

Unusual Oesophageal Inflammation

Dr Tim Andrews, Royal Liverpool University Hospital

Summary of 'what's out there'

- 30% last 500 pubmed citations for 'oesophagitis' related to eosinophilic oesophagitis
- Ten papers in 5 pathology journals over last 3 years.
- Recent review by Grin & Streutker in Arch Pathol Lab Med. 2015;139:723–729.
- My practice – lots of normals, reflux and Barrett's. Occasional eosinophilic, lymphocytic, granulomas, sloughing, CMV, HSV, ulcers, candida.

Topics

- When to biopsy the oesophagus, clinical information required, specimen handling.
- Patterns of oesophageal inflammation
 - Eosinophils
 - Lymphocytes
 - Granulomas
 - ‘Sloughing’ oesophagitis

EDUCATION IN PRACTICE

Guidance on the effective use of upper gastrointestinal histopathology

Maurice B Loughrey,¹ Brian T Johnston²

Frontline Gastroenterology 2014;5:88-95

‘...the endoscopist should consider whether biopsy of normal or abnormal appearing mucosa is likely to contribute to patient management, to ensure effective use of limited healthcare resources.’

Biopsies for 'simple' reflux - NO

In patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends against obtaining routine biopsies of the normal-appearing esophagus or GE junction regardless of immune status. (Strong recommendation, very low quality evidence).

Gastroenterology 2015;149:1082-1087

Endoscopic biopsy is not indicated unless there is clinical suspicion of another underlying cause of ulceration, such as infection, especially in the immunosuppressed setting, neoplasia or drugs (so-called 'pill oesophagitis'), or if there is clinical suspicion of CLO'

Frontline Gastroenterology 2014;5:88-95

Biopsies for Eosinophilic Oesophagitis

CORRECT CLINICAL SETTING – ‘Mucosal biopsies are therefore always indicated when a diagnosis of eosinophilic oesophagitis is considered clinically, even in the presence of a normal endoscopy...proximal and distal biopsies identified separately’

