

Transmutation and Dysplasia - Barrett's Oesophagus

Anubha Bajaj*

Department of Histopathology, Panjab University/A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University/A.B. Diagnostics, India.

Received: June 24, 2019; **Published:** July 21, 2019

Preface

Metaplasia and substitution of the regular squamous epithelial lining of distal oesophagus with intestinal-type columnar epithelium is cogitated as Barrett's oesophagus. Barrett's oesophagus is designated as the occurrence of salmon tinged columnar mucosa extending one centimetre or more beyond the gastro-oesophageal junction on endoscopy with the enunciation of intestinal-type columnar metaplasia on histology. Chronic gastro-oesophageal reflux disease (GERD) enunciates Barrett's oesophagus as a consequent detrimental phenomenon. Barrett's oesophagus is prevalent in an estimated 1% to 2% of adult population. Barrett's oesophagus also exemplifies a solitary and cogent premalignant condition for the emergence and rising incidence of oesophageal adenocarcinoma [1].

Oesophageal carcinoma frequently enunciates cancer associated morbidity and mortality. Oesophageal adenocarcinoma is the most common variant of oesophageal carcinoma whereas squamous cell carcinoma of the oesophagus depicts a declining frequency [1,2].

Disease characteristics

A critical precursor lesion for the occurrence of oesophageal adenocarcinoma is Barrett's oesophagus which inculcates an intestinal-type metaplasia of squamous epithelial mucosa exemplified in the distal oesophagus. Gastro-oesophageal reflux disease (GERD) is an essential element of metamorphoses of Barrett's oesophagus into an invasive oesophageal adenocarcinoma.

Oesophageal adenocarcinoma (EAC) is an exceptional and lethal neoplasm with an inferior 5 years survival rate of 15% to 20% and an overall median survival of below < one year in advanced malignancies. Evolution of Barrett's oesophagus into a distinctive oesophageal adenocarcinoma exhibits phases of transition from distinctive intestinal-type metaplasia metamorphosing into low grade dysplasia (LGD) with a subsequent emergence of high grade dysplasia (HGD) and a culmination into intra-mucosal oesophageal adenocarcinoma with sequential occurrence of invasive oesophageal adenocarcinoma [2,3].

Emergence of oesophageal adenocarcinoma is contingent to additional factors such as obesity, elderly population, a male preponderance and disease predisposition in Caucasians. Attributes such as abundant physical exercise, a vegetarian diet and administration of drugs such as proton pump inhibitors, non-steroidal anti-inflammatory drugs and statins incur a preventive role in the initiation of oesophageal adenocarcinoma. Oncogenic microorganisms such as *Helicobacter pylori*, which induce gastric adenocarcinoma, are cogent in preventing the development of Barrett's oesophagus and oesophageal adenocarcinoma.

Contemporary surveillance regimens for Barrett's oesophagus recommend monitoring of high risk fractions such as males beyond > 60 years of age and subjects with chronic, unrestrained gastrointestinal reflux.

Barrett's oesophagus can concur with conditions such as sliding hiatal hernia, reduced resting pressure of lower oesophageal sphincter, oesophageal stricture, peptic ulcer, ingestion of lye, reflux of bile or pancreatic juice and utilization of chemotherapeutic agents [3,4].

Clinical elucidation

Barrett's oesophagus are acquired in a majority and a few instances can be congenital. Mean age of discerning Barrett's oesophagus is 63 years, although children with gastro-oesophageal reflux due to cystic fibrosis are also incriminated.

Barrett's oesophagus is frequently elucidated in subjects with duodenal-gastric reflux or hiatal hernia.

Individuals can present with heartburn, acidity, dyspepsia, effluence and associated symptoms of gastro-oesophageal reflux with episodes of enhancing frequency and duration.

Nevertheless, subjects enunciating Barrett's oesophagus depict an identical mortality as the normal population and a majority (95%) of instances of oesophageal adenocarcinoma are devoid of concurring Barrett's oesophagus [4,5].

Intestinal metaplasia of the gastric cardia or gastro-oesophageal junction can occur on account of infection with oncogenic bacteria such as *Helicobacter pylori* which, however, infrequently depict a malignant conversion to oesophageal adenocarcinoma, in contrast to cancerous metamorphosis following metaplasia cogitated in Barrett's oesophagus.

