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Barretts's oesophagus

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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 neuro-endocrine 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 resection (EMR). Surgical 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).[11] 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.[12]

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 adenoncarcinoma 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, neuro-endocrine 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 will be possible.[1,9]

References available at www.cmej.org.za

Lymph node biopsy: Some aspects revisited

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Lymph node biopsy, if performed correctly, is likely to yield an optimal diagnostic result.[1-3] However, in view of the invasive nature of the procedure, biopsy should only be undertaken in patients with a definitive clinical indication. Less invasive investigations, such a full blood count and serology, and fine needle aspiration (FNA), may indeed provide a conclusive diagnosis especially if a careful medical history/examination reveals the most likely clinical cause for the lymphadenopathy, which is subsequently confirmed.

FNA as a tool to allow for a reliable diagnosis has gained increasing acceptance.[2-5] Larger/referral laboratories have access to additional specialised investigations, including immunophenotyping, flow cytometry, cytogenetics and other techniques that can be performed as part of FNA sampling aiding in/allowing for a conclusive diagnosis.[1,2] Unfortunately, of the latter depend on 'on site' sampling. As a very significant percentage of the population is, at least initially, managed at peripheral healthcare units, lacking readily accessible specialised work-up. More complicated cases in need of ancillary techniques cannot optimally be assessed in this way.

Guidelines for lymph node biopsy are provided in various surgical, medical and pathology textbooks.[1,2,4,5] In a clinical scenario where other means of arriving at a conclusive diagnosis have failed some of the more important indications for biopsy include:

- Persistent, unexplained lymph node enlargement. Decisions on further management will have to be based on other relevant considerations, i.e. age, general health, findings of clinical examination (site of involvement and whether lymphadenopathy is localised or generalised).
- Confirmation of clinically suspected diagnosis. Medical history and/or findings on examination may indicate that malignant disease is most likely, but conclusive histological diagnosis in most cases remains mandatory to allow for further management. Examination of draining nodes involved by metastatic disease of a primary tumour (i.e. where the latter is far less readily accessible for biopsy) may yield a definitive diagnosis.
- Assist in the investigation of a patient with a lymphadenopathy with associated clinical symptoms/signs that are difficult to explain conclusively (on the assumption that other relevant investigations have failed to provide a diagnosis). In this category conditions inducing non-neoplastic lymphadenopathy, which may have been overlooked, including infections, connective tissue disease and drug-related reactions may be relevant. Lymph node biopsy in these cases may indeed also be indicated to exclude the possibility of malignancy, including lymphomas with unusual presentation or unexpectedly widespread involvement by metastatic disease.
- Localised lymphadenopathy, especially of superficial nodes which are only moderately enlarged and soft, particularly in paediatric patients, may indeed be

due to reactive lymphadenopathy at a site draining a focus of infection. In our setting tuberculous lymphadenitis/HIV-related lymphadenopathy remains a relatively common cause for lymph node enlargement and can very often reliably be diagnosed by FNA.

- All non-invasive means should be used to arrive at a reliable diagnosis, and biopsy should only be performed if results of, for example, FNA remain worrisome but inconclusive or if other clinical indications, such as a lack of response to instituted antibiotic therapy, complicate the case.
- Hard or rubbery nodes generally need sampling for an urgent diagnosis.
- Additional indications include lymph node dissection as part of staging procedures as well as monitoring of response to treatment. The latter are largely part of specialist/tertiary management and therefore less relevant in general/primary care practice.

Lymph node biopsy technique[1,2]

Lymph node biopsy represents an invasive procedure which may require significant surgical expertise, depending on the site of involvement, general condition and age of the patient, nature of diseased nodes, etc. While optimally biopsies should be performed by surgical specialists, with the overall profound shortage of specialist medical professionals it is not feasible in the South African context. In peripheral/rural settings lymph node biopsies are indeed performed by non-specialist medical practitioners; in most cases with a sound clinical judgement as to feasibility and safety of the procedure. Less experienced staff need adequate training/supervision before an intervention of this nature. More complicated cases, however, may have to be referred to tertiary centres/specialists for sampling.

In cases where prior less invasive procedures have not provided a conclusive answer but the findings on, for example, FNA/needle biopsy remain very worrisome, needle or preferably excisional biopsy is indicated. While larger centres have ready access to ultrasound/CT-guided needle biopsies, this is unfortunately not the case at peripheral smaller medical units. If needle biopsy is performed numerous representative cores of diseased, viable tissue need to be submitted. For optimal histological assessment especially of unusual cases an intact node with minimal traumatisation artefact is preferred. Artefact is related largely to surgical procedure. A markedly traumatised biopsy may indeed not allow for a reliable morphological evalua-tion, therefore rendering a diagnosis impossible.

The optimal diagnostic yield also relates to choice of node for biopsy. If the patient presents with a single diseased node, this will obviously be the node to sample and submit. With more widespread disease additional considerations become relevant. Inguinal nodes should, more specifically in adults or patients with previous lymphadenitis at the site/persons known to often go barefooted, be avoided as changes related to previous lymphadenitis may significantly complicate interpretation. Axillary and cervical nodes are preferred.

In general the largest diseased node is likely to yield the most optimal tissue. Please note that easily accessible superficial/small nodes may not be representative and relevant disease may then be missed. If aggregates/matted nodes are identified, removal of several nodes may result in a more accurate final assessment (variability of involvement).