Frontline Gastroenterology 2014;5:88-95

ENOUGH BIOPSIES FROM THE RIGHT PLACE - Esophageal biopsies are required to diagnose EoE. 2 – 4 biopsies should be obtained from both the proximal and distal esophagus to maximize the likelihood of detecting esophageal eosinophilia in all patients in whom EoE is being considered. (Recommendation strong, evidence low)

*Dellon et al, Am J Gastroenterol 2013; 108:679–692
American College of Gastroenterology Guideline*

At least 4 biopsies (no more than 6) from mid and lower oesophagus separately in pt not on PPI to diagnose EoE.

Nielsen et al. Am J Gastroenterol 2014;109:515-20

DEEP ENOUGH BIOPSIES – ‘Given that EoE has changes in deeper tissues than surface epithelium, and these may differentiate from other conditions e.g. PPI responsive oesophageal eosinophilia, biopsy procedures which sample deeper may improve yield.’

Bussmann et al. Endoscopy Nov 2016 epub

What clinical information is required?

- Patient demographics
- Clinical presentation/symptoms
- Relevant PMH
 - Medications
 - Immune status
- Appearances at endoscopy
- Biopsy samples taken
 - Where from/how many
 - Has other material been sent to microbiology etc
- Working diagnosis/clinical query
- Ideally include endoscopy report



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Tissue pathways for gastrointestinal and pancreatobiliary pathology

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- Three levels H&E recommended with all other stains based on initial assessment.
- Lack of strong evidence for 'routine' specials, including in cases of immunocompromise.

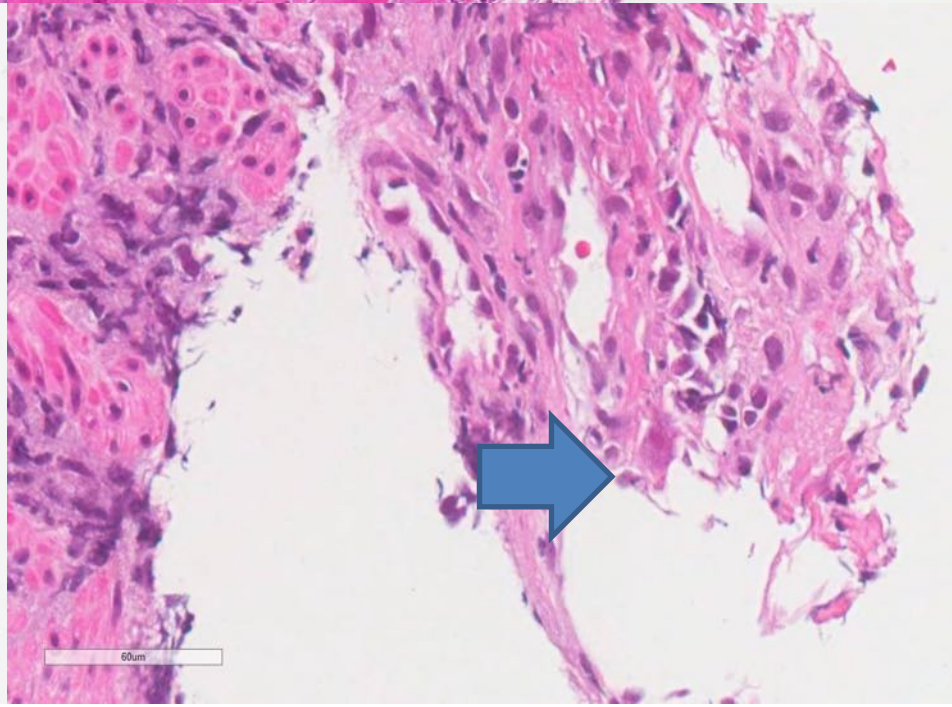
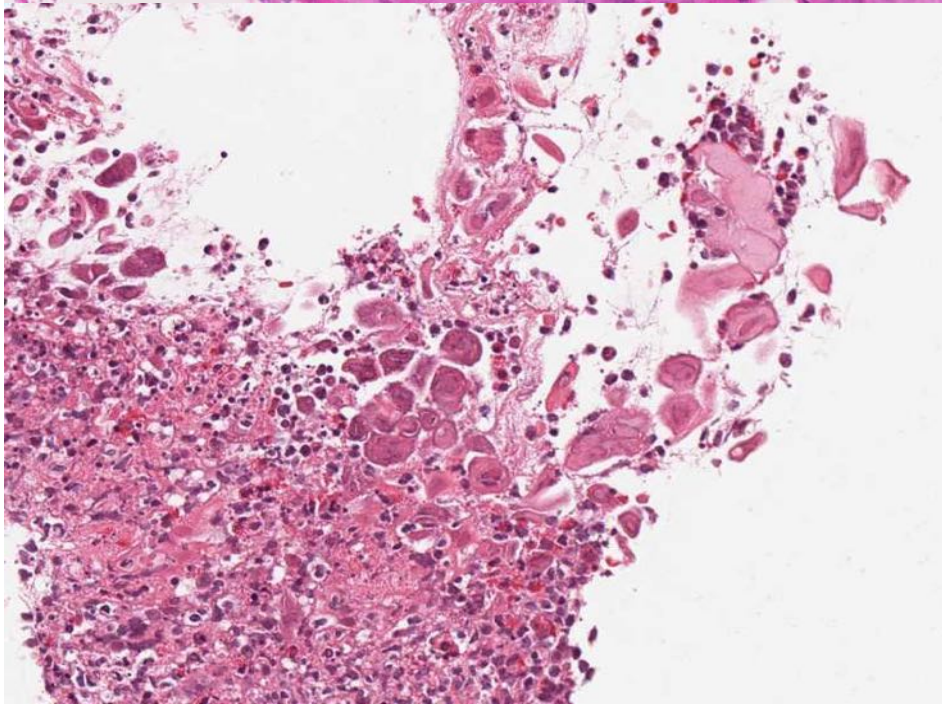
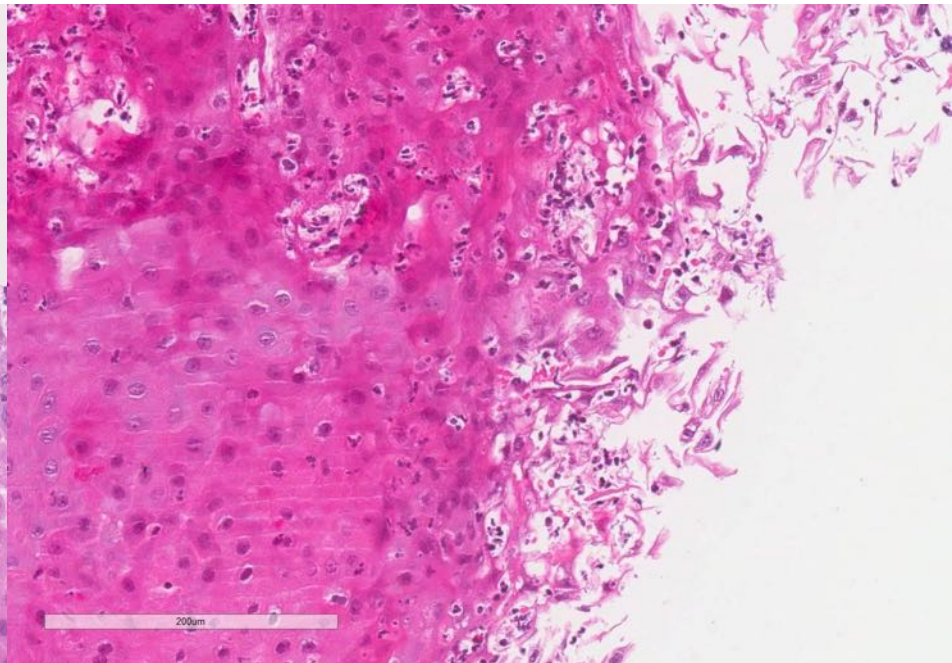
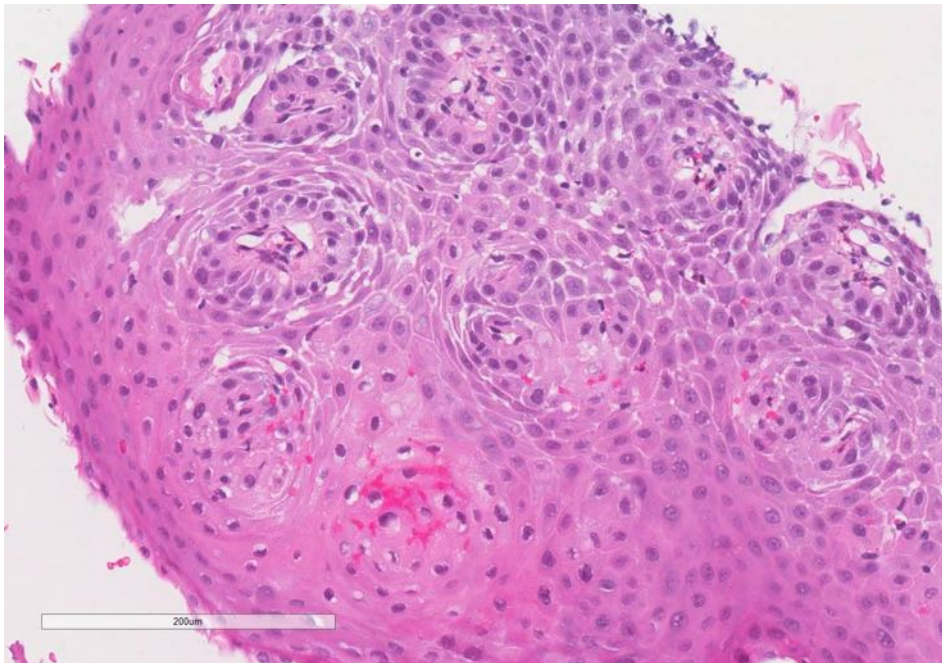
Which modality for diagnosis?