Barrett's oesophagus is classified into

- Long segment disease where Barrett's mucosa extends to beyond 3 centimetres.
- Short segment variant where Barrett's mucosa is enunciated beneath < 3 centimetres.
- Ultrashort segment category where the expanse of Barrett's mucosa is below < 1 centimetre [1,2].

Histological elucidation

Categorical diagnosis of Barrett's oesophagus requires a concordance of disease manifestations on upper gastrointestinal endoscopy and specific histological parameters.

Disease free distal oesophagus displays a whitish or pale pink mucosal layering of squamous epithelium which transforms into a salmon tinged intestinal-type mucosal metaplasia contingent to repetitive inflammatory stimuli such as gastro-oesophageal reflux. Appropriate identification of gastro-oesophageal junction and coinciding squamocolumnar junction or Z line is imperative on pertinent endoscopy.

Epithelial metaplasia with transformation into an intestinal- type columnar epithelium is the characteristic morphological feature of Barrett's oesophageal mucosa. Elongated segments of columnar mucosa are accompanied by proportionate enhancement of intestinal metaplasia. An estimated 46% probability of progression to oesophageal adenocarcinoma is elucidated in augmentation of Barrett's oesophagus by one centimetre.

Cogent detection of Barrett's oesophagus can be achieved by procuring a minimal of four tissue specimens from random locations within two centimetres of Barrett's mucosa or at least eight tissue samples from random sites in order to obtain maximal fragments diagnostic of histological intestinal metaplasia.

Suspicious instances of short segment Barrett's oesophagus necessitate a minimum of four random tissue specimens for evaluating one centimetre segment of circumferential columnar mucosa. Singular tissue specimens are required for assessing one centimetre of tongue-like projection of columnar mucosa. Foci of ulceration and nodule formation comprising of aberrant mucosa in Barrett's oesophagus require separate tissue sampling [5,6].

Elucidation and recognition of smattered goblet cells is mandatory for categorizing Barrett's oesophagus. Paraffin embedded sections routinely stained with haematoxylin and eosin depict goblet cells as simple columnar cells comprising of a miniature, compressed, basal nucleus and expansive globules of acidic, bluish-tinged mucin within the cytoplasm. Frequently, goblet cells are randomly scattered within the mucosal columnar epithelium.

Goblet cells necessitate a segregation from pseudo-goblet cells. Goblet cells appear as barred shaped, columnar cells with a triangular nucleus and significant quantities of bluish, cytoplasmic mucin. In contrast, pseudo-goblet cells enunciate parallel cellular aggregates with uniform, spherical or oblong nuclei and comprise of pinkish cytoplasmic mucin [5,7].

Employment of special stains such as alcian blue (pH 2.5) or periodic acid Schiff (PAS) exemplify goblet cells as bright blue or dark purple cells.

Appropriate evaluation of tissue specimens obtained during surveillance of Barrett's oesophagus is challenging.

Specimens are analysed in the categories of

- Negative for dysplasia.
- Indefinite for dysplasia.
- Low grade dysplasia.
- High grade dysplasia.

Tissue samples obtained in instances of "negative for dysplasia" (ND) depict a reactive mucosa with surface maturation, minimal nucleo-cytoplasmic (N/C ratio), uniform, evenly spaced nuclei with smooth outlines, parallel inclination and maintained polarity. Minimal atypia, when enunciated, is confined to the crypts and basal epithelium. Mucosa is devoid of nuclear hyperchromasia and polymorphism. Proportionate malignant evolution occurs in an estimated 0.12% to 0.5% instances per year and is approximately 11.3 times greater than general population. Subjects of "negative for dysplasia" require a regular endoscopic surveillance at an interval of 3 years to 5 years.

Endoscopic eradication therapy is not a cogent therapeutic option in such instances [1,2].

Specimens labelled as "indefinite for dysplasia" (IND) essentially define a grey zone where the columnar epithelium depicts a deranged glandular- stromal architecture and cytological atypia although the mucosa is devoid of definite dysplasia. Frequently, mild or significant atypia is cogitated interspersed within an extensive inflammatory exudate scattered in the background. Thus, differentiation amidst reactive or dysplastic mucosal epithelium can be enigmatic.

