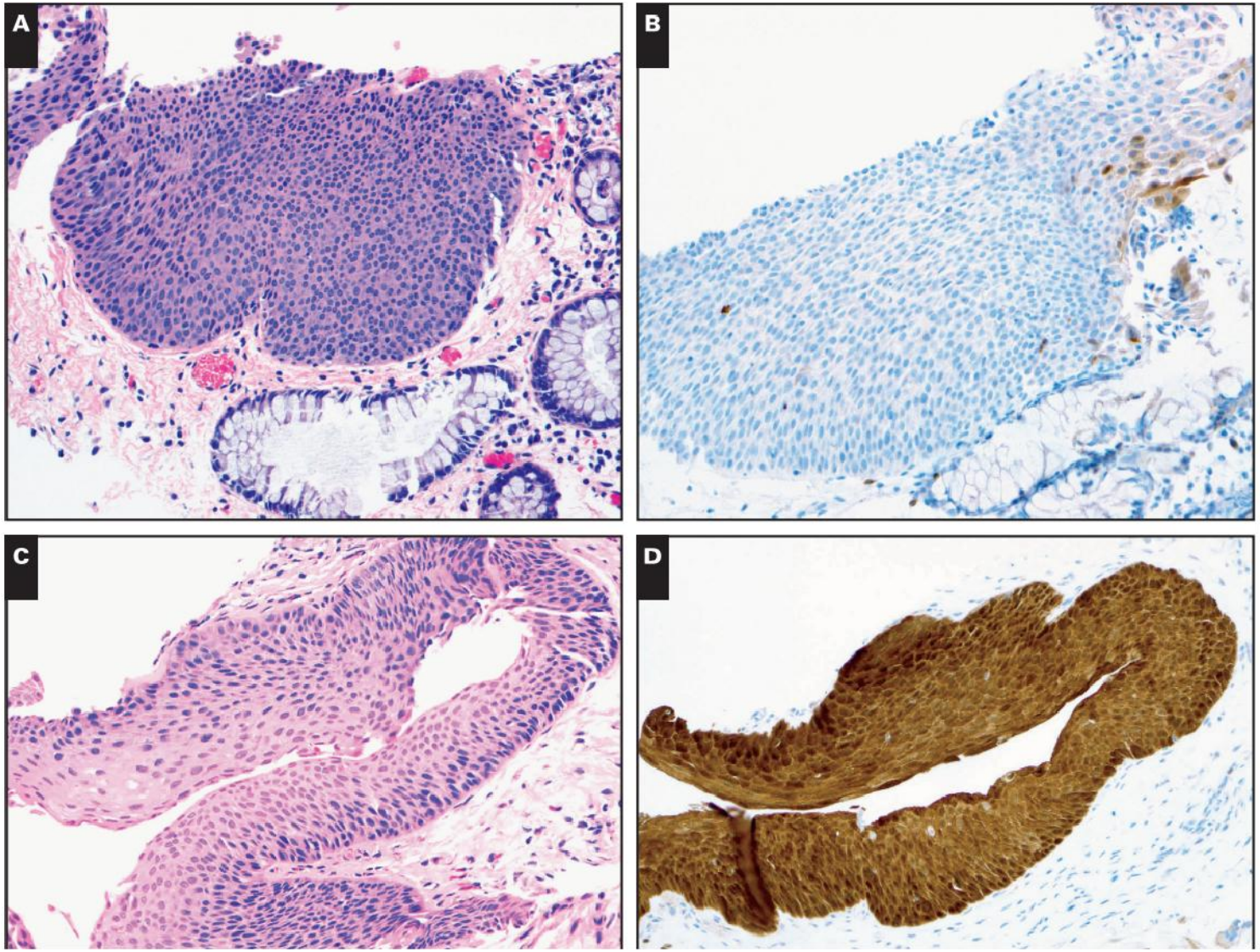

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Summary

- Clinical/morphological context and discussion of ‘difficult’ cases is crucial.

- ‘Non-conventional’ dysplasia subtypes are increasingly recognised throughout the GI tract
  - Rare lesions, significance incompletely understood

- Immunohistochemistry - convincing staining in the correct context
  - p53
  - MLH-1
  - p16