Biopsies of abdominal nodes, i.e. during laparotomy where lymphadenopathy was an unexpected finding, should be performed after diligent inspection to allow for most optimal sampling including, for example, retroperitoneal nodes. Note should also be taken of other relevant findings, e.g. regional pathology, organomegaly, or possible metastatic involvement.

Cases where lymph node biopsies need to be taken from sites that are technically difficult to sample, e.g. mediastinum/deep locations, should be referred for specialist management.

Specimen handling

For optimal tissue preservation intact lymph nodes need to be bisected without delay and fixed in 10% buffered formalin. Tissue cannot be 'kept' in saline as the latter has no fixative properties and profound autolytic change, rendering the tissue useless, will result.

(Requirements for MC&S are different and need to be discussed with the relevant laboratory prior to sampling.)

For surgical bisection of nodes good-quality instruments in optimal condition must be used to limit traumatisation artefact.

If specialised other techniques are indicated/desired, e.g. imprint cytology/electron microscopic assessment, the case needs to be discussed with the referral laboratory/pathologist to allow for optimal handling of the specimen. Prior to dispatching a specimen due care must be taken to check patient identity and appropriate labelling of the specimen. Full clinical information/findings of available investigations and possible pending results should be provided. While diagnosis in more straightforward cases may be readily forthcoming, other difficult cases may

be significantly delayed and discussion between the attending clinician and pathologist is then indicated. In such cases, patients should also be informed of the reason for the delayed diagnosis, e.g. the need for ancillary laboratory investigations, to lessen the distress for the patient and the family.

References available at www.cmej.org.za

Renal disease in the elderly – a new entity?

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Chronic renal disease (CRD) in adults is fairly common worldwide. CRD is often associated with cardiovascular mortality, which is increasing. In adults CRD is associated with systemic hypertension, diabetes mellitus and systemic lupus erythematosus (SLE) or glomerulonephritis (GN).[1,2]

Globally, there is an increasing tendency for patients to reach end-stage renal disease (ESRD). The diagnosis of CRD and ESRD is based on the estimated glomerular filtration rate (eGFR). In the West the population is ageing, e.g. in the USA the elderly will outnumber children within 10 years. Currently, life expectancy for men in Europe is 76.1 years and for women 82.2 years.[3,4] Although the incidence of ESRD is high in the elderly, progression to renal failure tends to be low.[3]

The Kidney Disease Outcome Quality Initiative (KDOQI) classification system is based on the reduction of the GFR. The fixed cut-off for abnormalities used in the classification system is for all ages and age-related renal function decline has been omitted.[3] In the elderly it is important to keep in mind that age-related changes occur in the kidney. With ageing there is a gradual structural and functional loss, starting around the age of 40 years, with a decrease in the GFR of 8 ml/min/decade.[3]

The histological changes that are found in the kidneys of the elderly are a gradual increase in glomerulosclerosis, interstitial fibrosis, tubular atrophy and chronic vascular disease, which is also known as nephrosclerosis. Age-associated changes may, however, also occur with systemic hypertension and diabetes mellitus.[3]

The presence of CRD in the elderly is increasingly recognised (KDOQI and National Kidney Foundation (NKF)), but staging of the CRD is also important. If the renal disease is recognised earlier, treatment can be improved with a focus on preventing progression.[4] The more advanced stages of CRD have a poor overall outcome, associated with increased mortality risk and hospitalisation.[5]

In the elderly it is important to establish whether there is progression to renal failure. Decline in renal function with ageing is physiological and not pathological. This must be taken into account before an elderly patient is labelled as having CRD.[5] However, if the eGFR is below 60 ml/min, even in the elderly, renal disease must be evaluated and managed.[5]

In the elderly there is seldom a single cause for CRD. They often have hypertension and/or diabetes, which is associated with ESRD. Sudden progression of decreased renal function is associated with infections, vasculitic symptoms or changes in medication.[5]

Primary glomerulopathies and vasculitis tend to be increasingly recognised in the elderly and must be included in the differential diagnosis of a patient with progression of renal disease. A renal biopsy may be required.[5,6] A renal biopsy is regarded as the gold standard in the evaluation/investigation of a patient with renal disease. It provides the diagnosis, and guides treatment and prognosis.[6]

Requesting a renal biopsy in the elderly is problematic, because the biopsy may reveal only age-related changes.[6] In the subgroup of patients over the age of 80 this is even more problematic. In this subgroup, however, properly indicated biopsies are almost always worthwhile, because the biopsy provides a diagnosis with therapy options and a prognosis and often prevents the patient receiving unnecessary therapy.[6]

It is important to remember that kidney diseases in adults and in the elderly overlap. A few types of glomerulopathy are more common in the elderly. Membranous and minimal-change glomerulonephritis is more common in the elderly, while other GNs tend to occur in younger adults. SLE renal involvement occurs exclusively in young adults.[6]

Tubulo-interstitial nephritis tends to occur in the elderly owing to age-related changes or the toxic effect of medication.

In the elderly there are some diseases that are more frequent and that require renal biopsy and careful evaluation in order to be excluded.[6]

These diseases include:

- crescentic glomerulonephritis due to ANCA-positive vasculitis
- amyloidosis/myeloma cast nephropathy due to paraproteins from plasma cell dyscrasias or lymphoplasmacytic proliferations
- atherosclerotic/athero-embolic renal disease.

Unfortunately, the elderly person with ESRD has a higher risk of frailty, an increase in syncope and a decrease in memory/increase in dementia. Life expectancy varies between 8.9 and 24 months. These risks may be aggravated by dialysis.[7]

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