Percentage of malignant progression is exemplified at 0.84% to 1.4% per year. Application of proton pump inhibitors (PPI) for a duration of three to six months with a subsequent tissue sampling is an efficacious protocol for evaluation.

Samples delineating "low grade dysplasia" (LGD) manifest specific features such as nuclear hyperchromasia, enlargement and stratification with expansion to cell surface. Metamorphosis betwixt regular, uninvolved and dysplastic epithelium is distinct.. Cells enunciating epithelial dysplasia retain nuclear polarity. Glandular and stromal architecture is maintained and cellular component is devoid of cribriform glands. Prominent nuclear pleomorphism and complex glandular architecture are absent in low grade dysplasia. Approximate incidence of conversion to oesophageal carcinoma is 0.5% to 1.4%. Endoscopic eradication therapy is a preferred modality for treating low grade dysplasia. Alternatively, endoscopic surveillance is suitable at twelve month interval [1,2].

Tissue designated as "high grade dysplasia" (HGD) characterize the presence of profound cytological atypia and architectural aberrations which extend to the mucosal surface. Dysplastic alterations are greater than mucosal anomalies cogitated in low grade dysplasia. Neoplastic glands demonstrate an intact, imperforate basement membrane. High grade dysplasia exemplifies specific cytological aberrations such as enlarged, pleomorphic nuclei with significant hyperchromasia, prominent nucleoli, frequent mitosis, enunciation of atypical mitosis, enhanced nuclear/cytoplasmic (N/C) ratio and irregular nuclear outline. Cellular and nuclear pleomorphism and an absence of nuclear polarity are cogent, objective diagnostic parameters. Architectural anomalies cogitated in high grade dysplasia specify cribriform glandular pattern with papillary configurations.

Prospective malignant conversion is estimated at 6% per year. Employment of endoscopic eradication therapy is the recommended treatment for high grade dysplasia.

Absence of cellular and nuclear maturation of the mucosal surface is the hall mark diagnostic feature of Barrett's oesophagus as delineated in tissue samples procured for surveillance [1,2].

"Deep crypt dysplasia" is a nomenclature assigned to mucosal aberrations cogitating features of low grade or high grade dysplasia and restriction of cytological anomalies to deep-seated crypts with preserved maturation of mucosal surfaces.

Deep crypt dysplasia is accompanied by conventional dysplasia in an estimated 47% instances. Molecular alterations such as aneuploidy and enunciation of p53 mutations are identical in deep crypt dysplasia and conventional dysplasia. Thus, surface maturation with deep crypt dysplasia is a cogent variant requiring appropriate exemplification. A comprehensive histological analysis with deep sections can be resorted to in suspicious or ambiguous instances which can be categorized as "indefinite for dysplasia". Accurate monitoring, morphological comparisons with preceding tissue specimens and a p53 immune stain is recommended for a decisive enunciation [6,7].

“Intra-mucosal carcinoma” necessitates a segregation from high grade dysplasia, particularly in subjects delineating predominant glandular and architectural derangement.

Intra-mucosal carcinoma can be contemplated as a cogent diagnosis in instances which are labelled as high grade dysplasia/marked architectural distortion (HGD/MAD) and demonstrate specific features such as

- a) Glandular crowding with diminished lamina propria or “back to back” mucosal glands.
- b) Cribriform pattern or “gland in gland” mucosal architecture.
- c) Exemplification of minimally three dilated glands demonstrating intraluminal debris [1,2].

Majority (92%) of Barrett's oesophagus display a duplicate layer of muscularis mucosae. Deep-seated muscularis mucosa is the original layer whereas superficial layer is constituted by recently configured muscle. Carcinomatous invasion betwixt dual layers of muscularis mucosae recapitulates the occurrence in intra-mucosal carcinoma thereby implying tumour infiltration of lamina propria and/or inmost layer of muscularis mucosae. Aforesaid tumour invasion is concordant with lymph node metastasis and tumour recurrence free survival. Additionally, identification of sub-mucosal glands and ducts and large calibre vasculature can assist pathological staging and depth of tumour invasion in improperly oriented specimens obtained by endoscopic mucosal resection [6,8].