- Studies in AIDS patients with ulcerative oesophagitis suggest
 - Viral culture has no advantage over histology in assessing the aetiology

Wilcox et al, Clinical Gastroenterology and Hepatology 2004; 2:564-7

- Use of PCR (with fresh tissue available) vs histology may improve pathogen detection but potentially confusing if multiple organisms are detected

Borges et al Dig Dis Sci 2009;54:1933 - 39

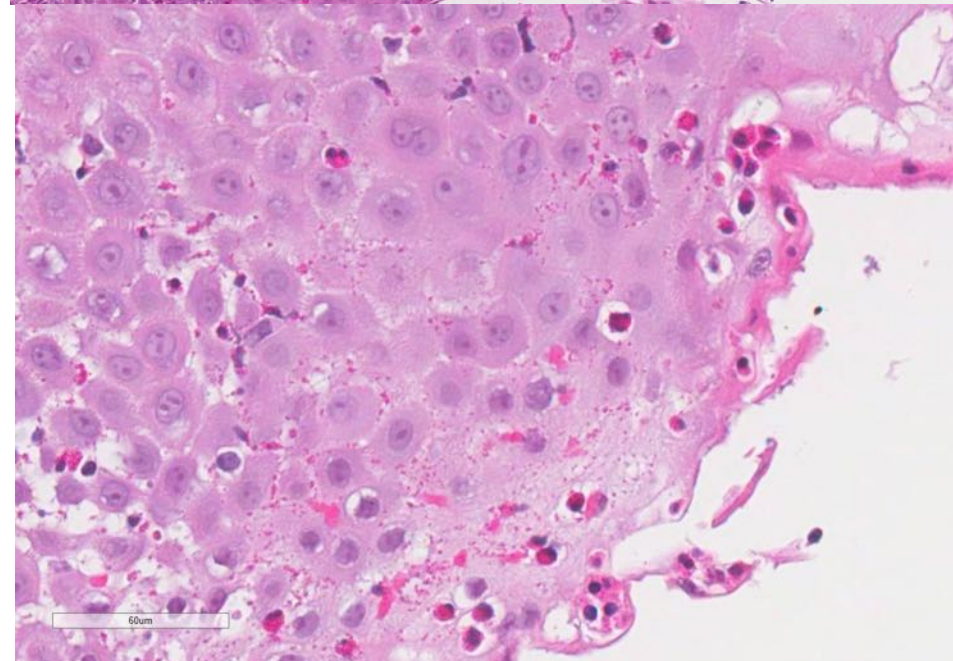
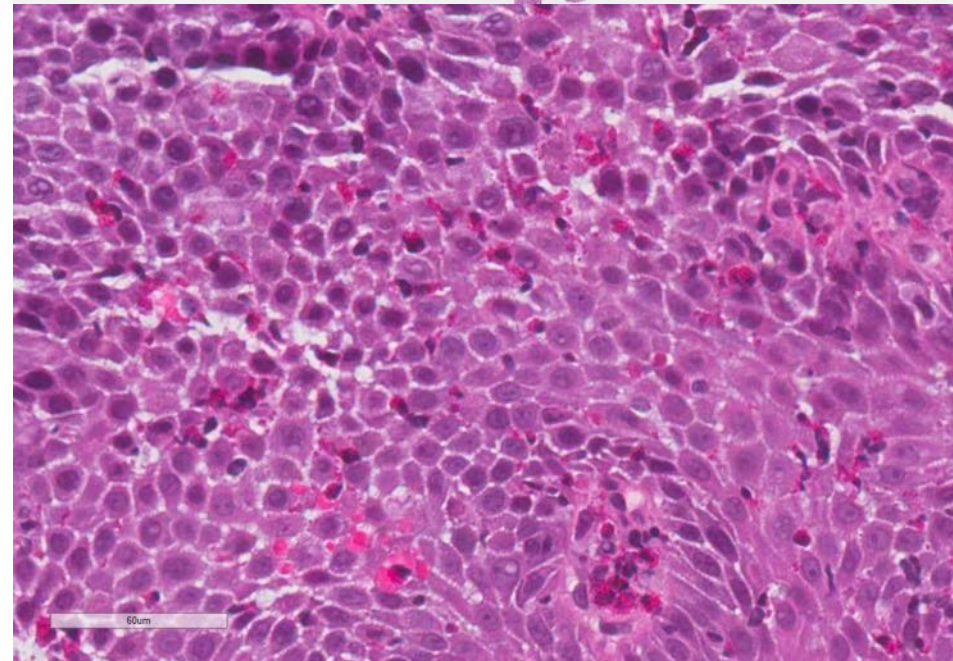
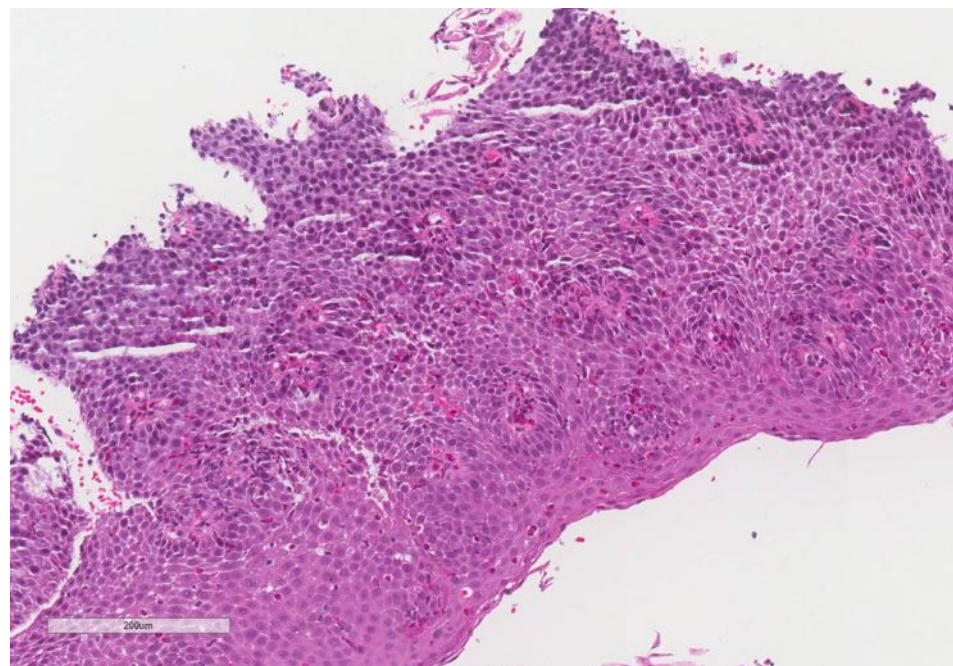
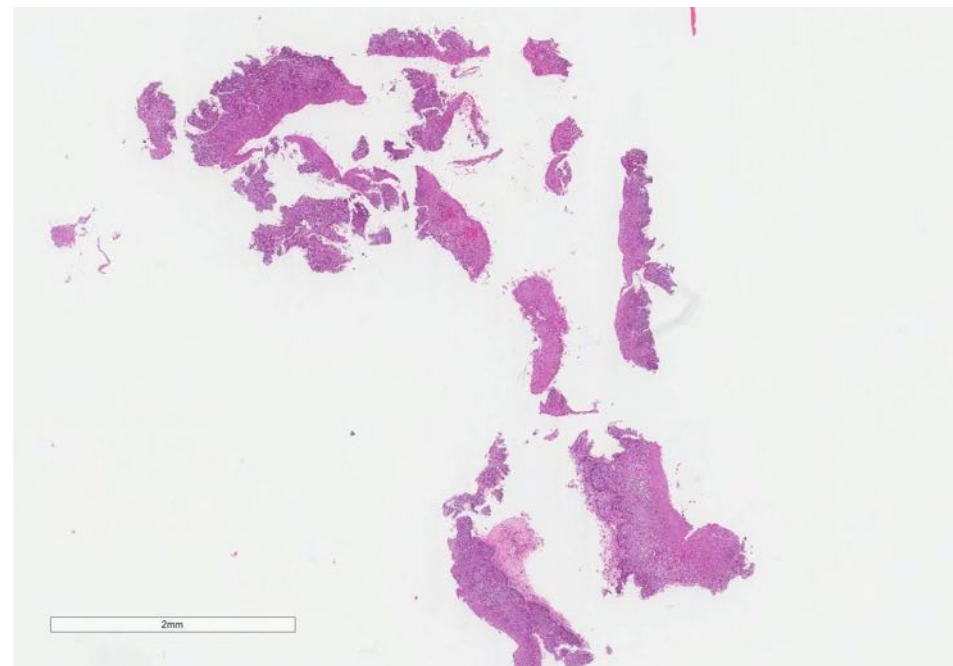


1. Eosinophils

- Reflux Oesophagitis
- Crohn's disease
- Reaction to drugs/Pill oesophagitis
- Infection (classically parasites)
- As part of more generalised eosinophilic syndromes
- **(Idiopathic) eosinophilic oesophagitis**
- **PPI Responsive Oesophageal Eosinophilia**
- GVHD
- Achalasia
- Systemic autoimmune and connective tissue disorders

Eosinophilic Oesophagitis (EoE)

- **Typical histological features**
 - Increased eosinophils
 - Eosinophil microabscess formation
 - Eosinophil degranulation
 - Spongiosis
 - Basal layer hyperplasia
 - Lamina propria fibrosis
- But remember EoE is a clinicopathological diagnosis



Diagnostic Criteria for EoE

- Clinical evidence of oesophageal dysfunction
- Biopsies show eosinophil predominant inflammation with ≥ 15 eos/hpf
- Mucosal eosinophilia isolated to the oesophagus
- (Mucosal eosinophilia persists after PPI trial)
- Other local and systemic causes of oesophageal eosinophilia excluded

Dellon et al Am J Gastroenterol 2013;108:679 – 92
Molina-Infante et al Gut 2016;65:524 - 31

Evidence base for ≥ 15 eosinophils/hpf

'...has been adopted as the histologic cut point in diagnostic algorithms but this value is largely empiric and its appropriateness has never been rigorously tested.'

Dellon et al, Mod Pathol 2015;28:383 - 390

Evidence base for ≥ 15 eosinophils/hpf

- Any more than occasional eosinophils in oesophageal biopsies should prompt search for pathology
- Eosinophils can be patchy so should be the maximum count obtained even if this is only present focally
- Eosinophil count performs better than other histological features in differentiating EoE from reflux

Evidence base for ≥ 15 eosinophils/hpf

Cut off of ≥ 15 /hpf

Sensitivity	100%
Specificity	96%
Positive predictive value	85%
Negative predictive value	100%

**But...its not just an eosinophil count -
record 6 cases of reflux with ≥ 15
eosinophils/hpf**

What is a 'high power field'?

- 0.24mm² average field size reported in the literature.

Repeat biopsies for response monitoring

- Required to diagnose PPI Responsive Eosophageal Eosinophilia – count of <15 on biopsies obtained after 8 weeks PPI.
- Threshold for response in EoE is not defined. Suggestions have ranged from <15 to 0.

Asher Wolf et al J Gastroenterol Hepatol Res. 2015; 4:1780–1787

- Does it matter as long as symptoms get better?

Are there markers to help in difficult cases?

- Increased staining for mast cell tryptase differentiates EoE from reflux.

Dellon et al Am J Gastroenterol. 2011;106:264–271

- A panel of IHC for major basic protein (MBP), eotaxin-3 and mast cell tryptase differentiates EoE from reflux (but not PPI-eosinophilia)

Dellon et al Clin Gastroenterol Hepatol. 2014;12: 2015–2022

- Presence of intrasquamous IgG4 deposits differentiates EoE from reflux

Zukerberg et al Histopathology 2016;68:968 - 976



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- Histological distinction of eosinophilic oesophagitis from reflux oesophagitis can be difficult. Correlation with clinical findings is advisable.

