MORE ABOUT

Barrett's oesophagus

P Eyal, MB ChB, MMed (Anat Pathol)

Senior Pathologist and Lecturer, Department of Anatomical Pathology, National Health Laboratory Service (NHLS), Tshwane Academic Division and University of Pretoria

Correspondence to: P Eyal (paula.eyal@up.ac.za)

What is Barrett's oesophagus?

Barrett's oesophagus (BO) is defined as the occurrence of metaplastic, specialised columnar epithelium lining the distal part of the oesophagus. [1] Evidence points to this as a metaplastic condition in reaction to ulceration and re-epithelialisation, the columnar epithelium replacing the normal stratified squamous epithelium. [2] Only specialised columnar epithelium consisting of a villiform growth pattern containing columnar, goblet, Paneth and endocrine cells (i.e. intestinal metaplasia (IM)) located above the lower oesophageal sphincter (LOS) qualifies as BO. [1,3]

BO has been divided into long-segment (the classic form involving 3 cm or more of the oesophagus) and short-segment (less than 3 cm) forms. Practically, however, these types are managed similarly. Ultra-short-segment BO has also been described where no endoscopic evidence of BO is seen but where IM is found on biopsy. This remains controversial. [1,4] BO is furthermore classified as a pre-cancerous condition predisposing to the development of oesophageal adenocarcinoma. [5]

Which patients are affected?

The large majority of patients are adults suffering from gastro-oesophageal reflux disease (GORD).^[2] A genetic predisposition has been reported.^[6] Children suffering from cystic fibrosis and who receive chemotherapy may also develop the condition.^[7] BO is found in 1.6% of the general population and in up to 10% of patients with symptomatic GORD.^[1]

How is the diagnosis made?

Barium swallow, manometric examinations and intra-oesophageal pH monitoring may provide supporting evidence; however, the definitive diagnosis requires endoscopy and biopsy specifically of the area above the LOS.

On endoscopy the affected mucosa appears red and velvety, extending proximally either circumferentially or advancing in one or several tongues. However, it may be difficult to measure and locate the metaplastic mucosa, and therefore the diagnostic criteria of BO are histological.

On biopsy, IM is the diagnostic feature of BO when located in the oesophagus, not when located in the upper part of the stomach. The mucosa is considered an incomplete form of IM. A villiform growth pattern is observed containing goblet cells with mucous cells, Paneth cells and neuroendocrine cells. [1,3] Mature absorptive intestinal cells with a brush border are rare. Foci of cardiac and fundal-type gastric mucosa are also identified in a patchwork fashion. [1,8]

In addition, *Helicobacter pylori* organisms may be identified in the metaplastic foci, and rarely pancreatic and osseous metaplasia may be identified. Reduplication of the muscularis mucosa is a frequent finding.

What are the complications?

Peptic ulceration and stricture formation may be seen, and in addition dysplasia and adenocarcinoma may develop.^[1,5]

How is Barrett's oesophagus treated?

The surveillance of patients diagnosed with BO entails endoscopy and biopsy. In the absence of dypslasia, medical acid suppression, laser and photodynamic therapy may be used. Various non-surgical treatments of early neoplastic lesions have emerged, including endoscopic mucosal (EMR). Surgical resection options include oesophagogastroplasty, fundoplication or posterior gastropexy. However, the indications for surgical intervention remain controversial. Factors influencing therapy include possible failure of medical therapy, the length of the BO and dysplasia.[9,10]

Malignancy

The progression to malignancy in BO follows the familiar metaplasia-dysplasia-carcinoma sequence.

Dysplasia/intra-epithelial neoplasia denotes architectural and cytological abnormalities confined to within the basement membrane of the affected gland. The dysplasia may be low grade (nuclei basally orientated within the cells) or high grade (haphazardly located nuclei). Dysplasia may be found in 5 - 10% of cases and is associated with carcinoma in up to 100%. The risk for the development of carcinoma in a patient with dysplasia is therefore much higher than in the general population. Description of the carcinoma in the general population.

Invasive carcinoma arising from BO is nearly always of the adenocarcinoma type. Five to 10% of all oesophageal tumours are associated with BO. The tumours may be multicentric and are often advanced at the time of diagnosis. Most patients are white men with an average age of 57 at the time of diagnosis.

Mutation and over-expression of p53, apoptosis-related genes, myc amplification, mutations of the cadherin/catenin membrane complex, microsatellite instability and expression of CD44 are included in the molecular alterations already identified in BO containing dysplastic/carcinomatous changes. [13]

The primary treatment of carcinoma is surgical resection, combined with chemotherapy and radiation.