High grade dysplasia can additionally delineate specific features “suspicious for invasive carcinoma” (HGD/S) which manifest as

- i) Solid or cribriform glandular and stromal architecture.
- ii) Ulcerated variant of high grade dysplasia.
- iii) Dilated and dysplastic glands with accumulation of intraluminal debris.
- iv) Predominant exudation of neutrophils within high grade dysplasia.
- v) Dysplastic mucosal glands infiltrating the superimposed squamous epithelium

Enunciation of greater than three dilated glands with intraluminal debris is an independent indicator of progression to oesophageal adenocarcinoma.

Currently, a conclusive histological elucidation of Barrett's oesophagus is the gold standard for diagnosis and appropriate evaluation of Barrett's oesophagus [8,9].

Determination of ancillary biomarkers

Barrett's oesophagus and early oesophageal adenocarcinoma are responsive to discernment by several biomarkers such as mucin glycoprotein 2 (MUC2), CDX-2, Das-1, SOX-9, Villin and Hep Par1.

Mucin glycoprotein 2 (MUC2) is a predominant and specific marker delineating goblet cell metaplasia in Barrett's oesophagus. CDX-2 is the chief regulator of intestinal differentiation within the colon and small bowel and can potentially control the elucidation of Barrett's oesophagus. Manifestation of CDX-2 is enhanced during intestinal metaplasia and declines as the condition progresses through dysplasia and overt carcinoma.

MUC2, CDX-2, Das-1, Villin and Hep Par 1 are cogitated as biomarkers indicative of intestinal metaplasia. However, aforesaid biomarkers do not conclusively assist the determination of Barrett's oesophagus and necessitate appropriate histological determination [9,10].

Elucidation of p53 mutation is a promising diagnostic and prognostic biomarker for discerning dysplasia contingent to Barrett's oesophagus. Manifestation of p53 aberration is 0% in Barrett's oesophagus- negative for dysplasia, around 9% in low grade dysplasia, approximately 55% in high grade dysplasia and an estimated 87% in oesophageal adenocarcinoma. Nevertheless, assessment of p53 as a biomarker is controversial on account of a proportion of false positive and negative detection.

Alpha-methylacyl- CoA racemase (AMACR) is considered as an efficacious biomarker for delineating dysplasia. Enunciation of the molecule (AMACR) is around 38% in low grade dysplasia, approximately 81% in high grade dysplasia and roughly 72% in oesophageal adenocarcinoma. Alpha-methylacyl- CoA racemase is devoid of elucidation in non- dysplastic oesophagus. Appearance of AMACR in Barrett's oesophagus is an indicator of enhanced possibility of progression to overt malignancy [1,2].

Human epithelial growth factor receptor 2 (HER2) is an authentic biomarker for detecting oesophageal adenocarcinoma. Targeted chemotherapy with Trastuzumab is contingent to enunciation of HER2 by the tumefaction. Overexpression of the molecule is elucidated in around 15% to 30% of primary oesophageal adenocarcinoma.

Recently, combination chemotherapy with administration of Trastuzumab is a contemplated as a cogent option for treating HER2 immune reactive metastatic oesophageal adenocarcinoma.

Analysis of HER2 is achieved by immune-histochemistry followed by employment of in situ hybridization (ISH).

Immune reactivity for HER2 is graded as negative or 0 (tumour cells stained on cell membrane), non-reactive or 1+ (faint/ minimally discernible membranous staining), equivocal or 2+ (weak or moderate complete basal and lateral membranous staining) and reactive or 3+ (strong, intense, complete, basal and lateral membranous staining). An estimated 10% of tumour resection specimen or a miniature cluster of five tumour cells exemplified within the biopsy specimen is the designated cut-off for HER2 immune reaction [1,2].

Equivocal or 2+ immune reactivity for HER2 requires a confirmation by in situ hybridization in order to discern genetic amplification of HER2. A cogent immune reactivity is denominated with human epithelial growth factor receptor2/ chromosome enumeration probe 17 (HER2/CEP17) ratio beyond ≥ 2 .

Concordance of immune-histochemistry with in situ hybridization or additional analysis with immune reactive levels of equivocal (2+), reactive (3+) or non-reactive (0 or 1+) is not necessitated [1,3].