2. Lymphocytes

- Small number are 'within normal limits'
- Reflux oesophagitis
- Seen as part of a non-specific infiltrate in a range of settings including Crohn's, Candida, radiation, drugs
- **Lymphocytic oesophagitis**
- Oesophageal Lichen Planus
- (Lymphoma)

Salaria et al Am J Surg Pathol 2013;37:1889–1894

Lymphocytic Oesophagitis (LyE)

- Pattern of chronic oesophagitis originally described by Rubio et al in 2006

Am J Clin Pathol 2006;125:432-437

- Histological findings
 - Increased numbers of intraepithelial lymphocytes
 - Absence of granulocytes (or minimal present)
 - Concentrated in a peripapillary distribution or diffuse (NOT interpapillary only)
 - (Candida excluded)

Diseases associated with lymphocytic oesophagitis

- Emerging and increasing, some argument that it is a form of reflux disease.
- Initial paper suggested association with Crohn's and younger patient age.
- Not replicated in a subsequent study leading Purdy et al to conclude 'we found no association between LE and any specific clinical condition'

Am J Clin Pathol 2008;130:508-513

Diagnostic Criteria are not well defined

- Reported to be a manifestation of UGI Crohn's disease in children.

- Criteria >50IEL/hpf & >50:1 IEL's to granulocytes

Ebach et al Inflamm Bowel Dis. 2011;17:45-9

- Recent association reported with non-achalasia primary oesophageal motility disorders.

- Initially reported lymphocytosis with 66-406 IEL's in a 0.237mm² hpf.

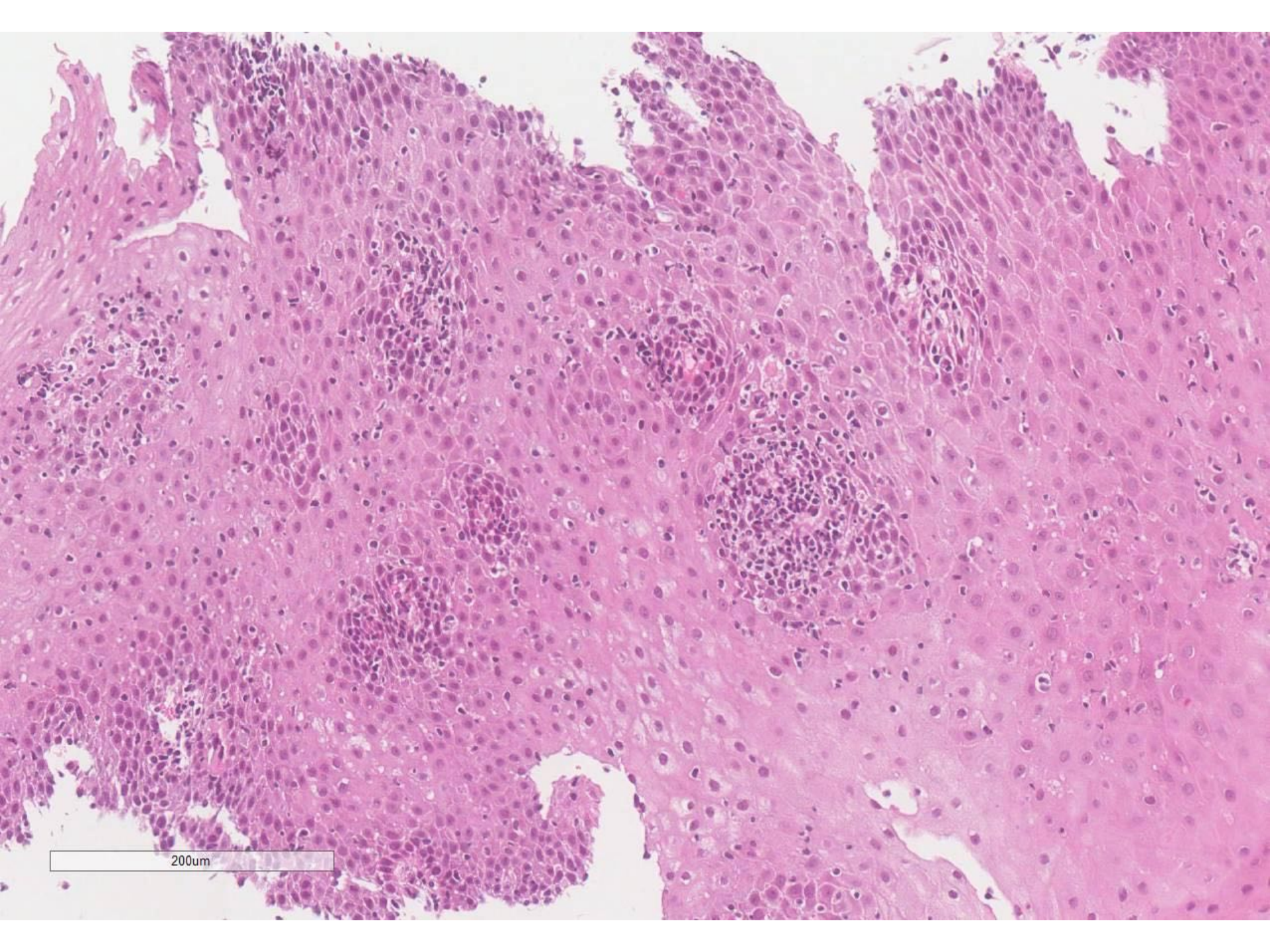
- Then used a cut-off of 41 IEL's/hpf at 10cm above GOJ

Xue et al Am J Surg Pathol. 2015;39:1558-67

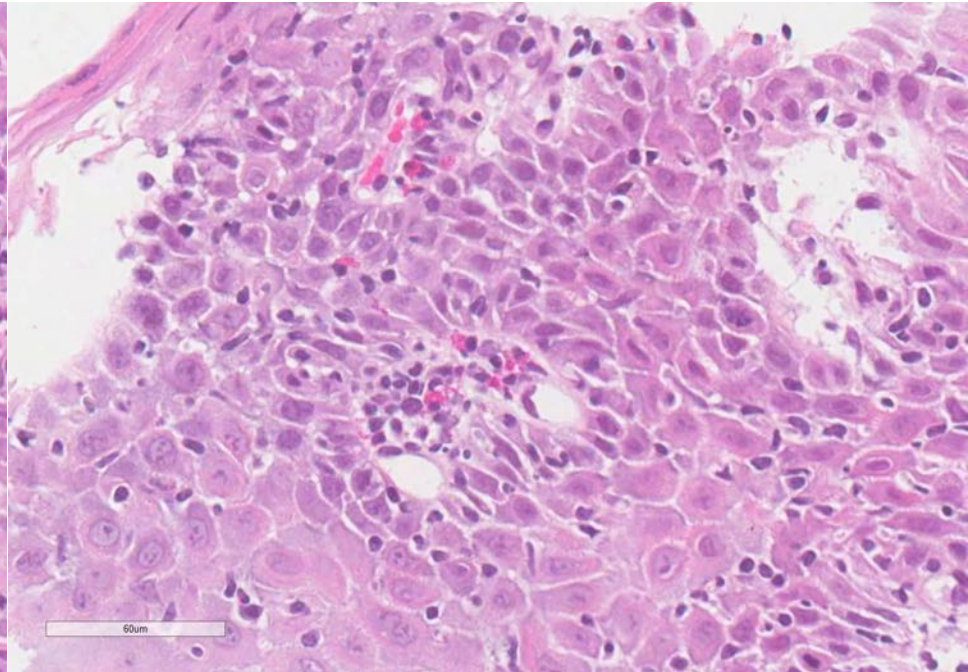
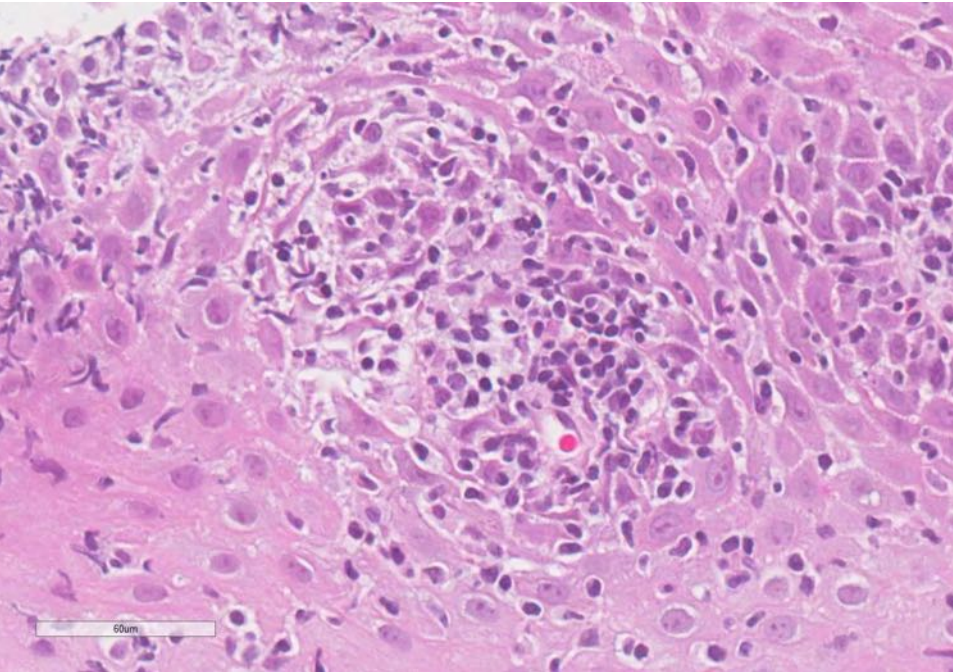
Putra et al Am J Surg Pathol. 2016;40:1679-1685