The prognosis of adenocarcinoma arising from BO is poor, with a 5-year survival rate of 14.5%. The prognosis is, however, similar to that of conventional squamous cell carcinoma of the oesophagus. Unusual malignancies arising from BO include adenosquamous carcinoma, squamous cell carcinoma, sarcomatoid carcinoma, neuroendocrine carcinoma, choriocarcinoma and yolk sac tumours.^[14]

The future

In the future, non-biopsy endoscopic methods including chromo-endoscopy and narrow-band imaging may be used, allowing a reduction in the number of biopsies. Other possibilities include light-induced fluorescence endoscopy, light-scattering spectroscopy and spectroscopy. However, further evaluation is necessary before clinical application is possible.^[1,9]

- Fléjou J-F, Svrecek M. Barrett's oesophagus a pathologist's view. Histopathology 2007;50:3-14.
- Phillips RW, Wong RK. Barrett's esophagus. Natural history, incidence, etiology, and complications. Gastroenterol Clin North Am 1991;20:791-816.
- 3. Goldblum JR. The significance and etiology of intestinal metaplasia of the esophagogastric junction. Ann Diagn Pathol 2002;6:67-73.
- Nobukawa B, Abraham SC, Gill J, et al. Clinicopathologic and molecular analysis of high grade dysplasia and early adenocarcinoma in short-versus long-segment Barrett's esophagus. Hum Pathol 2001;23:447-454.
- 5. Haggitt RC. Adenocarcinoma in Barrett's esophagus: a new epidemic? Hum Pathol 1992;23:475-476.
- Fahmy N, King JF. Barrett's esophagus. An acquired condition with genetic predisposition. Am J Gastroenterol 1993;88:262-1265.
- Hassall E, Weinstein WM, Ament ME. Barrett's esophagus in childhood. Gastroenterology 1985;89:1331-1337.
- 8. Paull A, Trier JS, Dalton MD, et al. The histological spectrum of Barrett's esophagus. N Engl J Med 1976;295:476-480.

- Rusch VW, Levine DC, Haggitt R, et al. The management of high grade dysplasia and early cancer in Barrett's esophagus. A multidisciplinary problem. Cancer 1994;74: 1225-1229.
- Conio M, Cameron AJ, Chak A, et al. Endoscopic treatment of highgrade dysplasia and early cancer in Barrett's oesophagus. Lancet Oncol 2005;6:311-321.
- 11. Geboes K, Van Eyken P. The diagnosis of dysplasia and malignancy in Barrett's esophagus. Histopathology 200;37:99-107.
- Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnarlined (Barrett's) esophagus. N Engl J Med 1985;313:35-39.
- Jankowski JA, Wright NA, Melter SJ, et al. Molecular evolution of the metaplasia-dysplasia – adenocarcinoma sequence in the esophagus. Am J Pathol 1999;154:965-973.
- Smith RRL, Hamilton SR, Boitnott JK, et al. The spectrum of carcinoma arising in Barrett's esophagus. A clinicopathologic study of 26 patients. Am J Surg Pathol 1984;8:563-573.

- American Diabetes Association. Standards of medical care in diabetes -2010. Diabetes Care 2010;33(Suppl 1):S11-61.
- ArodaVR, Ratner R. Approach to patient with prediabetes. Journal of Clinical Endocrinology and Metabolism 2008;93:3259-3265.
- Reaven GM. The metabolic syndrome: Requiescat in pace. Clin Chem 2005;6:931-938.
- Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final report. Circulation 2002;106:3143-3421.
- International Diabetes Federation Worldwide Definition of the Metabolic syndrome 2006. http://www.idf.org/webdata/docs/MetS_def_update2006. pdf (accessed 12 February 2012).
- 6. World Health Organization/International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of theWHO/IDF consultation. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf (accessed 16 February 2012).
- 7. Alberti K, Eckel R, Grundy S, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Association for the Study of Obesit Heart Federation; International Atherosclerosis Society; and International Association for the study of Obesity. Circulation 2009;120:1640-1645.
- 8. Wilcox G. Insulin and insulin resistance. Clin Biochem Reviews 2005;26:19-39.
- Sang Youl Rhee, Jeong-Taek Woo. The prediabetic period: Review of clinical aspects. Diabetes and Metabolism 2011;35:107-116

- 1. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-281.
- Cavalier E, Delanaye P, Cahpelle JP, Souberbielle JP. Vitamin D: current status and perspectives. Clin Chem Lab Med 2009;47:120-127.
- 3. Hypponen E, Laara E, Ruenanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358:1500-1503.
- 4. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770-1773.
- $\begin{tabular}{ll} 5. & Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. J Neurol 2009;256:1468-1479. \end{tabular}$
- 6. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes and Control 2005;16:83-95.
- Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension 2007;49:1063-1069.
- 8. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma

- epidemic? J Allergy Cllin Immunol 2007;120:1031-1035.
- 9. Cannell JJ. Autism and vitamin D. Med Hypotheses 2008;70:750-759.
- Altschuler EL. Low maternal vitamin D and schizophrenia in offspring. Lancet 2001;358:1464.
- Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:142-147.
- 12. Carter GD. 25-hydroxyvitamin D: a difficult analyte. Clin Chem 2012;58:486-488.
- 13. Farrell CL, Martin S, McWhinney B, et al. State-of-the-art vitamin D assays: a comparison of automated immunoassays with liquid chromatographytandem mass spectrometry methods. Clin Chem 2012;58:531-542.
- 14. Heaney RP. Vitamin D: how much do we need, and how much is too much? Osteoporos Int 2000;11:553-555.
- Heijboer AC, Blankenstein MA, Kema IP, Buijs MM. Accuracy of 6 routine 25-hydroxyvitamin D assays: influence of vitamin D binding protein concentration. Clin Chem 2012;58:54354-8.

- Goldman A, Graf C, Ramsay M. Molecular diagnosis of cystic fibrosis in South African populations. SAMJ 2003;93(7):518-519.
- The South African Cystic Fibrosis Consensus Document. 3rd ed. 2007. http://www.sacfa.org.za (accessed 20 March 2012).
- 3. Mishra A, Greaves R, Massie J. The limitations of sweat electrolyte reference intervals for the diagnosis of cystic fibrosis: A systematic review. Clin Biochem Rev 2007;28:60-76.
- Cystic Fibrosis. Up to Date. http://www.uptodate.com.ez.sun.ac.za/ contents/cystic-fibrosis-clinical-manifestations-and-diagnosis (accessed 20 March 2012).
- 5. Mishra A, Greaves R, Massie J. The relevance of sweat testing for the diagnosis of cystic fibrosis in the genomic era. Clin Biochem Rev 2005;26:125-149.

- Farrel PM, Rosenstein BJ, White BT, et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns Through Older Adults: Cystic Fibrosis Foundation Consensus Report. J Pediatr 2008;153(2):S4-S14.
- Coakley J, Scott S, Mackay R, et al. Sweat testing for cystic fibrosis: Standards
 of performance in Australia. Ann Clin Biochem 2009;46:332-337.
- Coakley J, Scott S, Doery J, et al. Australian Guidelines for the Performance of the Sweat Test for the Diagnosis of Cystic Fibrosis. Clin Biochem Rev 2006;27 Suppl 1:S1-S6.
- 9. Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK. http://www.acb.org.uk/docs/sweat.pdf (accessed 4 April 2012).
- Burtus CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. USA: Elsevier Saunders, 2006:994-999,1871.

- Hwang PH, Getz A. Acute sinusitis and rhinosinusitis in adults. Available at www.uptodate.com (accessed 5 January 2012).
- Rosenfield RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg 2007;137(3 Suppl):S1-S3.
- Thomas M, Yawn B, Price D, Lund V, Mullol J, Fokkens W. European Position Paper on Rhinosinusitis and Nasal Polyps Group. EPOS primary care guidelines: European position paper on the primary care diagnosis and management of rhinosinusitis and nasal polyps 2007 – a summary. Prim Care Respir J 2008;17(2):79-89.
- Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc 2011;86(5):427-443. Epub 2011; April 13.

- 5. Du Plessis DJ. Current approach to sinusitis. CME 2004;22(5):240-245.
- Sinusitis Update Workgroup. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol 2005;116:S13-47.
- 7. Scheid DC, Hamm RM. Acute bacterial rhinosinusitis in adults: part I. Evaluation. American Family Physician 2004;70(9):1685-1692.
- Scheid DC, Hamm RM. Acute bacterial rhinosinusitis in adults: part II. Treatment. American Family Physician 2004;70(9):1697-1704.
- 9. Working Group of the Infectious Diseases Society of southern Africa. Updated guideline for the management of upper respiratory tract infections in South Africa: 2008. SA Fam Pract 2009;51(2):105-114.

- 1. Greenburger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2002;110:685-692.
- 2. Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. Cochrane Database Syst Rev 2004;(3):CD001108.
- 3. Pasqualotto AC, Powell G, Niven R, Denning DW. The effects of antifungal therapy on severe asthma with fungal sensitization and allergic bronchopulmonary aspergillosis. Respirology 2009;14:1121-1127.
- $\label{lem:coley_J} A. Chishimba\,L, Niven\,RM, Cooley\,J, Denning\,DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. J Asthma 2012;49:423-433.$

?????????????????