Molecular determinants

Sequential manifestations of Barrett's oesophagus- dysplasia-adenocarcinoma spectrum displays multiple and severe genetic anomalies. Oesophageal adenocarcinoma depicts frequent genomic deletions of chromosome 17p (100%), 5q (80%), 9p (64%), 13q (43%), 18q (43%) and 1p (41%).

Deletion of chromosome 17p is around 14% in Barrett's oesophagus, around 42% in low grade dysplasia, nearly 79% in high grade dysplasia and roughly 75% in oesophageal adenocarcinoma.

Deletion of chromosome 18q is cogitated at 32% in Barrett's oesophagus, 42% in low grade dysplasia, 73% in high grade dysplasia and 69% in oesophageal adenocarcinoma [1,2].

Flow cytometry with deoxyribonucleic acid (DNA) can be contemplated as a prospective clinical indicator in diagnosis and risk stratification of Barrett's oesophagus.

Chromosomal deletion of 17p and 18q are frequent in oesophageal adenocarcinoma delineating an inferior prognosis.

Enunciation of tumour suppressor genes are correspondent to specific chromosomes Elucidation of p53 is with chromosome 17p, SMAD4 is delineated with chromosome 18q, APC is cogitated with chromosome 5q, p16 biomarker is denominated with chromosome 9q, RB1 is exemplified with chromosome 13q and ARID1a is demonstrated with chromosome 1p.

Whole genome sequencing of specimens of oesophageal adenocarcinoma depict somatic mutations and chromosomal insertions and deletions which are designated as TP53 (81%), ARID1a (17%), SMAD4 (16%), p16 (15%), KCNQ3 (12%), CCDC102B (9%) and CYP7B1 (7%) [1,2].

Genomic mutation of TP53 is a preliminary manifestation of Barrett's oesophagus with subsequent emergence of oesophageal adenocarcinoma through the expression of catastrophic aneuploidy and oncogene amplification.

Germ-line mutations are demonstrated within three specific genes by genome-wide mapping method, which are cogitated as MSR1, ASCC1 and CTHRC1, occurring in an estimated 11% instances of Barrett's oesophagus and oesophageal adenocarcinoma.

Additional, contemporary research tools for investigation of Barrett's oesophagus include epigenetic regulation, mi RNA profiling and microbiome study [9,10].

Therapeutic options

An initial diagnosis of Barrett's oesophagus mandates surveillance of the subjects for preliminary detection of malignant conversion with institution of antecedent and appropriate therapy in order to curtail the incidence and mortality incurred by Barrett's mucosa induced oesophageal adenocarcinoma. Mucosal anomalies and variable dysplasia arising in Barrett's oesophagus are preferably managed with endoscopic mucosal resection [10,11].

Adoption of endoscopic eradication therapy (EET) has significantly modified the management of Barrett's oesophagus and instances of concurrent neoplasm. Aforesaid technique is minimally invasive and prevents the morbidity and mortality associated with conventional esophagectomy. The contemporary procedure of endoscopic eradication therapy incorporates endoscopic mucosal resection (EMR) of visible, well delineated lesions displayed within the segment of Barrett's oesophagus along with application of effective ablative techniques, particularly radiofrequency ablation and cryotherapy. Endoscopic eradication therapy is contemplated as an efficacious, cogent and safe method for achieving comprehensive elimination of intestinal metaplasia (CE-IM). Endoscopic eradication therapy is pertinent in displaying therapeutic outcomes comparable with esophagectomy, especially in instances of Barrett's oesophagus with high grade dysplasia and mucosal oesophageal adenocarcinoma. Esophagectomy and/or endoscopic eradication therapy is competent and relevant in treating Barrett's oesophagus with variant invasion of upper one third (sm1), middle one third (sm2) and lower one third (sm3) of the oesophageal sub-mucosa [10,11].



Figure 1: Absent dysplasia in Barrett's oesophagus with minimal inflammation and scattered goblet cells [12].