- Reported in the setting of previous endotherapy for Barrett's Oesophagus
 - Peripapillary infiltrate of ≥ 20 lymphocytes/hpf associated with spongiosis and lack of granulocytes
 - Associated with cryotherapy, hyperlipidaemia and smoking
 - *EoE also reported in this setting but not seen in this study*
 - *?all related to reflux/the procedure*

Kissiedu et al Mod Pathol. 2016;29:599-606



200um



Confused? –

Combined lymphocytic-eosinophilic oesophagitis

Rubio CA, Ichiya T, Schmidt PT. J Clin Pathol Published Online First: doi:10.1136/jclinpath-2016-203782

Entity	Lymphocytes	Eosinophils
Lymphocytic infiltration	≤39	≤14
Lymphocytic oesophagitis	≥40	≤14
Eosinophilic Oesophagitis	≤39	≥15
Combined Lymphocytic-Eosinophilic Oesophagitis	≥40	≥15

Four groups described

Uses a combination of H&E and CD3 IHC

Defines a hpf as 0.18mm²

?what it all means

3. Granulomas

- **TB**
- **Crohn's**
 - Uncommon in adults (<10%) more often in children
 - Gastric and duodenal biopsies more often show granulomas
for example Biomed Res Int. 2014;2014:610767. doi: 10.1155/2014/610767
- Other infections
- Sarcoid
- Foreign body reaction (tablets/food debris – examine under polarised light)
- Wegener's

...Not everything with necrosis is TB

Rare disease

CASE REPORT

Oesophageal lesions as first manifestation of necrotising sarcoid granulomatosis

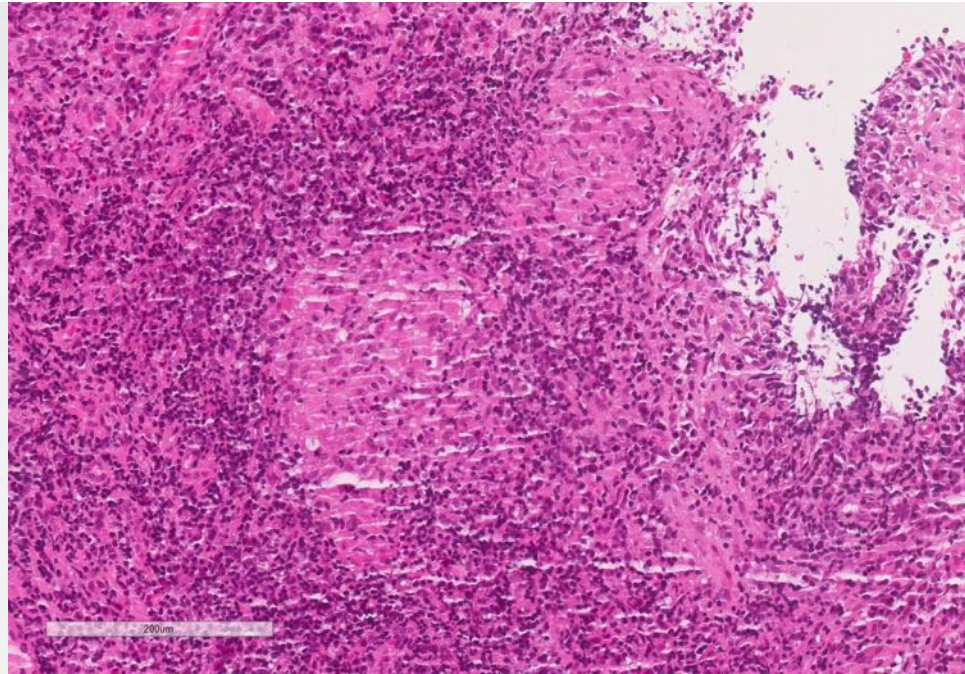
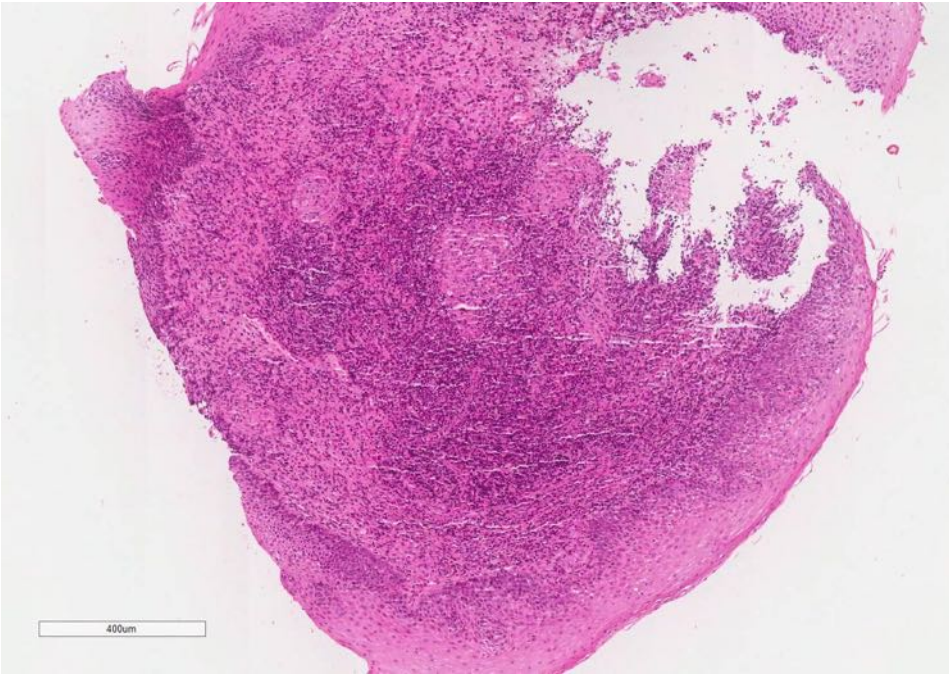
Rachid Attou,¹ Ruth Duttmann,² Arnaud Devriendt,³ David De Bels¹