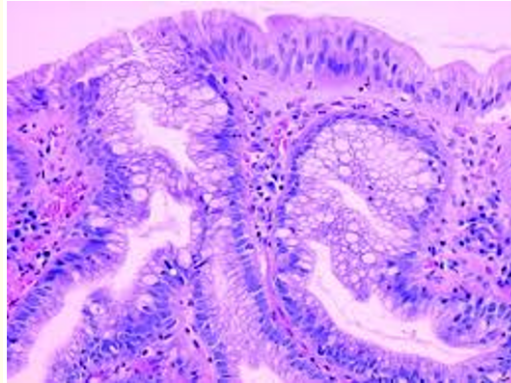


Figure 2: Barrett's oesophagus with intra-luminal and intra-cytoplasmic mucin, nuclear polarity and hyperchromasia [13].

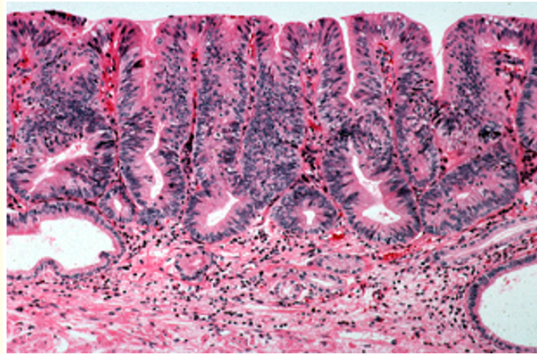


Figure 3: Depleted goblet cells with cellular and nuclear hyperplasia, hyperchromasia and moderate dysplasia in Barrett's oesophagus [14].

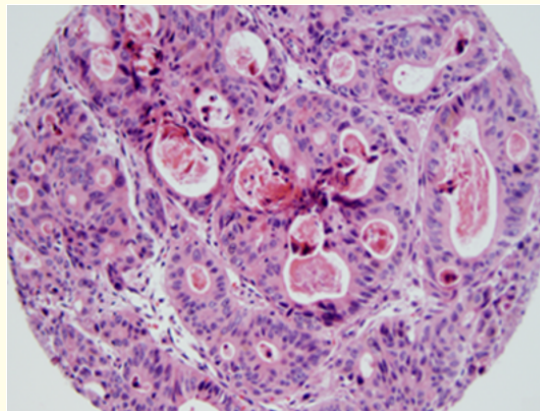


Figure 4: Moderate to severe dysplasia, cellular atypia and pleomorphism in Barrett's oesophagus [15].

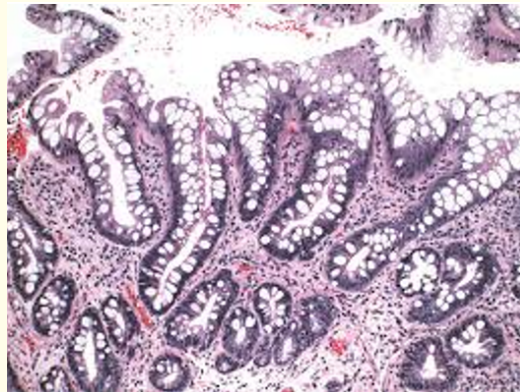


Figure 5 : Barrett's oesophagus with cellular pleomorphism, atypia, nuclear stratification and mild dysplasia [16].

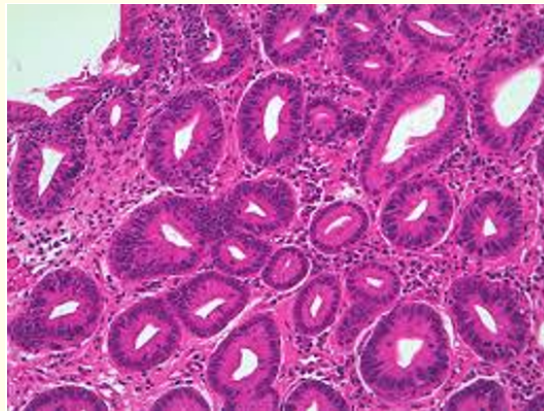


Figure 6 : Barrett's oesophagus with columnar cells, intra-cellular mucin and inflamed lamina propria [17].

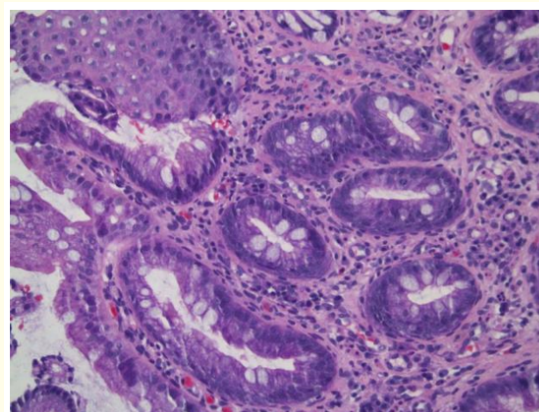


Figure 7 : Intestinal metaplasia with goblet cells, intra-cytoplasmic mucin, nuclear stratification and mild atypia in Barrett's oesophagus [18].

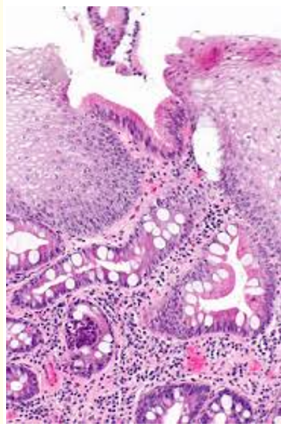


Figure 8 : Barrett' oesophagus with intra-luminal and intracellular mucin, loss of polarity, nuclear hyperchromasia, intestinal metaplasia and focal dysplasia [19].



Figure 9 : Barrett's oesophagus with intestinal metaplasia, cellular atypia and transitory squamo-columnar junction [20].

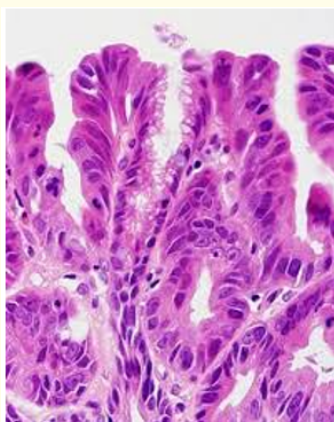


Figure 10 : High grade dysplasia with nuclear and cellular pleomorphism, anaplasia, lack of surface maturation and nuclear hyperchromasia in Barrett's oesophagus [21].

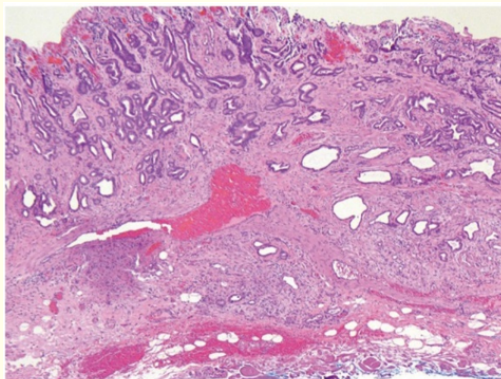


Figure 11 : Barrett's oesophagus with disseminated intestinal metaplasia, nuclear stratification, atypical columnar cells and loss of polarity [22].

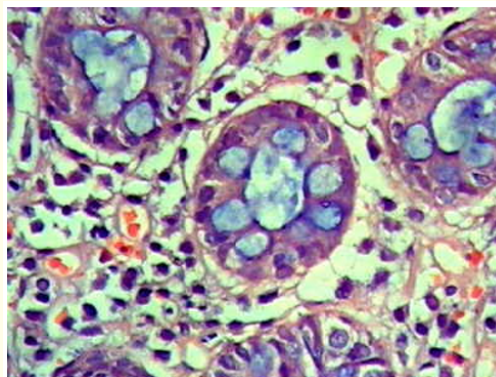


Figure 12 : Alcian blue stain in Barrett's oesophagus with delineated goblet cells displaying intra-cytoplasmic and intra-luminal mucin in Barrett's oesophagus [23].

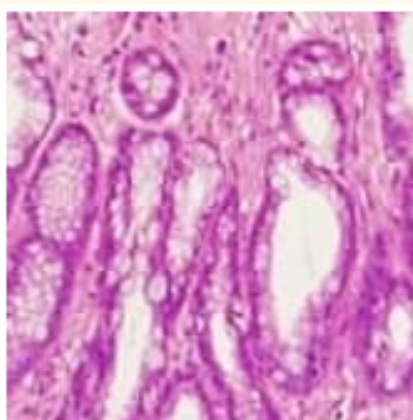


Figure 13 : Barrett's oesophagus with moderate nuclear and cellular pleomorphism, anaplasia, loss of polarity, goblet cell metaplasia and inflamed lamina propria [24].