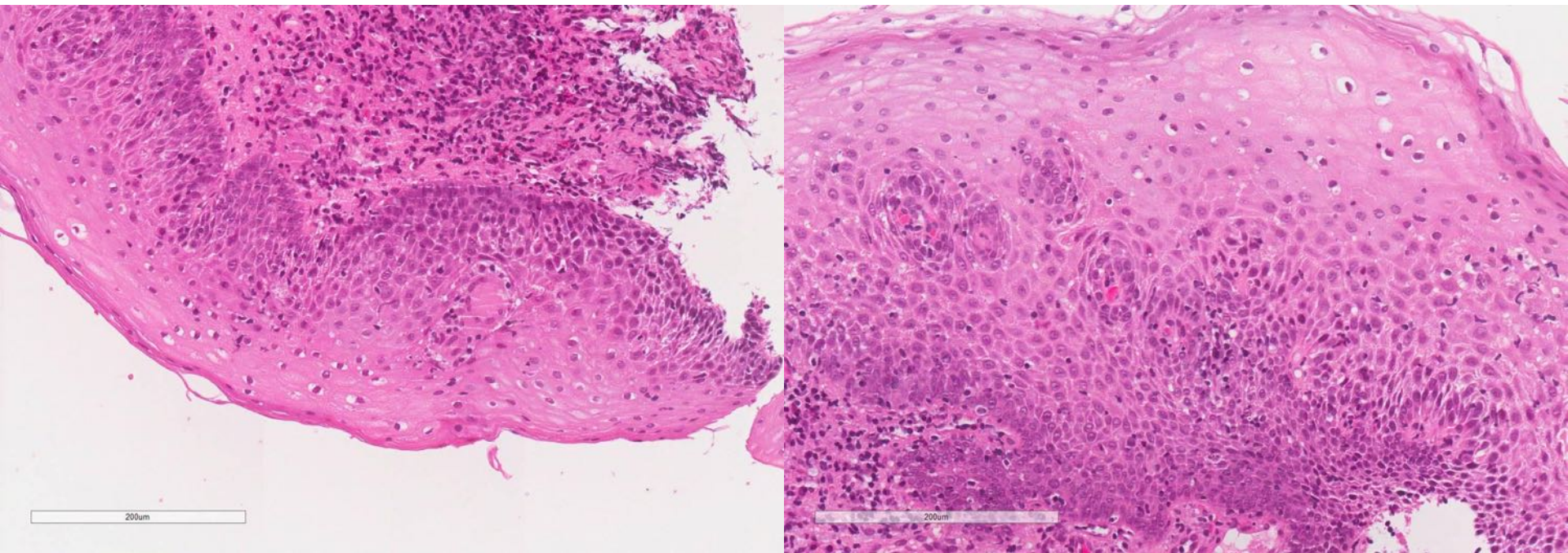
BMJ Case Rep 2015. doi:10.1136/bcr-2015-209471

To ZN stain or not?

?indicated when there is history of Crohn's
?microbiology or even PCR reaction of paraffin material

...clinical history is crucial





...20 year history of sarcoid

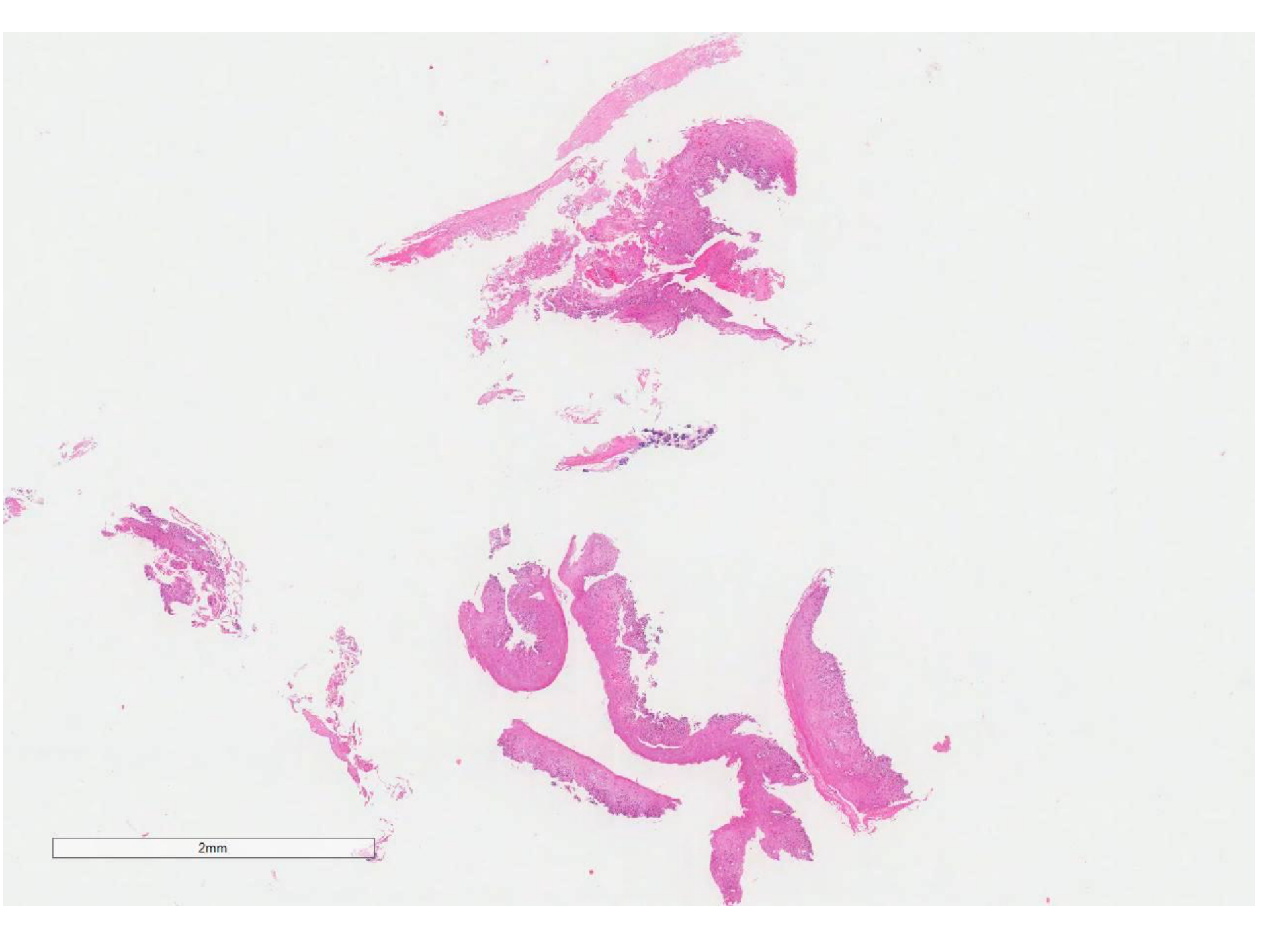
4. 'Sloughing' Oesophagitis

- 'Sloughing' oesophagitis/oesophagitis dissecans superficialis (ESD)/esophagitis dессicans/ desquamative oesophagitis.
- Studies vary in cases they include/exclude, ?can this diagnosis be made in the absence of typical endoscopic appearances
- Relatively little literature – case reports, small series
 - *Hart et al* Dig Dis Sci (2015) 60:2049–2057 – **41pt**
 - *Purdy et al* Modern Pathology (2012) 25, 767–775 – **31pt**
 - *Carmack et al* Am J Surg Pathol 2009;33:1789–1794 – **12pt (further 9 with histology only)**
 - *Wilcox et al* (2 abstracts) – **32pt**