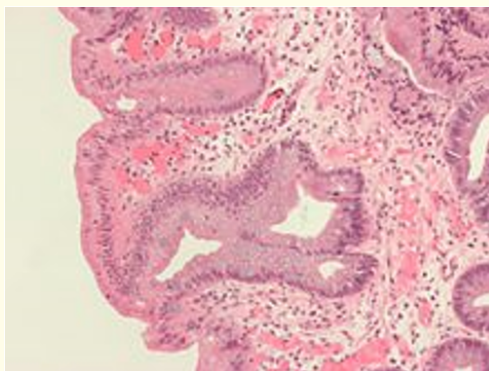


Figure 14 : Alcian blue stain in Barrett's oesophagus with predominant intra-luminal and intra-cellular mucin [20].

Bibliography

1. Yin F, *et al.* "Histopathology of Barrett's Oesophagus and Early -Stage Oesophageal Adenocarcinoma- Updated Review". *Gastrointestinal Disorders* 1.1 (2019): 147-163.
2. Wani S, *et al.* "Endoscopic eradication therapy for patients with Barrett's oesophagus associated dysplasia and intra-mucosal cancer". *Gastrointestinal Endoscopy* 87.4 (2018): 907-931.
3. Kuipers EJ, *et al.* "Natural history of Barrett's Oesophagus". *Digestive Diseases and Sciences* 63.8 (2018): 1997-2004.
4. Eros B, *et al.* "Helicobacter pylori infection reduces the risk of Barrett's Oesophagus; a meta analysis and systematic review". *Helicobacter* 23.4 (2018): e12504.
5. Bennett C, *et al.* "A large scale review and Delphi consensus for management of Barrett's Oesophagus with No Dysplasia, Indefinite for or Low Grade Dysplasia". *American Journal of Gastroenterology* 110.5 (2015): 662-682.
6. Naini BV, *et al.* "Barrett's oesophagus diagnostic criterion: Endoscopy and Histology". *Best Practice and Research: Clinical Gastroenterology* 29.1 (2015): 77-96.
7. Shaheen NJ, *et al.* "AGC Clinical Guidelines: Diagnosis and Management of Barrett's Oesophagus". *American Journal of Gastroenterology* 111.1 (2016): 30-50.
8. Pereira AD and Chaves P. "Low risk of adenocarcinoma and high grade dysplasia in patients with non-dysplastic Barrett's Oesophagus: results from a cohort from a country with low oesophageal adenocarcinoma incidence". *United European Gastroenterology Journal* 4.3 (2016): 343-352.
9. Kestens C, *et al.* "Risk of neoplastic progression in Barrett's Oesophagus diagnosed as indefinite for dysplasia: a nationwide cohort study". *Endoscopy* 47.5 (2015): 409-414.
10. Salomao MA, *et al.* "Substantial interobserver agreement in the diagnosis of dysplasia in Barrett's oesophagus upon review of a patient's entire set of biopsies". *American Journal of Surgical Pathology* 42.3 (2018): 376-381.

11. Srivastava A., *et al.* "The use of ancillary stains in the diagnosis of Barrett's oesophagus and Barrett's oesophagus associated dysplasia: recommendations from the Rodger C Haggitt gastrointestinal pathology society". *American Journal of Surgical Pathology* 41.5 (2017): e8-e21.
12. Image 1 Courtesy: Annals of Oesophagus.
13. Image 2 Courtesy: Gut.
14. Image 3 Courtesy: UW Pathology.
15. Image 4 Courtesy: Atlas of genetics and cyto-genetics in oncology and haematology.
16. Image 5 Courtesy: medcell.med.yale.edu.com.
17. Image 6 Courtesy: Digestive and liver disease.
18. Image 7 Courtesy: Cancer therapy advisor.
19. Image 8 Courtesy: Librepath.com.
20. Image 9 and 14 Courtesy: Wikipedia.
21. Image 10 Courtesy: LCA.com.
22. Image 11 Courtesy: Clinical Endoscopy.
23. Image 12 Courtesy: Gastrointestinal atlas.
24. Image 13 Courtesy: iupui.com.

Volume 6 Issue 8 August 2019

©All rights reserved by Anubha Bajaj.