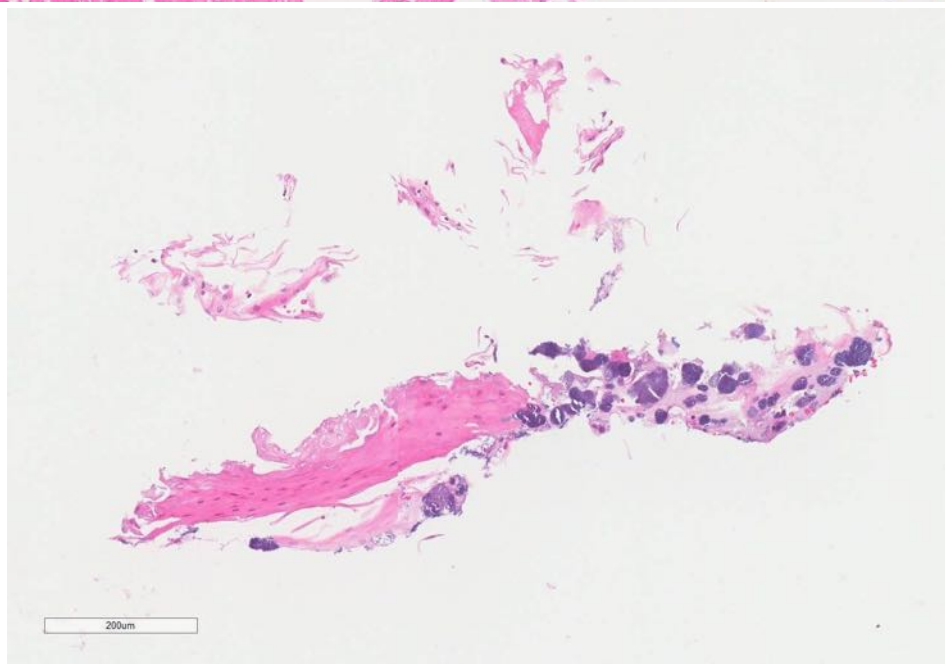
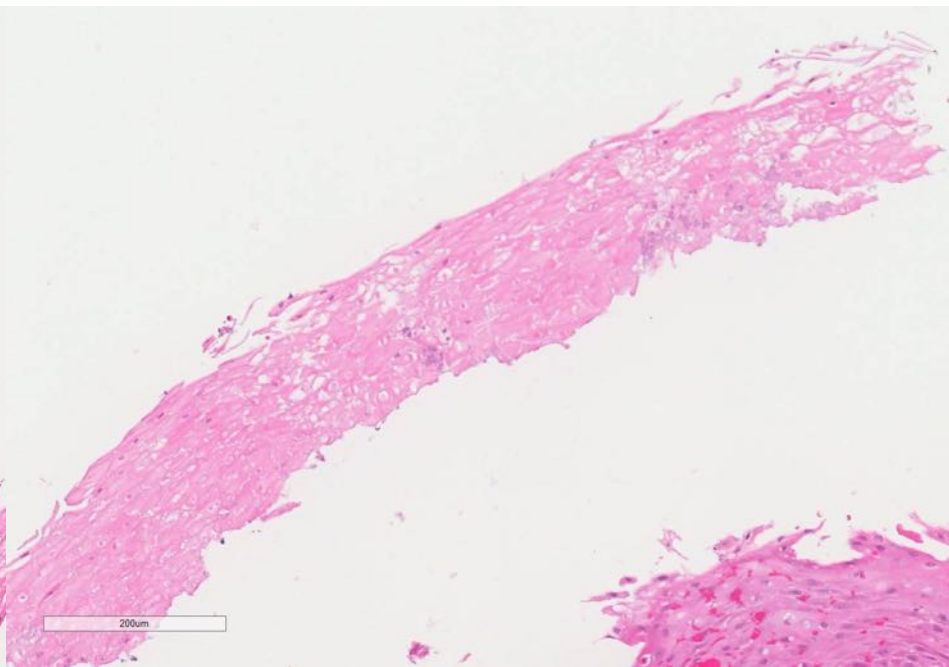
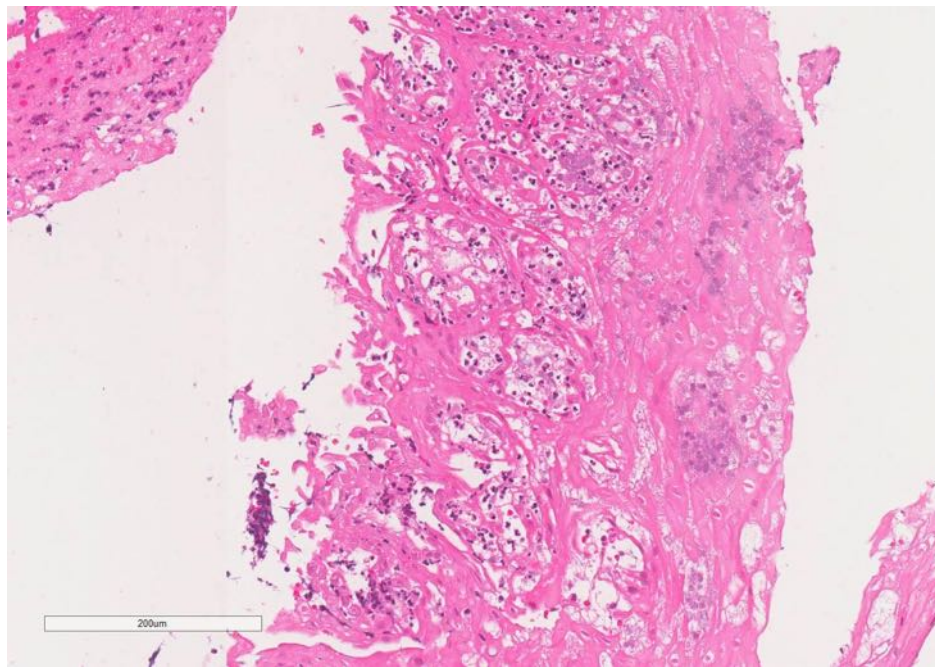
- **Typical endoscopic appearance**
 - Vertical mucosal sloughing resulting in free floating fronds of epithelium
- **Mechanism**
 - Contact injury (as opposed to ischaemia)
- **Treatment**
 - Symptomatic/supportive with generally good outcome

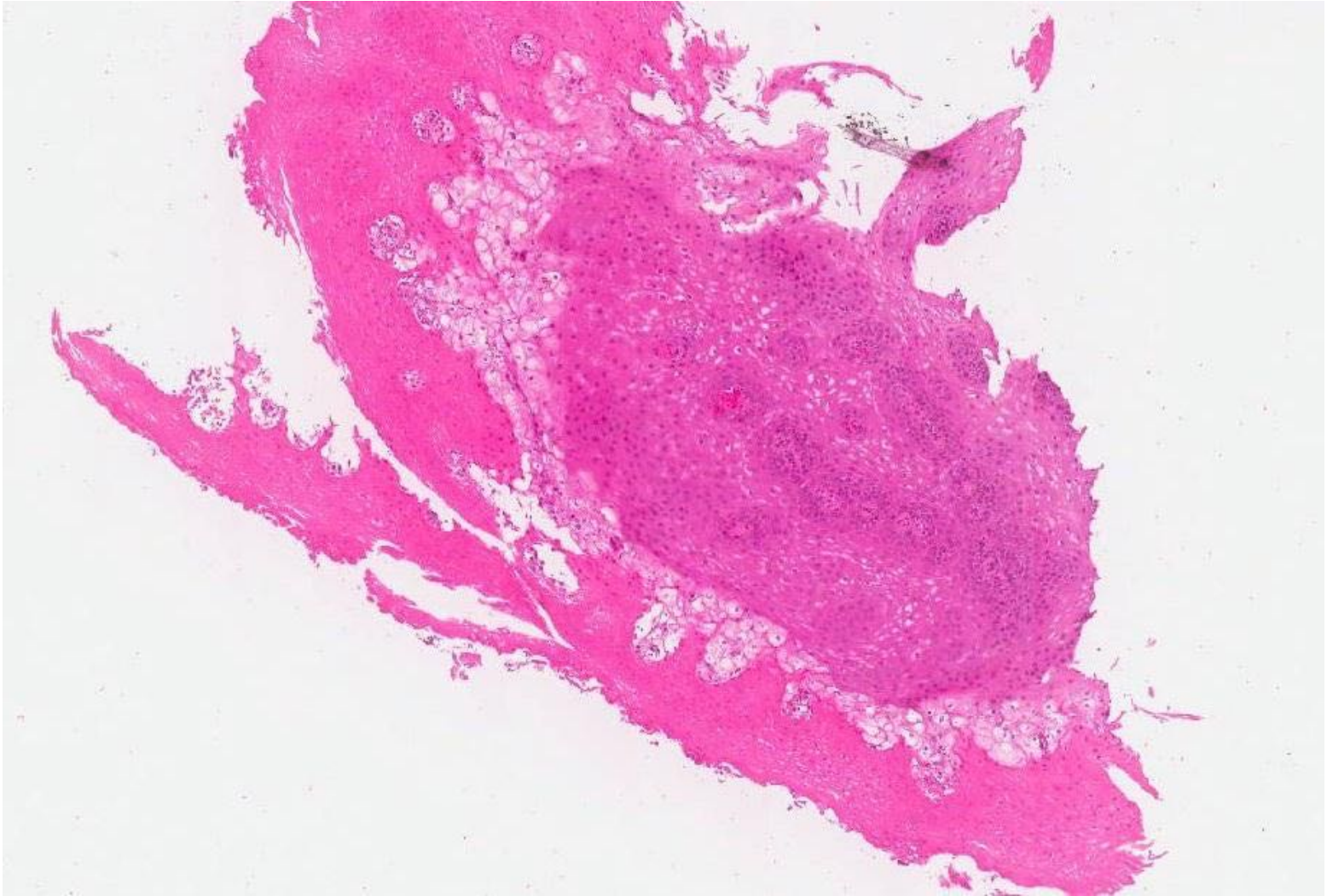
Histological Features

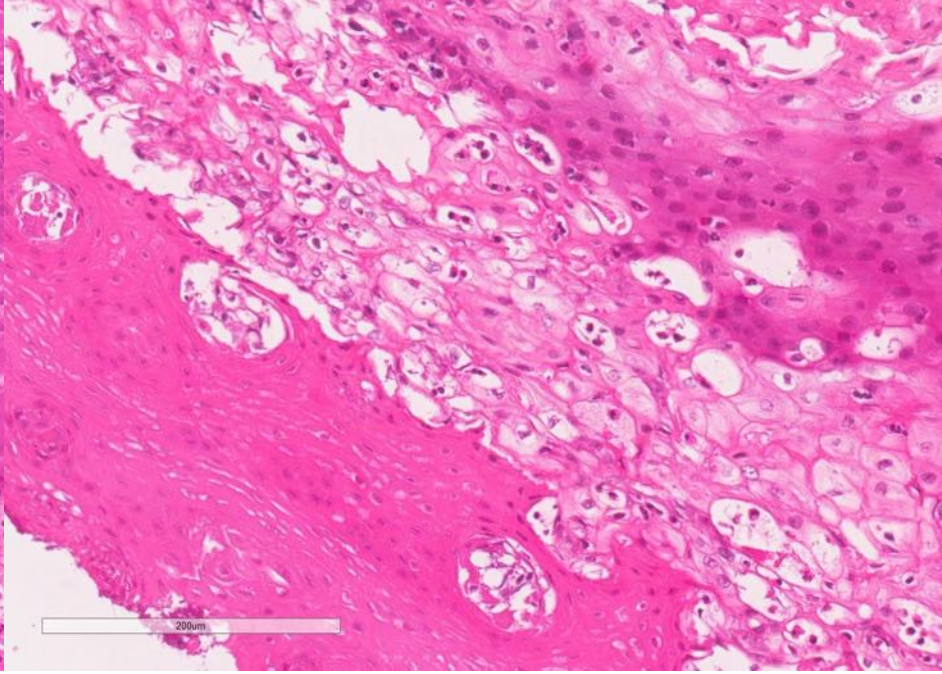
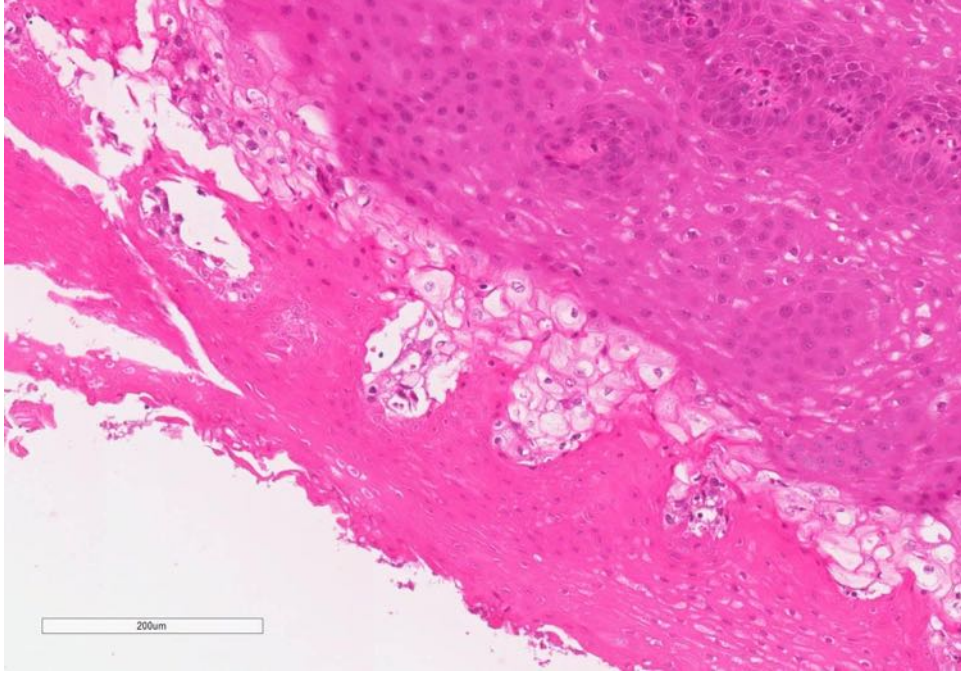
- Ortho/parakeratosis
- ‘Two-tone’ epithelium – necrotic upper layer and viable lower layer
- Separation of these two layers, some with complete detachment producing the ‘slough’
- Variable
 - Level of split
 - Amount of (neutrophilic) inflammation in the ‘split’
 - Presence of bacterial colonies



2mm







Conditions associated with 'sloughing oesophagitis'

- Ingestion of hot/corrosive liquids
- Multiple prescribed medications
- Debilitated state
- Recent intervention e.g. banding
- Coeliac Disease
- Achalasia
- Heavy Smoking
- Thymoma
- GVHD
- Immunosuppression
- IgG4 Disease
- Medications
 - NSAID's
 - Bisphosphonates
 - Doxycycline
 - Clindamycin
 - Dabigatran
 - Chemotherapy
 - Psychoactive medications e.g. SSRI

Keep taking the tablets...

- ‘Drugs’ can cause a wide range of patterns of mucosal injury and many drugs are implicated.
- Identification of tablet debris confirms the diagnosis, but may not be biopsied in the acute setting.
- ‘Pill’ and ‘Drug induced’ are used interchangeably
- Clues are in the history
 - Abrupt onset of symptoms related to the taking of medication or introduction of a new medication
 - History of medication known to cause oesophagitis
 - Debilitated patient – postural issues
 - Multiple medications
 - Failure to take adequate fluid with tablets
 - Spontaneous resolution of symptoms

Summary

- Clinicians should be encouraged to target the taking of oesophageal biopsies to maximise yield from histopathology
- Appropriate information should accompany specimens - medication history, immune status and biopsy location are crucial
- A pattern based approach as opposed to an entity based approach may be most appropriate
- Remember drugs and infection

- **Eosinophilic Oesophagitis**
 - Clinicopathological diagnosis
 - ≥ 15 eosinophils in any high power field
- **Lymphocytic oesophagitis**
 - Emerging entity, diagnostic criteria and associations not well defined
 - $? > 40$ peripapillary lymphocytes/hpf in mid oesophageal biopsies
- **Granulomas**
 - Rare in oesophageal Crohn's disease, differential is as for other sites
- **Sloughing oesophagitis**
 - Characteristic endoscopic and histological appearance, wide differential including bullous disorders

Acknowledgments

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